NHS
*National Institute for Health and Clinical Excellence*

# Single Technology Appraisal

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

# Evaluation Report

**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

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

**Contents:**

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

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Premeeting briefing

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

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

**The manufacturer was asked to:**

Provide further information on the clinical effectiveness including the overall survival data based on published data (hazard ratio 0.7) compared with an updated analysis (hazard ratio 0.72), the extrapolation of clinical effectiveness data beyond the duration of the trial, the rate of adverse events in trials of cabazitaxel in breast cancer and use of minimisation method during patient allocation.

Provide a rationale for assuming that the effect of treatment would differ by region and examine the statistical significance level of these differences.

Provide a rationale for the subgroup that formed the base case of the appraisal (European, ECOG performance status 0–1 and who had received a dose of at least 225 mg/m$^2$ docetaxel).

Provide further information on the cost effectiveness including using updated overall survival data, choosing a different time point for switching to a parametric curve, using parametric curves throughout and the effect of incorporating uncertainty of Kaplan–Meier data in probabilistic sensitivity analysis.

Clarify errors identified by the Evidence Review Group in the economic modelling.

### Licensed indication

Cabazitaxel (Jevtana, Sanofi-aventis) has a UK marketing authorisation for use in combination with prednisone or prednisolone for the treatment of people with metastatic hormone-refractory prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen.

# Key issues for consideration

## *Clinical effectiveness*

- Is the post hoc subgroup of the TROPIC trial comprising European patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and who had received at least three cycles of docetaxel, the most representative of the UK patients?
- Patients in the TROPIC trial received a maximum of ten cycles of cabazitaxel treatment. In clinical practice would patients receive more than ten cycles of cabazitaxel?
- What factors determine the discontinuation of cabazitaxel treatment in clinical practice? Are there any serious adverse events, other than neutropenia, that result in the discontinuation of the therapy? Is pain progression also an important consideration?
- Are the incidence and management of adverse events from cabazitaxel expected to be higher in clinical practice than in the TROPIC trial?

## *Cost effectiveness*

- The manufacturer's model used Kaplan–Meier curves for calculating transition probabilities (up to 37 cycles) in preference to parametric curves, considering use of empirical data more robust than 'best-fit mathematical function'. Is this approach appropriate?
- Is it appropriate to calculate transition probabilities for moving from stable disease to progressive disease based on progression-free survival data, given that calculation of progression-free survival in the TROPIC trial may be susceptible to bias?
- Are the utility values used in the model sufficiently robust, given that the incremental cost-effectiveness ratio (ICER) is highly sensitive to the utility value for the progressive disease state? Is it appropriate to assumes equal utility values for patients in the cabazitaxel and mitoxantrone arms in the stable as well as progressive disease state?

- The disutility and resource use associated with adverse events in cabazitaxel or mitoxantrone arms were modelled into the stable disease state only. Is this a valid assumption, given that nearly half of the patients in progressive disease were receiving post-second-line chemotherapy?
- Sensitivity analysis presented by the manufacturer showed that the ICER decreases considerably if vial wastage can be avoided. Is vial sharing feasible, given the number of patients who would receive cabazitaxel?

# 1 Decision problem

| | Final scope issued by NICE | Decision problem addressed in the manufacturer's submission |
|---|---|---|
| **Population** | Men who have metastatic hormone-refractory prostate cancer that has progressed following or during docetaxel-based treatment | Men who have hormone refractory metastatic prostate cancer that has progressed following or during docetaxel-based treatment |
| **Intervention** | Cabazitaxel in combination with prednisolone | Cabazitaxel 25 mg/m$^2$ (every 3 weeks) plus prednisolone (or prednisone) 10 mg/day – up to a maximum of ten cycles |
| **Comparator(s)** | Mitoxantrone in combination with prednisolone<br><br>Chemotherapy without cabazitaxel (for example, 5-fluorouracil, cyclophosphamide and carboplatin/etoposide) | *Considered in manufacturer's submission*<br>Mitoxantrone in combination with prednisolone<br><br>*Not considered in manufacturer's submission*<br>Chemotherapy without cabazitaxel (for example, 5-fluorouracil, cyclophosphamide and carboplatin/etoposide)<br><br>Manufacturer's submission mentioned the unavailability of good quality evidence of efficacy for 5-fluorouracil, cyclophosphamide and carboplatin/etoposide in men with mHRPC for any robust analysis. It also stated that these agents are used rarely in this population and their use could not be considered as standard UK practice. |

| | | |
|---|---|---|
| **Outcomes** | The outcome measures to be considered included:<br>• overall survival progression-free survival<br>• response rate<br>• prostate-specific antigen (PSA) level<br>• adverse events associated with treatment<br>• health-related quality of life | Primary outcome: overall survival<br><br>Secondary outcomes:<br>• progression-free survival<br>• time to tumour progression<br>• overall response rate<br>• PSA progression<br>• pain response measures and safety<br>• 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 (QALY)<br>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<br>*C*osts will be considered from an NHS and personal social services perspective | The cost-effectiveness of cabazitaxel is expressed as a cost per QALY<br>The time horizon in the base case is the patient's lifetime<br>Costs are considered from an NHS and personal social services perspective |
| **Other considerations** | If evidence allows, consideration will be given to subgroups defined by:<br>• baseline performance status<br>• duration of prior docetaxel exposure<br>• time since docetaxel treatment<br>Guidance will be issued only in accordance with the marketing authorisation | The primary outcome of overall survival was reported for a number of pre-planned subgroups from the TROPIC trial including:<br>• baseline performance status<br>• duration of prior docetaxel exposure<br>• time since docetaxel treatment<br>• geographic region<br>Manufacturers considered the European patients with an ECOG status of 0–1, and who have previously received at least 225 mg/m$^2$ of docetaxel as the base case for economic evaluation |

| | | |
|---|---|---|
| **Special considerations, including issues related to equity or equality** | Guidance will be issued only in accordance with the marketing authorisation | No additional issues relating to equity or equality were identified |

## *1.1 Evidence Review Group comments*

### 1.1.1 Population

The Evidence Review Group (ERG) stated that the patient population of the TROPIC trial (men with metastatic hormone refractory prostate cancer that has progressed following or during docetaxel therapy) was appropriate to the decision problem. The manufacturer presented the results for the entire population of the TROPIC trial and three subgroups: patients with an ECOG performance status of 0–1 who have previously received at least 225 mg/m$^2$ of docetaxel; European patients; and European patients with an ECOG performance status of 0–1 who have previously received at least 225 mg/m$^2$ of docetaxel (this was presented as the base case population for this appraisal). The ERG agreed with manufacturer that it is highly unlikely that ECOG performance status 2 patients would receive cabazitaxel in line with NICE guidelines. The ERG also expected that all patients would have received sufficient exposure to docetaxel before consideration for second-line chemotherapy. The ERG did not agree to restricting the base case population to the European patients and stated that patients from all regions should have been included in the base case.

### 1.1.2 Intervention

The ERG noted that because the dosing of cabazitaxel depends on the body surface area some people will need more than one pack per cycle. It also noted that even though the unopened vials of cabazitaxel have a shelf-life of 2 years, after opening the concentrate and solvent should be used immediately.

### 1.1.3 Comparators

The ERG noted that some of the comparators identified in the scope (5-flourouracil, cyclophosphamide and carboplatin or etoposide) were not included as comparators in the manufacturer's submission. The manufacturer's submission is limited to one comparator – mitoxantrone in combination with prednisone or prednisolone – because it was assumed to be the active treatment most commonly used in the UK in men with mHRPC that has progressed after docetaxel treatment, and that the use of the other comparators is not standard practice in the UK. The ERG agreed that there was no randomised controlled trial (RCT) evidence of the effectiveness of 5-flourouracil, cyclophosphamide and carboplatin for the second-line treatment of mHRPC. The ERG agreed that mitoxantrone in combination with prednisone or prednisolone is the most relevant comparator for this appraisal but highlighted a large RCT of abiraterone acetate (an androgen biosynthesis inhibitor) that reports that it is effective in this group of patients. The ERG noted that the results were published after the manufacturer's searches and agreed that it is not relevant to the decision problem because it is not licensed or routinely used in the UK.

### 1.1.4 Outcomes

The ERG noted that primary outcome of overall survival is the gold standard efficacy outcome in this patient population and that the secondary outcome of progression-free survival is a composite endpoint that includes time to tumour progression, PSA progression, pain progression or death from any cause. The ERG considered the definition of progression-free survival to be conservative because PSA progression precedes symptomatic and radiological progression and also noted that pain progression is a subjective outcome susceptible to bias.

### 1.1.5 Other relevant issues

The ERG noted that in the UK, the risk of prostate cancer is two to three times higher in black Caribbean and black African men, and that the risk in Asian men is lower than the national average.

It also noted that the cabazitaxel infusion contains 15% volume/volume ethanol, so it may be harmful to patients suffering from alcoholism.

## *1.2 Statements from professional/patient groups and nominated experts*

Submissions from clinical specialists noted that the aim of treatment in mHRPC is to slow the progression of the disease and prolong life.

Clinical specialists noted that second-line chemotherapy is widely used for the treatment of hormone resistant prostate cancer, although the absence of clear guidance means there is significant geographical variation in the choice of chemotherapy. Clinical specialists stated that currently used second-line treatment options in this patient group include mitoxantrone, retreatment with docetaxel (not recommended by NICE technology appraisal guidance 101), and ECarboF (epirubicin, carboplatin and fluorouracil). These have limited evidence of benefit. The specialists further stated that docetaxel retreatment and mitoxantrone are the most commonly used second-line treatments, and that a retrospective analysis of 148 patients with disease progression after docetaxel treatment reported that 34% patients received docetaxel retreatment and 48% received mitoxantrone. Clinical specialists also pointed out that mitoxantrone does not have UK marketing authorisation for the treatment of mHRPC and that although it does not improve overall survival it is widely used for the palliation of pain.

Clinical specialists stated that cabazitaxel is the only life-prolonging second-line treatment option after docetaxel failure in people with mHRPC. They also noted that current European Association of Urology guidelines on prostate cancer (updated January 2011) recommend that ‘cabazitaxel should be considered in the management of progressive HRPC following docetaxel therapy’ on the basis of level I evidence from the TROPIC trial.

Clinical experts noted emerging evidence of improved survival with abiraterone (CYP17 inhibitor) compared with placebo in the same population. However, they also emphasised that cabazitaxel and arbiraterone have

different mechanisms of action and are most likely to hold different positions in a treatment pathway for mHRPC for optimum results.

Patient organisations considered the main advantages of the cabazitaxel treatment to be prolonged survival, prolonged progression-free period, improved pain progression and a greater proportion of patients responding to the treatment. In an online survey of 30 people affected by prostate cancer, carried out by the Prostate Cancer Charity, 19 respondents identified the possibility of extended life that cabazitaxel offers as its most important benefit. Only seven respondents highlighted that the side effects of cabazitaxel were a serious concern to them. No survey respondent appeared to have any concerns that cabazitaxel treatment needed repeat hospital visits for administration, but this may be seen by some patients as a barrier.

# 2 Clinical effectiveness evidence

## *2.1 Clinical effectiveness in the manufacturer's submission*

### 2.1.1 Cabazitaxel compared with mitoxantrone — the TROPIC trial

The manufacturer's submission presented clinical-effectiveness evidence from one phase III, randomised, open label, multicentre trial carried out in 146 centres in 26 countries worldwide. The TROPIC trial compared the relative effectiveness of cabazitaxel and mitoxantrone (both in combination with prednisone or prednisolone) in 755 men older than 18 years (378 cabazitaxel, 377 mitoxantrone), with mHRPC and an ECOG performance scope of 0–2, with evidence of disease progression during or after docetaxel treatment. In this trial 402 (53%) patients were from European countries and [redacted]. The inclusion criteria were amended after the start of the trial on the basis of Prostate Cancer Clinical Trials Working Group recommendations to continue treatment with docetaxel for at least 12 weeks (three cycles or at least 225 mg/m$^2$ of docetaxel treatment). Before this

change 59 patients who received less than 225 mg/m$^2$ of docetaxel had already been recruited. Participants were randomised to receive cabazitaxel 25 mg/m$^2$ intravenously over 1 hour or mitoxantrone 12mg/m$^2$ over 15–30 minutes on day 1 of each 21-day cycle, up to a maximum of ten cycles. Patients in both arms received oral prednisone 10 mg (or equivalent doses of prednisolone) daily in addition to the study medication. Patients in the cabazitaxel arms received premedication consisting of single intravenous doses of an antihistamine, corticosteroid (dexamethasone 8 mg or equivalent), and histamine H2-antagonist (except cimetidine) 30 minutes or more before cabazitaxel. Antiemetic prophylaxis and other supportive care were given at the physicians' discretion.

Prophylactic granulocyte colony stimulating factor (G-CSF) was not allowed during the first cycle, but thereafter was permitted at physician's discretion and was compulsory in the presence of serious neutropenia.

Concomitant therapy with chemotherapeutic agents, radiotherapy or hormones was not permitted except luteinizing-hormone-releasing hormone (LHRH) agonists that were already being used before study entry, steroids and hormones for non-disease-related conditions (for example, steroids for adrenal failure or insulin for diabetes) and bisphosphonates.

In the case of drug toxicity, study treatment could be delayed for up to 2 weeks for neutrophil levels to recover, after which the cabazitaxel dose was reduced to 20 mg/m$^2$ and the mitoxantrone dose was reduced to 10 mg/m$^2$. Only one dose reduction was allowed per patient and if the reduced dose was intolerable, study treatment was stopped in those patients.

The manufacturer considered the baseline characteristics of the trial to be balanced between the two groups (for further information see table 5-4 in the manufacturer's submission).

The primary outcome measured by the trial was overall survival. Secondary outcomes included progression-free survival (defined as the time between randomisation and first appearance of any signs of disease progression –

defined by a rise in PSA level, tumour progression, pain progression or death), tumour response rate (assessed using RECIST criteria in patients with measurable disease), time to tumour progression, PSA progression, PSA response (assessed only in patients with baseline PSA of 20 nanograms/ml or more), pain progression, pain response (assessed only in patients with median present pain intensity 2 or more on McGill–Melzack scale and/or mean analgesic score 10 or more points at baseline), and adverse events.

The overall survival results were presented for the entire TROPIC population, and for predefined subgroups on the basis of ECOG performance status, disease measurability, number of prior chemotherapy regimens, age, region, pain at baseline, PSA status, time from last docetaxel to randomisation, total docetaxel dose received, and time to progression from last docetaxel. The results were also presented for: patients from the entire TROPIC population with ECOG status 0–1 who had received at least 225 mg/m$^2$ docetaxel; European participants; and European participants with an ECOG performance score of 0–1, who had previously received at least 225 mg/m$^2$ of docetaxel (the last group is the base case population defined by the manufacturer for this appraisal).

### 2.1.2 Results for the overall TROPIC population

The manufacturer presented a primary analysis conducted after 513 (234 in cabazitaxel and 279 in mitoxantrone) deaths had occurred at a median follow-up of 12.8 months, and an updated analysis performed almost 6 months later after 585 participants had died. For the primary endpoint in the primary published analysis, median overall survival was significantly longer in the cabazitaxel arm than in the mitoxantrone arm (15.1 months compared with 12.7 months, hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.59 to 0.83, $p < 0.0001$). The updated analysis reported similar median overall survival for both groups, (HR 0.72, 95% CI 0.61 to 0.84, $p <0.0001$).

Mean overall survival was estimated by fitting the trial Kaplan–Meier data into a Weibull parametric curve. This showed a mean overall survival of

14.0 months (95% CI 13.1 to 14.9) in the mitoxantrone arm compared with 18.2 months (95% CI 17.0 to 19.4) in the cabazitaxel arm.

The overall survival results of the pre-planned subgroup analyses (which included region and ECOG performance status) showed longer survival with cabazitaxel than mitoxantrone for all subgroups except people with people who had prior treatment with less than 225 mg/m$^2$ of docetaxel or who had taken part in the trial in centres outside North America and European (see figure 5-7 and 5-8 on pages. 66 and 67 of the manufacturer's submission)

Median progression-free survival was significantly longer in the cabazitaxel arm than in the mitoxantrone arm (2.8 months compared with 1.4 months, HR 0.74, 95% CI 0.64 to 0.86, p < 0.0001) arm. The majority of the progression events (40–50%) were attributed to PSA progression (see page 68 of the manufacturer's submission).

The median time to tumour progression was 8.8 months in the cabazitaxel arm compared with 5.4 months in the mitoxantrone arm (HR 0.61, 95% CI 0.49 to 0.76, p < 0.0001). The median time to PSA progression was 6.4 months in the cabazitaxel arm compared with 3.1 months for the mitoxantrone arm (HR 0.75, 95% CI 0.63 to 0.90, p = 0.001). There was no statistically significant difference in pain response between the treatment arms (9.2% for cabazitaxel compared with 7.7% for mitoxantrone, p = 0.63) or in time to pain progression (p = 0.5192). The TROPIC trial did not collect health-related quality of life data, and pain has an important influence on overall health-related quality of life. Because TROPIC showed no significant difference in pain response and time to pain progression between cabazitaxel and mitoxantrone, it was assumed that cabazitaxel may be similar to mitoxantrone in this aspect of quality of life (see page 72 of the manufacturer's submission).

The objective response rate of patients with measurable disease at baseline, evaluated according to RECIST criteria, was 14.4% in the cabazitaxel arm compared with 4.4% in the mitoxantrone arm (p = 0.0005). This represented

the proportion of people who had a partial response because none of the participants in either arm had a complete response to treatment.

The most common adverse events were neutropenia and its complications (febrile neutropenia and infections), asthenic conditions (asthenia and fatigue), and gastrointestinal toxicity (diarrhoea, nausea and vomiting) (see table 5-10 in the manufacturer's submission).

Neutropenia was reported by the manufacturer to be the most important adverse event associated with cabazitaxel therapy because of its serious clinical complications. Cabazitaxel was associated with higher rates of grade 3 or higher neutropenia (82% compared with 58% for mitoxantrone), and of infections and febrile neutropenia (28% compared with 5% for mitoxantrone). The clinical consequences of neutropenia were related to seven deaths in the cabazitaxel arm and one death in the mitoxantrone arm. TROPIC investigators were subsequently advised to strictly follow the protocol regarding dose modification and G-CSF prophylaxis according to American Society of Clinical Oncology (ASCO) guidelines and no further deaths related to neutropenia were reported. Logistic regression analysis of neutropenia and diarrhoea incidence (all grades) suggested that patients were more prone to diarrhoea ($p < 0.1$) if they were aged 75 years or older, or had received prior radiotherapy. Similarly, patients were more prone ($p < 0.1$) to neutropenia if they were aged 65 years or older, or had received prior radiotherapy. The rate of neutropenia in European patients was also lower (16.1%) than in the North Americans (25.7%) or in the patients from other countries (35.1%) ($p < 0.1$)(see table 21, page 60 of ERG report). There were no differences in the rates of neutropenia for pre-specified subgroups defined by race, baseline liver function, baseline renal function, ECOG performance status, or prior chemotherapy.

Patients in the cabazitaxel group received study treatment for longer (a median of six treatment cycles compared with four cycles in the mitoxantrone group), but dose reductions were reported in more patients in the cabazitaxel group (12% patients and 9.8% cycles) than in the mitoxantrone group (4%

patients and 9.8% cycles). Similarly, treatment delays occurred more in the cabazitaxel group (104 patients, 28% of cycles) than the mitoxantrone group (56 patients, 15% of cycles).

### 2.1.3 Results of post hoc subgroup analyses

The manufacturer conducted post-hoc analysis of the clinical effectiveness in three populations:

- European patients ([redacted] of the trial population)
- all patients with an ECOG performance status of 0–1 who received at least 225 mg/m$^2$ docetaxel ([redacted] of the trial population)
- European patients with an ECOG performance status of 0–1 who received at least 225 mg/m$^2$ docetaxel ([redacted] of the trial population).

The manufacturer presented European patients with an ECOG performance status of 0–1 who had received at least 225 mg/m$^2$ docetaxel as the base-case population because it was considered the most representative of patients who would receive cabazitaxel in clinical practice in the UK.

Results of post-hoc subgroup analysis are presented in table 1.

## Table1 Results of post-hoc subgroup analysis of TROPIC trial[1]

| | Mitoxantrone plus prednisone/prednisalone | | | Cabazitaxel plus prednisone/prednisalone | | | Cabazitaxel vs mitoxantrone (both plus prednisone/prednisalone) | |
|---|---|---|---|---|---|---|---|---|
| **Overall survival** | | | | | | | | |
| **Subgroups** | **Number dead/n (%)** | **Median survival (95% CI)** | **Mean survival** | **Number dead/n (%)** | **Median survival (95% CI)** | **Mean survival** | **Hazard ratio** | **Difference** |
| Whole population | 279/377 (74.0%) | 12.7 (11.6–13.7) | 14.0 (13.1 – 14.9) | 234/378 (61.9%) | 15.1 (14.1–16.3) | 18.2 (17.0–19.4) | 0.70 (0.59–0.83) | 2.4 median<br>4.2 mean |
| European patients ECOG PS 0–1 ≥ 225 mg/m$^2$ docetaxel | 117/159 (73.6%) | [redacted] | [redacted] | 109/181 (60.2%) | [redacted] | [redacted] | [redacted] | [redacted] |
| ECOG PS 0–1 ≥ 225 mg/m$^2$ docetaxel | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| European patients | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 0.68 (0.53–0.86) | [redacted] |
| **Progression-free survival (PFS)** | | | | | | | | |
| **Subgroups** | **Number event/n (%)** | **Median PFS (95% CI)** | **Mean PFS** | **Number event/n (%)** | **Median PFS (95% CI)** | **Mean PFS** | **Hazard ratio** | **Difference** |
| Whole population | 367/377 (97.3%) | 1.4 (1.4–1.7) | 3.06 | 364/378 (96.3%) | 2.8 (2.4–3.0) | 4.14 | 0.74 (0.64–0.86) | 1.4 median<br>1.08 mean |
| European patients ECOG PS 0–1 ≥ 225 mg/m$^2$ docetaxel | 156/159 (98.1%) | [redacted] | [redacted] | 177/181 (97.8%) | [redacted] | [redacted] | [redacted] | [redacted] |
| ECOG PS 0–1 ≥ 225 mg/m$^2$ docetaxel | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| European patients | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status. | | | | | | | | |

[1] Table 6-37, page 151 of the manufacturer's submission.

## *2.2 Evidence Review Group comments*

The ERG agreed that the manufacturer's submission included the only known RCT of cabazitaxel plus prednisone or prednisolone (TROPIC) in the relevant population. The methodological quality of the study was judged to be good and statistical tests were considered appropriate. However, the ERG noted that this was an open-label study, so results were susceptible to bias in the assessment of subjective outcomes such as pain and symptomatic disease progression.

The ERG considered cabazitaxel (plus prednisone or prednisolone) to be associated with improved overall survival, progression-free survival, PSA response, time to PSA progression, objective tumour response, and time to tumour progression relative to mitoxantrone (plus prednisone or prednisolone). The ERG noted that the assessment of tumour response may not be robust because the number of patients with missing data exceeds the number of people with a tumour response. The ERG was concerned about the increased rate of many adverse events in people older than 65, given that 75% of new diagnoses of prostate cancer occur in this age group.

The ERG noted that although the manufacturer's submission reported no improvement in pain response or time to pain progression with cabazitaxel, pain outcomes are biased in favour of cabazitaxel because of the lower prevalence of bone metastases (80% in the cabazitaxel arm compared with 87% in the mitoxantrone arm). The ERG noted that TROPIC trial had insufficient power to detect differences in the incidence of specific adverse events. It also highlighted the limitation of RCT study design to detect rare adverse events. Because the TROPIC study used more stringent criteria relating to dose modifications and discontinuations of cabazitaxel therapy than were included in the product specification, the ERG indicated that the incidence of adverse events associated with cabazitaxel may be higher in clinical practice than observed in TROPIC. The ERG indicated that cardiac and renal complications other than deaths appear to be poorly reported in the manufacturer's submission. It also highlighted the US Food and Drug

Administration's recommendations for post-marketing review of renal toxicity and serious toxicity in general.

## *2.3 Statements from professional/patient groups and nominated experts*

Professional organisations considered that the TROPIC trial reflected UK clinical practice and that patients included in the trial represented the NHS patients who would be considered for cabazitaxel treatment. They noted that two recently reported randomised phase III trials in hormone resistant prostate cancer patients previously treated with docetaxel show a survival advantage for second-line treatment with cabazitaxel and arbiraterone acetate. Experts noted that TROPIC also shows improvement in median progression-free survival with cabazitaxel.

Professional organisations noted the most common adverse events associated with cabazitaxel were myelosuppression, diarrhoea and infection, and therefore careful patient selection by oncologists with expertise in this setting is needed. Concerns were raised over the higher incidence of death from neutropenic sepsis in patients treated with cabazitaxel. However, clinical experts observed that these appear to have resulted from poor sepsis management in some Eastern European and Indian centres and the risk is likely to be less severe in the presence of established chemotherapy support teams and clear algorithms for management of neutropenic sepsis. Professional organisations noted that the toxicity profile of cabazitaxel is not markedly different in magnitude and severity from that of other taxane chemotherapy agents (such as docetaxel), and the infrastructure for the safe delivery of these already exists.

Professional organisations noted that subgroup analysis for overall survival in a variety of clinically relevant subgroups in the TROPIC trial (for example, performance status, presence of measurable disease, number of prior chemotherapy regimens received, age, presence of pain, presence of a rising PSA, cumulative docetaxel dose received, and disease progression during or after docetaxel) failed to show any significant interactions between these

subgroups and treatment outcome. Professional organisations agreed that there is no known subgroup of patients with more capacity to benefit from cabazitaxel.

# 3 Cost effectiveness

## *3.1 Cost effectiveness in the manufacturer's submission*

### 3.1.1 Health economic model and parameters

No published studies were identified evaluating the cost effectiveness of cabazitaxel for the treatment of hormone refractory metastatic prostate cancer progressed after docetaxel.

The manufacturer submitted a de novo Markov model comparing cabazitaxel with mitoxantrone (both in combination with prednisone or prednisolone) in European patients with an ECOG performance status of 0–1 who had received at least 225 mg/m$^2$ docetaxel, from an NHS and personal social services perspective. People received either 25 mg/m$^2$ cabazitaxel or 12 mg/m$^2$ mitoxantrone every 3 weeks, plus 10 mg/day of prednisolone or prednisone, for a maximum of 10 cycles.

Treatment was modelled over a lifetime (15 years) based on the transition of people in 3-weekly cycles through three health states: stable disease, progressive disease and death. All patients entered the model in the 'stable disease' state, which comprised patients receiving second-line treatment with cabazitaxel or mitoxantrone (plus prednisolone or prednisone) who had not experienced any event of progression (rise in PSA level, tumour progression or pain progression), and could move to either progressive disease or death. The costs and disutilities of grade 3 adverse events were included only for patients in the stable disease state. Patients stayed in the progressive disease state until death. The probability of moving from stable to progressive state was derived from progression-free survival data, and the probability of moving from stable or progressive disease to death was based on overall survival data from TROPIC trial. The model used data from the Kaplan–Meier curves

from the TROPIC trial, until the point at which the manufacturer considered the small number of patients made the data unreliable. After this, transition probabilities were calculated from fitted parametric curves (see appendix 15 of the manufacturer's submission). Patients were assumed to remain on treatment for a maximum of ten cycles of active treatment, in line with the TROPIC protocol, or until progression.

Costs for the stable disease state included the acquisition cost of active treatment, acquisition cost of premedication and concomitant medication, costs of chemotherapy administration, cost of disease management including hospitalisation and testing and treatment of adverse drug reactions (see table 6-8, page 117 of the manufacturer's submission). All future costs and utility gain were discounted at the rate of 3.5% (see table 6-12, page 126 of the manufacturer's submission). Drug acquisition costs in the base case scenario were based on the dose used in the TROPIC trial (25 mg/$m^2$ cabazitaxel or 12 mg/$m^2$ mitoxantrone every 3 weeks, in combination with 10 mg/day of prednisolone or prednisone) based on an average body surface area of 2.01 $m^2$. The base case did not include vial sharing for either cabazitaxel or mitoxantrone. Cabazitaxel is supplied in vials containing 60 mg of drug, so it was assumed that no cabazitaxel patients would need more than one vial. Mitoxantrone comes in 20 mg vials, and the model stipulated cost based on average of number of vials used (1.871) (see table 6-7 of the manufacturer's submission).

General resource use was based on expert clinical opinion and a retrospective audit of five major UK cancer centres (see appendix 13 of the manufacturer's submission) and the cost was estimated using BNF and National Schedule of Reference Costs (2009/10). There were no data available on resource use for patients receiving cabazitaxel in the audit and it was assumed that other resource use would be similar in patients receiving cabazitaxel or mitoxantrone. Adverse event management costs for people with stable disease were considerably higher in the cabazitaxel arm, primarily because of the higher average rate per cycle of G-CSF primary prophylaxis to

prevent of neutropenia in the TROPIC trial (25% in the cabazitaxel arm compared with 10% in the mitoxantrone arm).

Patients in the progressive disease health state received best supportive care or a mix of post-second-line chemotherapy based on those received by patients in TROPIC trial (see table 6-10, page 123 of the manufacturer's submission). These treatments were assumed not to affect survival or utility.

Costs in the progressive disease state comprise acquisition costs for post-second-line active chemotherapy and best supportive care treatments including administration, and cost of disease management including hospitalisations and testing. Based on TROPIC data it was assumed that [redacted] would receive post-second-line chemotherapy, including docetaxel retreatment, mitoxantrone, etopside, and estramustine. The remaining [redacted] would receive best supportive care, including analgesics, steroids, palliative radiotherapy and bisphosphonates. The mix of post-second-line chemotherapies received was also taken from TROPIC (see table 6-10 in the manufacturer's submission) for the base case scenario. UK audit data for the proportion of patients receiving best supportive care (80%) and a UK-specific treatment mix (see table 6-11 in the manufacturer's submission) were applied as a sensitivity analysis. Because of the high cost of treatment at the end of life, an additional cost of £[redacted] was also added to the last month of life in the model (see table 6-12 in the manufacturer's submission).

**Table 2 Cost variables used in the base-case scenario[2]**

| Items | Cabazitaxel | Mitoxantrone |
|---|---|---|
| **Stable disease** | | |
| Drug cost (per vial) | £3696 | £100 |
| Mean cost of technology treatment (per cycle) | £3696 | £187.14 |
| Administration cost (per cycle) | £285.95 | £285.95 |
| Premedications (per cycle) | £88.58 | £36.53 |
| Concomitant medications (per cycle) | £75.61 | £75.61 |
| Adverse event management costs (total) | £487 | £178 |
| Additional costs (tests, hospitalisations) (per cycle) | £241.2 | £241.2 |
| **Progressive disease** | | |
| [redacted] (per cycle) | [redacted] | [redacted] |
| [redacted] (per cycle) | [redacted] | [redacted] |
| [redacted] (per cycle) | [redacted] | [redacted] |
| **End of life** | | |
| [redacted] | [redacted] | [redacted] |
| | | |

Health related quality of life data were not collected in the TROPIC trial. The utility value for patients with stable disease was based on data generated from an early access program (EAP) which is an open label, single arm study collecting EQ-5D data from [redacted] patients receiving cabazitaxel treatment in nine UK centres (see pages 102–3 of manufacturer's submission). A utility value of [redacted] was calculated based on the utility of people in their second cycle of cabazitaxel treatment. When people move to the progressive disease state a utility decrement of 0.070 is applied (derived from literature on the health related quality of life in people with mHRPC) to give a utility value of [redacted]. The disutility values associated with different adverse events were based on the disutility of adverse events in breast cancer and non-small-cell lung cancer treatment (see page 109 of the manufacturer's submission).

[2] Based on table 6-7, page 117 of the manufacturer's submission.

**Table 3 Utility values used for base-case scenario[3]**

| Markov state/adverse effects | Utility values used for both arms | Source |
|---|---|---|
| Stable disease | [redacted] | Cabazitaxel EAP |
| Progressive disease | [redacted] | Decrement from Sullivan (2007) applied to EAP stable disease value |
| Dead | 0.000 | Standard approach |
| Neutropenia | −0.090 | Nafees et al. (2008 |
| Febrile neutropenia | −0.120 | Lloyd et al. (2006) and Nafees et al. (2008) |
| Diarrhoea | −0.047 | Nafees et al. (2008) |
| Fatigue | −0.094 | Lloyd et al. (2006) and Nafees et al. (2008) |
| Asthenia (weakness) | −0.094 | Assumption |
| Leucopenia | −0.090 | Assumption |
| Back pain | −0.069 | Doyle et al. (2008) |
| Anaemia | −0.125 | Lloyd et al. (2008) |
| Thrombocytopenia | −0.090 | Assumption |
| Pulmonary embolism | −0.145 | Gould et al. (1999) and Treasure et al. (2009) |
| Dehydration | −0.151 | Lloyd et al. (2006) |
| Nausea/vomiting | −0.076 | Lloyd et al. (2006) and Nafees et al. (2008) |
| Bone pain | −0.069 | Doyle et al. (2008) |
| Deep vein thrombosis | −0.160 | Gould et al. (1999) |
| Neuropathy | −0.116 | Lewis et al. (2010) |
| Abbreviations: EAP, early access programme | | |

### 3.1.2 Manufacturer's base case results

The manufacturer's original base case ICER was £74,908 per QALY gained. During clarification the manufacturer made the following amendments to the model, as suggested by the ERG: a value of 2.97 days for total inpatient days per neuropathy episode replaced the previous figure of 2.77; the risk ratio for neutropenia prophylaxis, previously left blank, was updated to 0.077; the risk of adverse events was divided by 365.25 instead of 365; the disutility for pulmonary embolism was corrected to 0.145 instead of 0.245. This led to an

[3] Based on table 6-6, page 111 of the manufacturer's submission.

updated base case ICER of £74,938 per QALY gained. The correction in the relative risk of neutropenia did not have any effect on the base case ICER.

**Table 4 Deterministic base case results**[4]

| | Total Costs (£) | Total QALYs | Δ Cost (£) | Δ QALY | Cost per QALY (£) |
|---|---|---|---|---|---|
| Mitoxantrone | 13,047 | 0.849 | | | |
| Cabazitaxel | 35,372 | 1.147 | 22,325 | 0.298 | 74,938 |
| Abbreviations: QALY, quality-adjusted life year. | | | | | |

### 3.1.3 Manufacturer's base case sensitivity analyses

The manufacturer carried out one-way sensitivity analyses on various model parameters including: varying [redacted]; reducing drug and administration cost (−50%); reducing post-second-line drugs and administration cost (−50%); varying other costs (±50%); varying utility values for stable disease and progressive disease (±20%); excluding adverse event disutility; using time horizons of 1, 2, 3, 5 and 10 years; varying the discounting rate of cost and benefits (0 and 6%); and varying the proportion of people in both groups who would need primary G-CSF prophylaxis (0, 20, 40, 60, 80 and 100%). The results were most sensitive to the time horizon, [redacted] and the utility value assigned to the progressive disease state. All ICERs were above £61,000 per QALY gained except when drug and administration cost were reduced to 50% resulting in ICER of £41,945 per QALY gained. Further information on the deterministic sensitivity analysis can be found on page 141 of the manufacturer's submission and clarification letter.

Scenario analysis (defined as sensitivity analysis using an alternative assumption for a parameter in the model) was used to explore: the sensitivity of the ICER to parametric fitted curves for overall survival and progression-free survival during the trial period; progression-free survival using Weibull instead of Lognormal distribution; an alternative utility decrement for moving to progressive disease; UK post-second-line treatment or G-CSF usage (rather

[4] Table 30, page 76 of the ERG report.

than the usage in the TROPIC trial); and equivalent costs for progressive disease in both arms. These had little effect on the ICER. The results of the scenario analyses are presented in table 5

**Table 5 Results from scenario analyses[5]**

| | Difference in total costs (£) | QALY difference | ICER (£) |
|---|---|---|---|
| Base case | 22,325 | 0.298 | 74,908 |
| Fitted curves used throughout | 23,088 | 0.278 | 82,950 |
| Using a Weibull distribution for PFS in the mitoxantrone arm | 22,310 | 0.298 | 74,786 |
| Post-second-line treatment set to that of a UK audit rather than TROPIC (see table 6-10 and 6-11 in the manufacturer's submission) | 22,642 | 0.298 | 75,972 |
| No vial wastage assumed | 18,159 | 0.298 | 60,928 |
| Using UK-estimated BSA (1.9 $m^2$) rather than that from TROPIC (2.01 $m^2$) | 22,354 | 0.298 | 75,003 |
| Using UK-specific G-CSF use [redacted] | 22,146 | 0.278 | 74,387 |
| Using the SD to PD decrement estimated from Sandblom et al. 2004 (0.085) | 22,325 | 0.293 | 76,171 |
| Excluding adverse event-related disutilities | 22,325 | 0.300 | 74,536 |
| Assuming equal costs post-progression for cabazitaxel and mitoxantrone | 20,329 | 0.298 | 68,210 |
| Abbreviations: BSA, body surface area; ICER, incremental cost-effectiveness ratio; PD, progressive disease state; PFS, progression-free survival; QALY, quality-adjusted life year; SD,stable disease state . | | | |

Cabazitaxel is currently supplied in the vials containing 60 mg of the drug, which results in the wastage. The manufacturer suggested that vial sharing could reduce the ICER from £74,908 to £60,928 per QALY gained.

[5] Table 34, page 80 of the ERG report.

The manufacturer conducted an additional scenario analysis at the request of the ERG. This excluded deaths occurring within 30 days of randomisation, which increased the ICER from £74,908 to £78,319 per QALY gained.

Scenario analysis indicated that using fitted curves throughout resulted in an ICER of £82,950 per QALY gained. Because the time-point at which Kaplan–Meier data were considered unreliable and switched to parametric distribution in the model was purely based on subjective decision, the ERG asked the manufacturer to explore the effect of choosing different time points for this switch. In its response the manufacturer stated that in the base case, for overall survival, the switch was performed when four consecutive cycles reported zero events at week 114 (cycle 38) for overall survival; for different time points for the switch (week 3 to week 118) the ICER varied between £72,184 and £90,786 per QALY gained (see clarification letter).

The manufacturer's original probabilistic sensitivity analysis using parametric distributions for model inputs (see pages 132–3 of the manufacturer's submission) and 1000 iterations showed a low level of uncertainty around the base case result. The original submission did not assign distributions to the Kaplan–Meier data, and thus underestimated the uncertainty in the survival estimates. During clarification the manufacturer submitted a separate 'probabilistic model' that can be run only for probabilistic sensitivity analysis. The updated analysis showed a high level of uncertainty around the base case ICER. The probability of cabazitaxel being cost effective ranged from 9.4% at a threshold of £60,000 to 75.4% at a threshold of £90,000.

### 3.1.4 Post hoc sub-group analyses

The manufacturer's results for subgroup analyses are presented in table 6.

**Table 6 Results for post hoc sub-group analyses[6]**

| | Difference in total costs (£) | QALY difference | ICER (£) |
|---|---|---|---|
| Base case (European patient with ECOG 0–1 who had received docetaxel≥225 mg/m$^2$) | 22,325 | 0.298 | 74,938 |
| Whole TROPIC population | 21,368 | 0.244 | 87,684 |
| European patients | 21,966 | 0.260 | 84,540 |
| All TROPIC patients with ECOG performance status 0–1 who had received ≥ 225 mg of docetaxel | 21,408 | 0.259 | 82,538 |
| Abbreviations: ECOG, Eastern Cooperative Oncology Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year. | | | |

## *3.2 Evidence Review Group comments*

### 3.2.1 ERG critique of manufacturer's submission

The ERG noted that the conceptual model used by manufacturer appeared generally to be robust and transparent, allowing both variability and uncertainty in the model inputs to be altered and assessed. The ERG acknowledged that the inclusion of additional costs (for example from adverse events) reflected the clinical pathway likely to be encountered by patients receiving the treatment.

The ERG queried the use of hazard ratios based on overall survival data from the published analysis (HR 0.70) rather than the updated analysis (HR 0.72). An updated analysis received during clarification, based on the updated HR in which parametric curves were fitted to the data throughout, increased the ICER from £82,950 to £82,963 per QALY gained for the manufacturer's base case population.

The ERG considered that before conducting subgroup analysis there should be a rationale for considering that the results may differ between subgroups. The Group did not consider there to be an a priori clinical hypothesis as to

[6] Based on table 31, page 77 of the ERG report.

why the results may differ between different geographical regions, and noted that the statistical interaction of treatment by region was not significant (p = 0.1535). The statistical interaction between those patients with an ECOG performance status of 0 or 1 who also received at least 225 mg/m$^2$ docetaxel was also not statistically significant (p = 0.4098); however, the ERG did consider it biologically plausible that the efficacy of cabazitaxel treatment would be lower in people who had received insufficient prior treatment with docetaxel. It also agreed that it would be extremely unlikely that patients with an ECOG performance status of 2 would receive cabazitaxel. The ERG considered the most appropriate base case to be all patients from the TROPIC population who received at least 225 mg/m$^2$ of first-line docetaxel and had an ECOG performance status of 0 or 1.

The ERG also expressed concern over the use of data from Kaplan–Meier curves in the model and recommended use of parametric curves throughout. The ERG considered the use of parametric curves to be more appropriate than Kaplan–Meier curves in the model because this avoids over-fitting of the data, and parametric curves are more likely to be generalisable to the population who would receive cabazitaxel in clinical practice in the UK. The ERG also considered the selection of the time point (38 cycles) at which the proportions from the fitted curve was preferred to the Kaplan–Meier data in the model to be arbitrary, and that this could significantly affect the ICER (see clarification response).

The ERG considered the choice of sampling utility for stable disease in the EAP at cycle 2 to be plausible but noted the imprecision of the results, as shown by the relatively wide confidence intervals around the mean.

[redacted]. The ERG showed that independent sampling of the utilities for stable disease and progressive disease gave a higher utility for progressive disease than for stable disease on more than 3% of simulations, which the ERG considered not clinically plausible.

A very minor error in the implementation of the discount rate in the model (see clarification response) was identified but had minimal impact on the ICER.

The ERG did not consider sensitivity analysis based on the cost of [redacted]post-second-line drugs to be appropriate, given the availability of a list price. The ERG also considered alternating utility values to be arbitrary, noting that because the utilities for stable disease and progressive disease have been varied separately, improbable combinations of values were generated in two of the four scenarios and gave utility values for progressive disease larger than for stable disease. For example a 20% reduction in stable disease (SD) utility resulted in utility of [redacted] and utility of progressive disease ([redacted]; increasing PD utility to 20% resulted in a [redacted]). The ERG noted that the choice of utility values, in particular that of PD had a large impact on the ICER, emphasising the need to obtain robust estimates of utility values.

The ERG did not consider the scenario analyses in the manufacturer's submission related to vial sharing, the exclusion of disutility from serious adverse events and the equal cost of post-progression treatment with cabazitaxel and mitoxantrone to be appropriate. Vial sharing was not considered to be feasible given the proposed number of patients to be treated. The disutilities associated with adverse events have an impact on quality of life so they should be included in the modelling. The assumption of equal post-progression costs in both arms is not plausible because the prolonged survival in the cabazitaxel arm would incur additional cost for men in the progressive disease state.

The ERG noted that the way that probabilistic sensitivity analyses were implemented is likely to overestimate the uncertainty (see page 84 of the ERG report). It also noted that the manufacturer provided a cost-effectiveness plane and a cost-effectiveness acceptability curve but did not report the actual ICER.

### 3.2.2 Exploratory analyses undertaken by the ERG

The ERG altered the manufacturer's base case model by using parametric curves for the entire duration of the model, calculating the utility for progressive disease applying a mean decrement of 0.07 with an arbitrarily defined standard deviation of 0.02 to the utility of stable disease, and correcting an error to the discount rate. The ERG also used the population of all TROPIC patients who received at least 225 mg/m$^2$ of first-line docetaxel and had an ECOG performance status 0 or 1. A number of sensitivity analyses were undertaken to determine the robustness of the ERG ICERs to altering parameter values within the model.

**Table 7 Deterministic ICERs from the ERG's exploratory analyses for cabazitaxel compared with mitoxantrone**

| Amendment to the manufacturer's base case | ΔCost (£) | ΔQALY | Cost per QALY (£) |
|---|---|---|---|
| None (manufacturer's base case) | 22,325 | 0.298 | 74,938 |
| Using parametric curves for the entire time horizon | 23,088 | 0.278 | 82,986 |
| Using ERG base-case (≥ 225 mg/m$^2$ of first-line docetaxel, ECOG performance status 0 or 1) | 21,408 | 0.259 | 82,538 |
| Amending discount rate | 22,331 | 0.298 | 74,865 |
| All three amendments applied together | 22,233 | 0.248 | 89,476 |
| Abbreviations: ECOG, Eastern Cooperative Oncology Group; ERG, Evidence Review Group; QALY, quality-adjusted life year. | | | |

The additional work conducted by the ERG demonstrates that parametric curve fitting and the amended population had a largest impact on the ICER, which increased from £74,938 per QALY gained to £82,986 per QALY gained with parametric curves and £82,538 per QALY gained with the amended population. The combined effect of these amendments was to increase the base case ICER from £74,938 to £89,476 per QALY gained.

Probabilistic sensitivity analysis of the ERG model gave an ICER of £89,684 (based on an incremental cost of £22,439 and incremental QALY gain of 0.250).

The ERG undertook a number of sensitivity analyses to assess the robustness of the ERG-base case ICER to plausible changes in assumptions as follows: using the entire TROPIC population; using the upper and lower 95% confidence intervals for the utility of stable disease estimated from EAP at cycle 2; and using the 0.085 utility decrement from Sandblom rather than the 0.070 estimate from Sullivan et al. The use of different utility values for stable disease had the greatest impact on the ICER, as can be seen below.

**Table 8 Sensitivity analyses undertaken by the ERG[7]**

| **Sensitivity analyses** | **ΔCost (£)** | **ΔQALY** | **Cost per QALY (£)** |
|---|---|---|---|
| None (ERG base case) | 22,233 | 0.248 | 89,476 |
| Using subgroup 1 (entire TROPIC population) | 22,283 | 0.239 | 93,177 |
| Upper 95% of SD from the EAP at cycle 2 [redacted] | 22,233 | 0.298 | 74,620 |
| Lower 95% of SD from the EAP at cycle 2 ([redacted] | 22,233 | 0.199 | 111,719 |
| Utility difference between SD and PD estimated from Sandblom | 22,233 | 0.245 | 90,865 |
| Abbreviations: EAP, early access program; ERG, Evidence Review Group; PD, progressive disease state; QALY, quality-adjusted life year; SD, stable disease state. | | | |

When men dying within 30 days of randomisation were removed from the analysis, the ERG base case led to a £2000 increase in the ICER, from £89,476 to £91,465 per QALY gained.

[7] Table 38, page 94 of the ERG report.

### 3.2.3 End of life consideration

**Table 9 End of life criteria in manufacturer's submission and ERG report**

| | Criteria published by NICE | Manufacturer's submission | ERG's assessment |
|---|---|---|---|
| Life expectancy | The treatment is indicated for patients with a short life expectancy, normally less than 24 months | Manufacturer estimated the median life expectancy in men with metastatic hormone-refractory prostate cancer to be around 12 months | In the ERG's deterministic base case model men who did not receive cabazitaxel had a mean life expectancy of 1.17 years (approximately 14 months) |
| Extension of life | 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 | For manufacturer's base case (European patients with ECOG 0–1, who had already received ≥ 225 mg/m$^2$ docetaxel) cabazitaxel provided a [redacted] | The ERG considered there to be uncertainty as to whether its base case population (all patients with ECOG 0–1 who had already received ≥ 225 mg/m$^2$ docetaxel) met the extension of life criteria.<br>The probabilistic ERG base case model estimated the mean extension of life to be 0.35 years (approximately 4 months) whereas in the TROPIC study the median extension of life in the ERG base case was [redacted] |
| Licensed indication for small patient populations | The treatment is licensed, or otherwise indicated, for small patient populations | Manufacturer estimated that cabazitaxel would be indicated in 1938 men in England and Wales per year (see figure 2-1, page 23 of the manufacturer's submission) | The ERG estimated the eligible population to be 1823 (smaller than the manufacturer's estimate, see table 1, page 17 of the ERG report) |
| Abbreviations: ECOG, Eastern Cooperative Oncology Group; ERG, Evidence Review Group. | | | |

# 4 Equalities issues

No issues that could have potential impact on equality were identified during the development of scope or in any of the submissions received during the course of the appraisal.

# 5 Innovation

The manufacturer's submission stated that cabazitaxel is the first drug to provide a statistically significant improvement in survival for men with mHRPC who have progressed after first-line treatment with docetaxel. It resulted in an increase of approximately 30% in life expectancy in this patient population. Manufacturer's submission also stated that cabazitaxel was specifically developed to overcome taxane resistance which eventually develops with docetaxel therapy. In preclinical studies cabazitaxel showed activity in docetaxel resistant as well as docetaxel sensitive cell lines and animal models.

# 6 Authors

Anwar Jilani, Eleanor Donegan, with inputs from the lead team (Roderick Smith, Ray Armstrong and Cliff Snelling).

# Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by School of Health and Related Research (ScHARR), The University of Sheffield:

- Stevenson M, Lloyd Jones M, Kearns B, Littlewood C, Wong R. Cabazitaxel for the second-line treatment of hormone refractory, metastatic prostate cancer: A Single Technology Appraisal. ScHARR, The University of Sheffield, 2011

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Sanofi-aventis

II Professional/specialist, patient/carer and other groups:

- British Uro-Oncology Group
- University of Southampton/Southampton University Hospitals NHS Trust
- PCaSO Prostate Cancer Network and Prostate Cancer Support Federation
- The Prostate Cancer Charity

C Additional references used:

[Author A, Author B, Author C [et al. if more than three] (Year of publication) Title of article. Volume: page numbers].

[Author A, Author B, Author C [et al. if more than three] (Year of publication) Title of article. Volume: page numbers].

**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**

**Health Technology Appraisal**

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

**Final Scope**

## Remit/appraisal objective

To appraise the clinical and cost effectiveness of cabazitaxel within its licensed indication for the second line treatment of hormone refractory, metastatic prostate cancer that has progressed following or during docetaxel-based treatment.

## Background

Prostate cancer is a disease in which tumours develop in the prostate, a gland in the male reproductive system. It is the most common cancer in men in England and Wales, with 32,188 new cases diagnosed in 2006. The incidence of prostate cancer increases with age, with around 80% of cases occurring in men over the age of 65 years. In 2007, 9222 deaths from prostate cancer were recorded in England and Wales.

The cause of prostate cancer is thought to be multifactorial, involving both environmental and genetic factors. Prostate cancer growth is stimulated by androgens (male sex hormones) and men with the disease therefore may receive hormone therapy to reduce androgen levels. Fifty-five to sixty percent of prostate cancers will become metastatic – that is, they will spread to other parts of the body (most commonly the bones). For men with metastatic disease, hormonal treatment forms the cornerstone of treatment. Standard hormonal treatments for metastatic disease are orchidectomy (surgical removal of testes) or use of a gonadotrophin releasing hormone analogue such as goserelin, leuprorelin or triptorelin.

Metastatic prostate cancer will initially respond to hormone therapy in around 80% of men. However, after around 12 to 18 months of treatment, the disease usually becomes androgen-independent, where the cancer no longer requires androgen to progress. Alternative treatment strategies are therefore required. The cancer may respond to additional hormonal strategies, but ultimately the cancer becomes unresponsive to further hormonal manipulation. This stage is called hormone refractory prostate cancer (HRPC). The prognosis is poor for patients with HRPC: survival is not expected to exceed between 7 and 15 months. The aim of treatment for HRPC is to alleviate symptoms, prolong life and slow progression of the disease.

NICE Technology Appraisal no. 101 recommends docetaxel as a treatment option for men with HRPC who have a Karnofsky performance-status score of 60% or more. Men with metastatic HRPC that has progressed during or after

a docetaxel-based treatment may receive a combination of palliative treatments. Management options include mitoxantrone with or without steroids such as prednisolone, and a variety of chemotherapy regimens such as 5-fluorouracil, cyclophosphamide and carboplatin/etoposide.

**The technology**

Cabazitaxel (Jevtana, Sanofi-aventis) is a taxane anti-neoplastic agent. It works by stopping the polymerisation of microtubules that are essential for mitotic and interphase cellular functions and thereby causes inhibition of cell division and cell death. It is administered by intravenous infusion.

Cabazitaxel does not currently have a UK marketing authorisation for the treatment of HRPC. It is being studied in clinical trials (in combination with prednisone) compared with mitoxantrone and prednisone in men with prostate cancer previously treated with docetaxel and with documented progression of disease.

| | |
|---|---|
| **Intervention(s)** | Cabazitaxel in combination with prednisolone |
| **Population(s)** | Men who have hormone refractory metastatic prostate cancer that has progressed following or during docetaxel-based treatment |
| **Comparators** | • Mitoxantrone in combination with prednisolone<br>• Chemotherapy without cabazitaxel (for example 5-fluorouracil, cyclophosphamide and carboplatin/etoposide) |
| **Outcomes** | The outcome measures to be considered include:<br>• Overall survival<br>• Progression-free survival<br>• Response rate<br>• Prostate-specific antigen level<br>• Adverse effects of treatment<br>• 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.<br>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.<br><br>Costs will be considered from an NHS and Personal Social Services perspective. |
| **Other considerations** | If evidence allows, consideration will be given to subgroups defined by<br><br>• baseline performance status<br>• duration of prior docetaxel exposure<br>• time since docetaxel treatment<br><br>Guidance will only be issued in accordance with the marketing authorisation. |
| **Related NICE recommendations** | Related Technology Appraisals:<br><br>Technology Appraisal No. 101, Jun 2006, 'Docetaxel for the treatment of hormone refractory prostate cancer', Review date June 2013.<br><br>Technology Appraisal No. 194, Jul 2010; 'Denosumab for the treatment of therapy-induced bone loss in non-metastatic prostate cancer'. Terminated appraisal.<br><br>Technology Appraisal in Preparation, 'Dutasteride for reducing the risk of developing prostate cancer in men who are considered to be at increased risk of developing the disease', Earliest anticipated date of publication TBC.<br><br>Suspended Technology Appraisal, 'Atrasentan for hormone refractory prostate cancer', Earliest anticipated date of publication TBC.<br><br>Proposed Technology Appraisal, 'Abiraterone for the treatment of advanced metastatic castration resistant prostate cancer'. Earliest anticipated date of publication TBC.<br><br>Proposed Technology Appraisal, 'Abiraterone for the treatment of advanced metastatic castration resistant prostate cancer in people who are chemotherapy-naive'. Earliest anticipated date of publication TBC.<br><br>Related Guidelines:<br><br>Cancer Service Guidance Urological Cancer, Sep 2002, Improving outcomes in urogenital cancers', Anticipated review date TBC,<br><br>Clinical Guideline No. 58, Feb 2008, 'Prostate cancer: diagnosis and treatment', Anticipated review date Feb |

| | |
|---|---|
| | 2011.<br><br>Related Interventional Procedures:<br><br>Interventional Procedure Guidance No. 258, Apr 2008, 'Intraoperative red blood cell salvage during radical prostatectomy or radical cystectomy'.<br><br>Interventional Procedure Guidance No. 193, Nov 2006, 'Laparoscopic radical prostatectomy'.<br><br>Interventional Procedure Guidance No. 174, May 2006, 'High dose rate brachytherapy in combination with external-beam radiotherapy for localised prostate cancer'.<br><br>Interventional Procedure Guidance No. 145, Nov 2005, 'Crytotherapy as a primary treatment for prostate cancer'.<br><br>Interventional Procedure Guidance No. 132, Jul 2005, 'Low dose rate brachytherapy for localised prostate cancer'.<br><br>Interventional Procedure Guidance No. 119, May 2005, 'Crytotherapy for recurrent prostate cancer'.<br><br>Interventional Procedure Guidance No. 118, Mar 2005, 'High-intensity focused ultrasound for prostate cancer'. |

**Appendix C**

## NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

## Matrix of consultees and commentators

| **Consultees** | **Commentators (no right to submit or appeal)** |
|---|---|
| Manufacturers/sponsors<br>• Sanofi-aventis (cabazitaxel)<br><br>Patient/carer groups<br>• Afiya Trust<br>• Black Health Agency<br>• Bob Champion Cancer Trust<br>• Cancer Black Care<br>• Cancer Equality<br>• CANCERactive<br>• Chinese National Healthy Living Centre<br>• Counsel and Care<br>• Equalities National Council<br>• Everyman<br>• Helen Rollason Heal Cancer Charity<br>• Macmillan Cancer Support<br>• Maggie's Centres<br>• Marie Curie Cancer Care<br>• Muslim Council of Britain<br>• Muslim Health Network<br>• Orchid<br>• PCaSO – Prostate Cancer Network<br>• Prostate Cancer Charity<br>• Prostate Cancer Support Federation<br>• Prostate Help Association<br>• South Asian Health Foundation<br>• Specialised Healthcare Alliance<br>• Sue Ryder Care<br>• Tenovus<br><br>Professional groups | General<br>• Board of Community Health Councils in Wales<br>• British National Formulary<br>• Care Quality Commission<br>• Commissioning Support Appraisals Service<br>• Department of Health, Social Services and Public Safety for Northern Ireland<br>• Healthcare Improvement Scotland (previously - NHS Quality Improvement Scotland)<br>• Medicines and Healthcare Products Regulatory Agency<br>• National Association for Primary Care<br>• NHS Alliance<br>• NHS Commercial Medicines Unit<br>• NHS Confederation<br>• NHS Quality Improvement Scotland<br>• Public Health NHS Trust<br>• Scottish Medicines Consortium<br><br>Possible comparator manufacturers<br>• Hospira (mitoxantrone)<br>• Sandoz (mitoxantrone)<br>• Teva UK (mitoxantrone)<br>• Wockhardt (mitoxantrone)<br><br>Relevant research groups<br>• Cochrane Prostatic Diseases Urologic Cancers Group<br>• CORE - Digestive Disorders Foundation |

| **Consultees** | **Commentators (no right to submit or appeal)** |
|---|---|
| • Association of Cancer Physicians<br>• British Association for Services to the Elderly<br>• British Association of Urological Nurses<br>• British Association of Urological Surgeons<br>• British Geriatrics Society<br>• British Prostate Group<br>• British Psychosocial Oncology Society<br>• British Uro-Oncology Group<br>• Cancer Networks Pharmacists Forum<br>• Cancer Research UK<br>• National Pharmacy Association<br>• Pelican<br>• Royal College of General Practitioners<br>• Royal College of Nursing<br>• Royal College of Pathologists<br>• Royal College of Physicians<br>• Royal Pharmaceutical Society<br>• Royal Society of Medicine<br>• United Kingdom Clinical Pharmacy Association<br>• United Kingdom Oncology Nursing Society<br><br><u>Others</u><br>• Department of Health<br>• Derbyshire County PCT<br>• NHS Warwickshire<br>• Welsh Assembly Government | • Institute of Cancer Research<br>• MRC Clinical Trials Unit<br>• National Cancer Research Institute<br>• National Cancer Research Network<br>• National Institute of Health Research<br>• Ovarian & Prostate Cancer Research Trust<br>• Policy Research Institute on Ageing and Ethnicity<br>• Pro-Cancer Research Fund<br>• Prostate Action (formerly Prostate UK/Prostate Cancer Research Foundation)<br>• Prostate Cancer Research Centre<br>• Research Institute of the Care of Older People<br><br><u>Evidence Review Group</u><br>• Liverpool Reviews & Implementation Group, University of Liverpool<br>• National Institute for Health Research Health Technology Assessment Programme<br><br><u>Associated Guideline Groups</u><br>• National Collaborating Centre for Cancer<br><br><u>Associated Public Health Groups</u><br>• None |

NICE is committed to promoting equality and eliminating unlawful discrimination.

Please let us know if we have missed any important organisations from the lists contained within the matrix and which organisations we should include who 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 manufacturer(s) or sponsor(s) of the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England.

Consultees can participate in the consultation on the draft scope, the Assessment Report and the Appraisal Consultation Document, they are invited to prepare a submission dossier and all non-manufacturers/sponsors consultee organisations can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee. All consultees are given the opportunity to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare a submission dossier, and that receive the FAD for information only, without right of appeal. These organisations are: manufacturers of comparator technologies; NHS Quality Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*.

All non-manufacturers/sponsors commentator organisations can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

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 manufacturer/sponsor evidence submission to the Institute.

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

**8 June 2011**

# Contents

# Executive summary

**Executive summary**

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items:

- The UK approved name, brand name, marketing status and principal mechanism of action of the proposed technology.
- The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost.
- The indication(s) and any restriction(s).
- The recommended course of treatment.
- The main comparator(s).
- Whether the key clinical evidence in the submission comes from head-to-head randomised controlled trials (RCTs), from an indirect and/or mixed treatment comparison, or from non-randomised studies.
- The main results of the RCTs and any relevant non-RCT evidence.
- In relation to the economic evaluation, details of:
- the type of economic evaluation and justification for the approach used
- the pivotal assumptions underlying the model/analysis
- the mean costs, outcomes and incremental cost-effectiveness ratios (ICERs) from the evaluation.
- Tabulation of the base-case results

**Cabazitaxel indication and marketing status**

Cabazitaxel (Jevtana) in combination with prednisone or prednisolone is indicated for the treatment of patients with metastatic hormone-refractory prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen.[1] Cabazitaxel is the first drug to be licensed for this indication. Marketing authorisation for cabazitaxel was granted by the European Commission on 17 March 2011. The European regulatory agency reported that cabazitaxel has a positive risk-benefit profile (in the European Public Assessment Report (EPAR)) (see section 1.1–1.5).[2]

**Mechanism of action of cabazitaxel**

Cabazitaxel is a new taxane chemotherapy. Taxanes are cytotoxic agents; they act by disrupting microtubule function in cells, inhibiting cellular function and thus leading to tumour cell death. Taxanes are a well-established class of chemotherapy agents and the taxane docetaxel has become the gold standard first-line chemotherapy for mHRPC. However, the effectiveness of currently marketed taxanes is limited by the development of resistance. Cabazitaxel was specifically developed to overcome taxane resistance, in a development programme that screened over 450 candidate molecules.

Preclinically, cabazitaxel demonstrated activity in docetaxel-resistant cell lines[3] and animal models.[4] It was therefore expected that cabazitaxel would be clinically active against tumours that have developed resistance to docetaxel (section 1.2).

**Cabazitaxel dose regimen and price**

Cabazitaxel is supplied in 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).

The list price is £3,696 per vial. The dosing regimen for cabazitaxel is 25 mg/m$^2$ intravenously every three weeks, with prednisolone 10 mg orally given daily (prednisone and prednisolone are considered to be equivalent; only prednisolone is available in the UK). Based on the modelled duration of treatment, the expected cost of a course of treatment is [redacted] per patient, including administration, premedications and concomitant medication (section 1.10).

**Disease burden of mHRPC and unmet need**

mHRPC is the most advanced stage of prostate cancer. Cabazitaxel is indicated for mHRPC that has progressed following docetaxel treatment. The initial treatment approach to metastatic prostate cancer is to use hormonal agents to reduce circulating testosterone to castrate levels. However, eventually the cancer becomes resistant to such therapy and is categorised as mHRPC. In contrast to early-stage cancer, which may be largely asymptomatic, mHRPC is associated with a range of symptoms. In particular, bone metastases are common in metastatic prostate cancer, which can cause severe bone pain and other adverse events (AEs).[5] The goal of treatment for mHRPC is to prolong survival, control symptoms and thereby improve quality of life (QoL). The standard first-line chemotherapy for mHRPC patients with good performance status is docetaxel in combination with prednisolone, which is recommended by The National Institute for Health and Clinical Excellence (NICE) for this indication.[6] However, disease progression following docetaxel therapy is inevitable. There is currently no available treatment that has demonstrated an improvement in survival in patients who have progressed after docetaxel. There is, therefore, an urgent need for therapies that can prolong survival and control symptoms in patients who are able and willing to tolerate second-line chemotherapy (section 2.1).

**Comparators considered in this submission**

Cabazitaxel is the first therapy to demonstrate a survival benefit in patients progressing after docetaxel and is currently the only therapy licensed for this indication. Today, the most commonly used therapy for mHRPC patients in the UK who have progressed during or following docetaxel therapy is mitoxantrone. Mitoxantrone is used principally for its palliative benefits on pain, demonstrated in two Phase III trials.[7,8] Because it is the most commonly used agent, mitoxantrone is judged to be the most relevant comparator for cabazitaxel, in accordance with the decision problem and scope for this appraisal.[9]

The decision problem scope listed a second set of comparators, described as 'chemotherapy without cabazitaxel, for example 5-fluorouracil, cyclophosphamide and carboplatin/etoposide'. Other than mitoxantrone, information from an audit of UK practice suggests the rate of use of any one individual chemotherapy agent is low. More importantly, however, there are limited data available in this setting for any chemotherapy other than mitoxantrone in this patient population. A systematic review of all randomised controlled trials (RCTs) in second-line mHRPC found seven trials in total, which investigated five separate chemotherapy agents. These were cabazitaxel, mitoxantrone, docetaxel, ixabepilone and satraplatin. Satraplatin failed to improve survival, ixabepilone is not reported to be used at all in UK practice, and docetaxel rechallenge is not a suitable comparator for an agent designed to overcome docetaxel resistance, and is not recommended by NICE beyond the first-line setting.

A systematic review of non-RCTs identified a limited number of studies of other chemotherapies, but all studies were small (fewer than 50 patients) and uncontrolled. Because a robust comparison against these agents would not be possible, and since these agents cannot be considered part of standard UK clinical practice, the second comparator specified in the scope is judged to be less pertinent to the decision problem (section 2.6, 5.2.7, 5.8). We therefore focus on mitoxantrone in this submission.

**Cabazitaxel Phase III trial**

The pivotal Phase III TROPIC trial compared cabazitaxel with mitoxantrone. This provides direct head-to-head evidence for cabazitaxel against the most relevant comparator in UK clinical practice. TROPIC was an open-label multicentre trial, which randomised 755 patients to cabazitaxel 25 mg/m$^2$ or to mitoxantrone 12 mg/m$^2$, both in combination with prednisolone (section 5.3.2).[10] TROPIC was carried out in 26 countries in Europe, North America, South America, Asia and Africa.

**Efficacy of cabazitaxel**

In the TROPIC trial, cabazitaxel demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of overall survival (OS). Median survival was 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group ($p<0.0001$), with a hazard ratio of 0.70 (95% CI, 0.59–0.83) in favour of cabazitaxel corresponding to a 30% reduction in the risk of death.[10]

[redacted] The EPAR concluded that the observed OS benefits with cabazitaxel are clinically important, considering that in late line cancer, dramatic effects in OS are rare due to the advanced stage of disease[2]. Mean survival was estimated using a Weibull extrapolation of the OS curves: this showed an improvement in mean survival of 4.2 months for cabazitaxel over mitoxantrone (section 5.5).[11]

Significant OS improvement was consistent across subgroups. Only two groups had a HR close to 1: a group of patients who had received <225 mg/m$^2$ prior docetaxel (a protocol amendment subsequently excluded such patients, and this group constituted only 59 patients in the TROPIC population), and the subgroup of countries other than the US and Europe. In Europe, the hazard ratio was 0.68 (0.53 - 0.86).

In support of the results for the primary endpoint, cabazitaxel produced statistically significant improvements in the secondary endpoints of progression-free survival (PFS), time to tumour progression, response rate measured by RECIST criteria, prostate-specific antigen (PSA) progression, and PSA response rate.

Pain management is a critical objective in mHRPC treatment, and, importantly, there was no significant difference between cabazitaxel and mitoxantrone for the outcomes of pain response and pain progression (as assessed by the present pain intensity scale on the McGill-Melzack questionnaire). This indicates that, at the least, cabazitaxel is not significantly worse than mitoxantrone, a drug used in this setting for its palliative benefits on pain (section 5.5).

**Safety of cabazitaxel**

As a more potent chemotherapy, cabazitaxel was expected to have higher rates of AEs than mitoxantrone, considered to be a well-tolerated and safe drug. The most common AEs observed in the cabazitaxel group were neutropenia and its complications (febrile neutropenia and infections), asthenic conditions (asthenia and fatigue), and gastrointestinal toxicity (diarrhoea, nausea and vomiting). These are common to the taxanes as a class and were expected to be associated with cabazitaxel use; the nature of the adverse effects of

cabazitaxel are therefore known to UK oncologists, can be considered predictable, and are already managed very effectively (e.g. with docetaxel in the first-line setting) (section 5.9, 5.10). The intended cabazitaxel dose could be delivered as indicated by the high median relative dose intensity (96.1%), consistent with the drug being well tolerated. Overall, the higher risk of AEs with cabazitaxel is outweighed by the efficacy benefits, and this is reflected in the regulatory opinion stating that there was a positive risk-benefit profile for cabazitaxel[2].

**Cabazitaxel impact on quality of life**

For the NICE appraisal of cabazitaxel, a key limitation of the TROPIC trial was that QoL data were not collected. Therefore, the UK 'Early Access Programme' for cabazitaxel is collecting EQ-5D data for patients receiving cabazitaxel (at baseline and at cycles 2, 4, 6, 8 and 10, and 30 days after the last treatment). Only an interim analysis was available in time for this submission, though further analyses will be made available as the data mature. The interim data include baseline and Cycle 2 estimates (very few patients had reached cycle 4 or progressed at the time of reporting). [redacted] These data suggest that, at the very least, there is not a decrease in utility on cabazitaxel treatment, and that utility may even increase, possibly as a result of improved disease and symptom control on active treatment (section 6.4.3).

**Cost-effectiveness model population**

In the base-case, the population in the cost-effectiveness model is patients with an ECOG performance status 0 -1, who have received at least 225 mg/m$^2$ docetaxel, and is based on European data from TROPIC. This population was chosen as being most representative of patients likely to receive cabazitaxel in UK clinical practice. Clinical opinion is that in UK practice, patients with ECOG status 2 are highly unlikely to receive cabazitaxel and indeed only 61 patients in TROPIC were ECOG status 2. In line with NICE guidance, it is expected that all UK patients would receive sufficient exposure to docetaxel before consideration for cabazitaxel, and the exclusion of patients receiving <225 mg/m$^2$ docetaxel (approximately 3 cycles) is consistent with an amendment introduced to the TROPIC protocol. The use of European data in the base-case is because European treatment patterns and patient characteristics are considered most similar to UK treatment patterns and patient characteristics. TROPIC included a number of countries (in Asia, Africa, and the Americas) where treatment patterns differ considerably from UK clinical practice. Such differences could be expected to affect the treatment outcomes of cabazitaxel and indeed differences were seen in TROPIC in both efficacy - with the group of countries outside North America and Europe showing a HR of 1.0 - and in AE rates by geographic region[10] (section 5.5.1.1.1 and 5.9.2). This patient group (European patients with ECOG 0 -1 and received ≥ 225 mg/m$^2$

docetaxel) represents [redacted]% of the total TROPIC population. By using data from a group considered most representative of those likely to receive cabazitaxel in UK clinical practice, it is believed the cost-effectiveness results will most closely match the cost-effectiveness of cabazitaxel expected in UK practice.

[redacted]

As sensitivity analyses we present results for the entire TROPIC population, the subgroup of European patients, and the subgroup of patients with ECOG 0 -1 and who had received ≥ 225 mg/m$^2$ docetaxel.

**Cost-effectiveness model methods**

To evaluate the cost-effectiveness of cabazitaxel, a Markov model was developed. The model has a lifetime time horizon and compares the cost-effectiveness of cabazitaxel with mitoxantrone from the perspective of the NHS. The model has three health states: stable disease, progressive disease and death (section 6.2). The cycle length is three weeks, to match the treatment regimen for cabazitaxel and mitoxantrone treatment (section 6.2). The model was based on inputs from TROPIC: the probability of moving from stable to progressive disease was based on PFS data, while the probability of moving from stable or progressive disease to death was based on OS data. AEs were not included as separate states, but a per cycle rate was calculated for each Grade ≥3 AE based on the rates from TROPIC and disutilities and costs were assigned accordingly. Patients are assumed to remain on treatment until they progress or until they have received a maximum of ten cycles of active treatment, in line with the TROPIC protocol. On progression, it is assumed patients receive best supportive care (BSC) or a mix of post-second-line chemotherapy agents based on those received by patients in the TROPIC trial. Post-second-line chemotherapy was added as a cost, but assumed to have no impact on efficacy, as this would have been accounted for within the TROPIC survival rates (section 6.3).

The model assigns costs and outcomes based on the health state patients are in. Outcomes are measured in quality-adjusted life years (QALYs) consistent with the reference case. For the utility of patients in the stable disease state, the model uses the mean utility reported at Cycle 2 in the EAP. As there are not yet data available from the EAP for utility in progressive disease, the model applies a decrement based on the literature to calculate utility in the progressive disease state (section 6.4.9). To provide robust resource use data, an audit of five major UK centres was undertaken to identify resource use for second-line and post-second-line mHRPC; these estimates were used within the model (section 6.5.3). Costs included in the model are those for: active treatment, chemotherapy administration, premedications and concomitant medications, AE management, post-second-line

chemotherapy medications, post-second-line BSC, cost of staff time, cost of hospitalisations, and costs of tests and imaging.

### Cabazitaxel cost-effectiveness results

**Table 0.1. Base-case cost-effectiveness results**

| | Intervention | Comparator 1 |
|---|---|---|
| Technology acquisition cost | [redacted] | [redacted] |
| Other costs | [redacted] | [redacted] |
| Total costs | £35,372 | £13,047 |
| Difference in total costs | N/A | £22,325 |
| LYG | 1.584 | 1.171 |
| LYG difference | N/A | 0.413 |
| QALYs | 1.147 | 0.849 |
| QALY difference | N/A | 0.298 |
| ICER | N/A | £74,908 |

Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year

*Includes administration, premedication and concomitant medication.

Three groups were considered in addition to the main population:

- Patients with ECOG performance status 0–1 who received ≥225 mg of docetaxel
- All European patients
- Whole TROPIC population

**Table 0.2. Results for sub-group analysis**

| | Patients with ECOG performance status 0–1 who received ≥225 mg of docetaxel | European patients | Whole TROPIC population |
|---|---|---|---|
| Median OS difference | [redacted] | [redacted] | 2.4 months |
| Mean OS difference | [redacted] | [redacted] | 4.2 months |
| Difference in total costs | 21,408 | 21,966 | 21,368 |
| LYG difference | 0.359 | 0.361 | 0.338 |
| QALY difference | 0.259 | 0.260 | 0.244 |
| ICER | 82,530 | 84,510 | 87,685 |

Key: ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year

### Special criteria applying to cabazitaxel

Cabazitaxel is indicated for mHRPC patients whose disease has progressed following docetaxel. It is estimated that there are fewer than 2000 such patients in England and Wales

(section 2.2). The life expectancy of this population is around 12 months (based on the TROPIC control arm). In TROPIC, cabazitaxel produced an improvement in median OS of 2.4 months, and a mean survival improvement of 4.2 months. In the population considered most representative of patients likely to receive cabazitaxel in UK clinical practice, the [redacted]. Therefore, cabazitaxel should be considered as an end-of-life drug, which produces a meaningful clinical benefit in a small patient population with severe illness and short life expectancy.

# Acknowledgements

To be confirmed

# Section 1. Description of technology under assessment

## 1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Jevtana®

Approved name: cabazitaxel

Therapeutic class: taxane

## 1.2 What is the principal mechanism of action of the technology?

Cabazitaxel (XRP6258) (see Figure 1-1) 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.[3,4,12]

Microtubules play a critical role in cell division, intracellular transport and the development and maintenance of cell shape. Cabazitaxel binds to tubulin, which is the basic building block of microtubules, and inhibits microtubule disassembly.[12] This leads to the stabilisation of microtubules, which results in the inhibition of mitotic and interphase cellular functions, leading to tumour cell cytotoxicity.

**Figure 1-1. Cabazitaxel: molecular structure**

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. The resistance mechanism most commonly described for current taxanes is the multidrug-resistance phenotype mediated by the 170 kD P-glycoprotein efflux pump, encoded by the mdr-

1gene.[12] *In vitro*, cabazitaxel is more potent than docetaxel against mdr-1-expressing tumour cell lines resistant to standard chemotherapeutic agents, including docetaxel.[3]

*In vivo*, cabazitaxel demonstrated anti-tumour activity against murine and human tumour models that had weak or no sensitivity to docetaxel, such as UISO BCA-1, 1 human HER2 mammary carcinoma xenografted in mice, which is fully insensitive to docetaxel.[4] In addition, cabazitaxel is active in human prostate tumour xenograft DU145, which suggested it would have efficacy in prostate cancer.[4]

## 1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Marketing authorisation was granted by the European Commission on 17 March 2011.

## 1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

The main feedback from the European regulatory submission, as described in the European Public Assessment Report (EPAR), was that cabazitaxel had a positive risk-benefit profile, with clinically meaningful benefits, and no requirement for a special risk-minimisation plan.[2]

## 1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

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.[1]

## 1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

The main clinical trial supporting the licensed indication (see Section 1.5) is EFC6193 (TROPIC study) (NCT00417079). This trial is complete and published. An updated survival analysis is expected Q3/Q4 of this year.

There is an ongoing early access trial programme (EAP) for cabazitaxel. This was initiated in December 2010 in the UK, and is anticipated to be complete by the end of 2011. This is collecting EQ-5D data. An interim analysis was conducted in May 2011. An *ad hoc* analysis is planned for August, with full analysis on completion.

As part of the clinical development of cabazitaxel and part of the commitment to the US Food and Drug Administration (FDA) there are a number of planned and ongoing trials. Of these, only one is likely to provide data over the next 12 months: an ongoing Phase I study to assess the potential effect of cabazitaxel on the QTcF interval (QTc Fridericia) in cancer patients; the estimated completion date for the primary endpoint is June 2011.

## 1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Cabazitaxel received European marketing authorisation on 17 March 2011. Cabazitaxel was made commercially available in the UK from 20th May 2011.

## 1.8 Does the technology have 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 mHRPC previously treated with a docetaxel-containing regimen.[13]

Cabazitaxel received European marketing authorisation on 17 March 2011,

Cabazitaxel has also obtained regulatory approval in Brazil, Israel, Curacao, Chile, South Korea, Switzerland and Uruguay.

## 1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

A submission to the Scottish Medicines Consortium (SMC) is planned for summer 2011.

## 1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

**Table 1-1. Unit costs of technology being appraised**

| | |
|---|---|
| Pharmaceutical formulation | Cabazitaxel 60 mg/1.5 ml concentrate and solvent for infusion is supplied as a kit consisting of the following:<br>• One single vial of cabazitaxel concentrate 60 mg/1.5 ml (contains 60 mg cabazitaxel in 1.5 ml polysorbate 80)<br>• 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).<br>Both items are in a blister pack in one carton. |
| Acquisition cost (excluding VAT) | £3696 per vial |
| Method of administration | IV infusion over 60 minutes |
| Doses | 25 mg/$m^2$ |
| Dosing frequency | Day 1, 25 mg/$m^2$ intravenously 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). |
| Average length of a course of treatment | In TROPIC, the median number of cycles received was six. (The maximum number of permitted cycles is ten). |
| Average cost of a course of treatment | [redacted] (including administration, pre and concomitant medications. Based on modelled mean number of cycles from TROPIC). |
| Anticipated average interval between courses of treatments | It is intended that only one course of cabazitaxel will be provided. |
| Anticipated number of repeat courses of *treatments | No repeat courses will be given. |
| Dose adjustments | In TROPIC, the dose could be delayed and then reduced to 20 mg/$m^2$ for cabazitaxel and 10 mg/$m^2$ for mitoxantrone when necessary, as presented in Section 8.5.1 of the protocol. A dose that had been reduced for toxicity was not to have been re-escalated. Only one dose reduction was allowed per patient. If a second dose reduction was required per the modification criteria, the patient was to go off study. For example, for febrile neutropenia or prolonged Grade ≥3 neutropenia (greater than one week) despite appropriate medication (such as G-CSF), cabazitaxel was to be delayed until neutrophil counts recover to a level of >1,500/$mm^3$, and the dose reduced to 20 mg/$m^2$ for the subsequent cycle. |

## 1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

## 1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

There are no additional tests or investigations needed for selection of patients for treatment.

Cabazitaxel is an intravenously administered chemotherapy drug. As such, cabazitaxel requires specialist administration similar to other intravenous (IV) chemotherapies and will require pharmacist time for preparation. Cabazitaxel is supplied as a kit consisting of the following: cabazitaxel concentrate 60 mg/1.5 ml (contains 60 mg cabazitaxel in 1.5 ml polysorbate 80) and diluent for cabazitaxel (contains approximately 5.7 ml of 13% [w/w] ethanol in water for injection).

Cabazitaxel should be administered under the supervision of a qualified physician experienced in the use of anti-neoplastic medicinal products and in an environment where full treatment facilities are readily available to allow appropriate management of complications.

## 1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Two considerations in using cabazitaxel that necessitate monitoring are infusion-related hypersensitivity reactions, in 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.

As with other infusions of this kind, cabazitaxel has been associated with infusion reactions that 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.[1] Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions.

To minimise the risk of neutropenia and its complications, monitoring of complete blood counts is advisable on a weekly basis during Cycle 1 and before each treatment cycle thereafter, so that 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.

## 1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

- Premedication regimen at least 30 minutes prior to each dose of cabazitaxel to reduce the risk and/or severity of hypersensitivity. This consists of:
    - Antihistamine (chlorpheniramine, dexchlorpheniramine-maleate, diphenhydramine-HCl or diphenhydramine)
    - Corticosteroid (dexamethasone 8 mg or equivalent steroid)
    - $H_2$ antagonist (ranitidine 50 mg or equivalent $H_2$ antagonist).
- Anti-emetic prophylaxis is recommended and can be given orally or intravenously as needed.
- G-CSF may be given at clinical discretion as primary prophylaxis to patients considered to be 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.

# Section 2. Context

## 2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Prostate cancer is the cancerous proliferation of normal semen-secreting prostate gland cells. Prostate cancer is the most common form of cancer among men in the UK; one-quarter of all new cases of cancer diagnosed in men in England and Wales are prostate cancers.[14] It is the second most common cause of cancer death in UK men after lung cancer[14] – in 2008, 9,150 men in England and Wales died from prostate cancer.[15] The main risk factors for prostate cancer are age, ethnicity, family history, diet and hormone metabolism.[16] The primary risk factor for prostate cancer is increasing age: 60% of cases occur in men older than 70, while over 80% occur in men aged over 65 years.[14,17]

The tumour-node-metastasis (TNM) system[18] is the most commonly used system for classifying the extent of tumour progression, and takes into account the primary tumour (T), the extent of involved lymph nodes (N), the extent of metastases (M) and the histological grade of the tumour as measured by Gleason grade.[19] Metastatic cancer is classified as Stage IV in this system.[6]

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; all of these can also occur with more benign prostate conditions and are insufficient to establish diagnosis.[20] By contrast with early stage disease, 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.[21] Bone metastasis is a common form of metastatic disease in prostate cancer, with some studies reporting percentages as high as 80%.[5,22,23] 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.[5]

Treatment is guided by cancer stage and grade (along with patient performance status and suitability for treatment).

The initial approach to metastatic prostate cancer (Stage IV) is medical (or, infrequently, surgical) castration to reduce levels of circulating testosterone. Hormonal therapy to reduce androgen levels is effective in inhibiting prostate cancer growth. LHRH agonists and more recently LHRH antagonists are used as first-line hormonal agents,[24-26] but in all patients the disease will become refractory (median duration of response of eight to 24 months).[27] Following development of resistance to first-line hormone therapy, further hormonal manipulations in the form of addition of anti-androgens, followed by anti-androgen withdrawal, are used.[24,28] Other secondary, unlicensed hormonal options include the use of ketoconazole, oestrogens (such as diethylstilboestrol) and corticosteroids.[29] Although second- and third-line hormonal manipulations can produce a subjective response in approximately 25% of patients, the responses are also only short-lived (approximately four months) and unequivocal clinical benefit from these treatments has not been shown with any of the agents listed.[24,29]

Ultimately, metastatic prostate cancer becomes unresponsive to hormonal manipulation. There is no universally accepted definition of hormone refractory disease.[25,30] According to the National Institute for Health and Clinical Excellence (NICE), the disease can be considered to be hormone refractory when androgen withdrawal therapy or combined androgen blockade is no longer controlling the PSA or the symptoms of the disease, or when there is radiological evidence of progression despite androgen withdrawal therapy.[25] However, hormone refractory disease, so defined, may still respond to agents such as oestrogens or corticosteroids that probably work via the androgen receptor. Even when the disease becomes hormone refractory, the androgen receptor on the cancer cells can remain active and LHRH therapy is usually continued..

mHRPC is the most advanced stage of prostate cancer; the median survival in patients receiving active first-line chemotherapy is around 19 months from initiation of chemotherapy.[31] The aim of mHRPC treatment is dependent on the individual patient. For those with poor performance status, the aim is to alleviate symptoms and improve QoL. For fitter patients with a good performance status, the aim is to prolong survival and slow progression of the disease while maintaining good symptom control and high QoL. The standard chemotherapy for mHRPC patients with good performance status (Karnofsky performance status score 60% or more) is docetaxel in combination with prednisolone, which is recommended by NICE for this indication.[6] Following progression on or after docetaxel, there is currently no approved second-line treatment which has demonstrated an improvement in survival. For the mHRPC patients who are able and willing to tolerate further chemotherapy, there is no effective treatment available. Mitoxantrone (an established palliative treatment), novel agents in clinical trials, and best supportive care (BSC) alone are

the main options used. BSC in this patient group is extensive and costly, due to the nature of advanced mHRPC, including high rates of bone metastases. Typical therapies include opioids and other analgesics to relieve pain associated with bone metastases, bisphosphonates to treat bone metastases, systemic radionucleotides such as strontium, surgery in case of medullar compression or fracture and steroids. Patients frequently require hospitalisation as part of BSC provision.

Cabazitaxel is indicated for the second-line chemotherapy of metastatic hormone refractory prostate cancer in patients progressing after docetaxel. This indication represents a population with advanced prostate cancer, which no longer responds to hormone therapy or docetaxel chemotherapy.

## 2.2 How many patients are assumed to be eligible? How is this figure derived?

### 2.2.1 How many patients are assumed to be eligible?

It is estimated that there are approximately 1,938 patients who are eligible for cabazitaxel in England and Wales (see Figure 2-1).

### 2.2.2 How is this figure derived?

The incidence of prostate cancer in England and Wales in 2011 is estimated as 36,105. This is based on absolute incidence data from 2008 from Cancer Research UK statistics and an observed annual rate of increase of 2.6%, based on Cancer Research UK annual rates.[32]

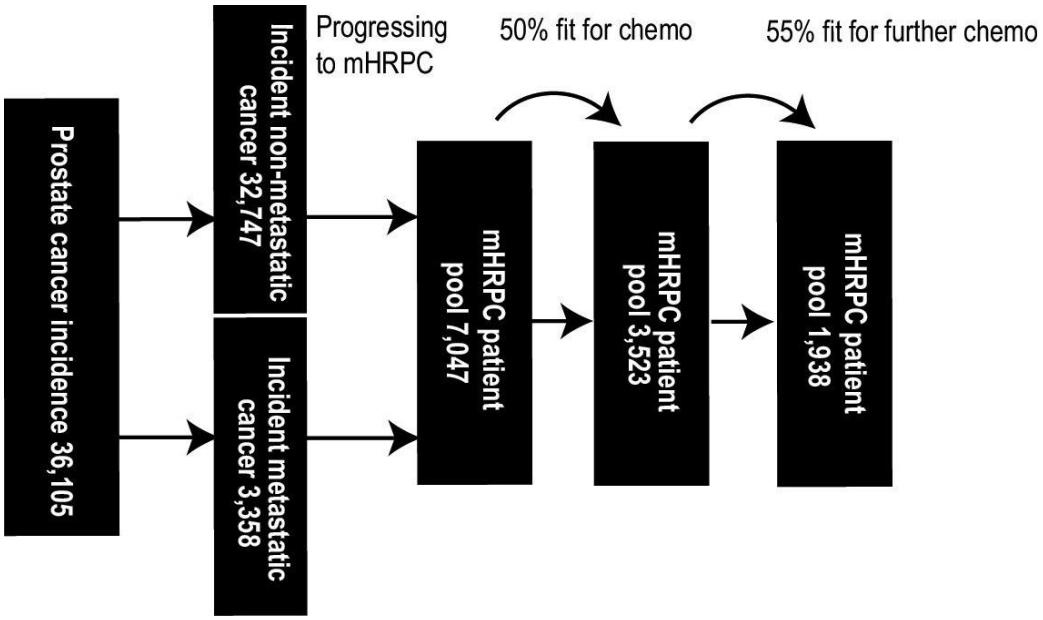
Establishing the incidence of mHRPC is problematic, as no published data exist. In order to address this, an epidemiological model was developed internally at sanofi-aventis. This was based on data from a number of sources. The proportion of patients with metastatic cancer at diagnosis was quoted as 9.3% in the latest figures from the British Association of Urological Surgeons, giving an estimate of 3,358 cases.[33] The proportion of patients progressing to metastatic cancer from earlier stages was based on studies by Cooperberg (2008) and Stephenson (2005).[34] These studies estimated the risk of progression from earlier stages, based on a distribution of different risk groups at baseline provided in the Cooperberg study.[35] To calculate the number of mHRPC patients from the number of metastatic cases, it was assumed that patients would progress to the hormone-refractory state within 3 years, whatever primary therapy was administered. Progression rates of 80% at year 1 and 20% in following years were applied, adjusted for patients dying before developing hormone-refractory cancer (according to 2008 NCDB survival reports).[36]

This gave an estimate of the total number of mHRPC cases of 7,047. In support of this, data from Cancer Research UK estimated that there were 9,150 deaths in England and Wales in 2008. Given that the majority but not all deaths from prostate cancer are likely to occur in the mHRPC setting, the figure of 7,047 mHRPC cases seems reasonable.

Given the existence of multidisciplinary teams managing prostate cancer in the UK, it is assumed all mHRPC patients will be referred to an oncologist. However, not all of these patients are eligible to receive chemotherapy first line. Recent market research (commissioned by sanofi-aventis) shows that 50% of patients (3,523) treated by oncologists are eligible to receive docetaxel first line.[37]

Of these patients, 55% are fit to receive further chemotherapy following docetaxel based on the above market research. Thus, there are estimated to be around 1,938 mHRPC patients eligible for second-line chemotherapy in England and Wales.[37]

**Figure 2-1. Current second-line mHRPC patient pool in England and Wales**




## 2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

- NICE. *Guidance on Cancer Services, Improving Outcomes for Urological Cancers: The Manual.* London, National Institute for Health and Clinical Excellence, 2002. NICE

guidelines for the provision of services and treatments for patients with urological cancers.

- NICE. *Atrasentan for hormone refractory prostate cancer.* London, National Institute for Health and Clinical Excellence, 2004 (appraisal suspended).
- NICE. *Technology Appraisal Guidance 101: Docetaxel for the treatment of hormone refractory metastatic prostate cancer.* London, National Institute for Health and Clinical Excellence, 2007. NICE has recommended the use of docetaxel, within its licensed indications, as a treatment option for men with mHRPC only if their Karnofsky performance status score is 60% or more. A maximum of 10 cycles is recommended.
- NICE. *Clinical Guideline 58: Prostate Cancer Diagnosis and Treatment*. London, National Institute for Health and Clinical Excellence, 2008. NICE guidelines for the diagnosis and treatment of patients with prostate cancer.

## 2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Docetaxel is the standard of care first-line chemotherapy for mHRPC. Indeed, the combination of docetaxel and prednisone/prednisolone is the only chemotherapy regimen licensed for the first-line treatment of mHRPC in the UK. NICE Technology Appraisal Guidance 101 recommends docetaxel, within its licensed indication, as a treatment option for men with mHRPC with a Karnofsky performance status score of 60% or more.[6] The recommended maximum number of cycles is ten.[6] Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy.[25]

There is no licensed treatment for patients with mHRPC that has progressed after docetaxel. No agents (until recently) have demonstrated a survival benefit in this setting. Cabazitaxel is the first agent to demonstrate a significant survival benefit in patients who have progressed after docetaxel. Several cytotoxic chemotherapies have been used in a clinical setting, including mitoxantrone, carboplatin, epirubicin, 5-fluorouracil and etoposide, alone or in combination. In particular, mitoxantrone is widely used in the UK – even though it is not licensed – due to its established palliative benefits in mHRPC.[6] Beyond these, the only option for patients who have progressed on or after docetaxel (even those fit for chemotherapy) is BSC, typically involving radiotherapy, bisphosphonates, steroids and

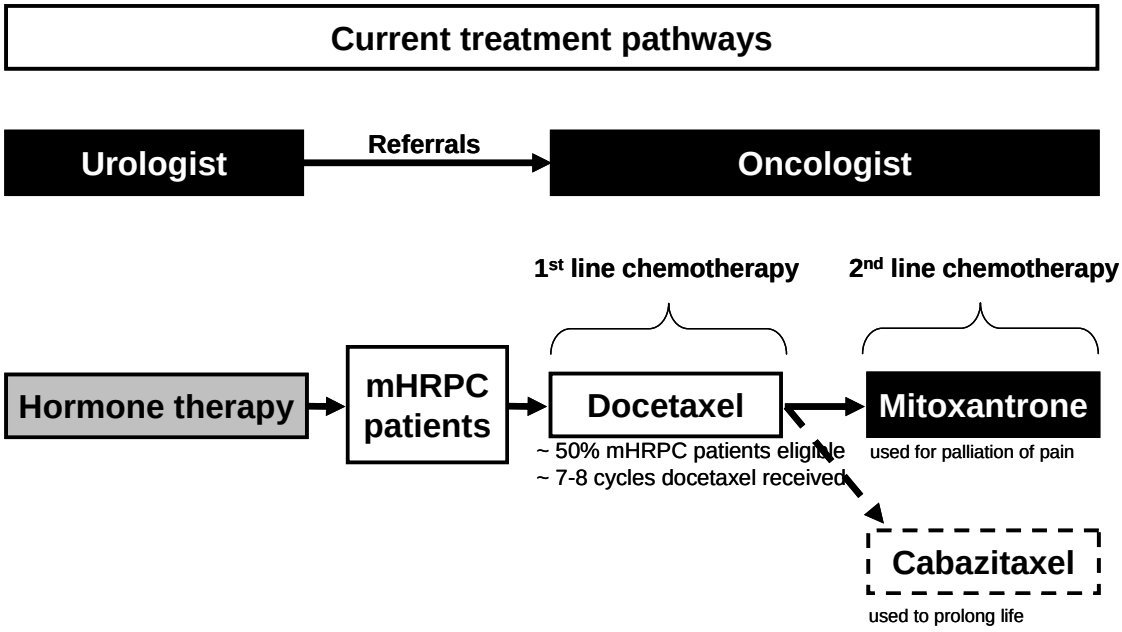
analgesics.[6] Retreatment with docetaxel is used in second-line mHRPC patients, however this use is outside NICE guidance, is not supported by clinical trial evidence, and is unlikely to be effective in patients who are refractory to docetaxel.[6,38]

A number of agents are currently in trials in this indication. Recently, the androgen biosynthesis inhibitor abiraterone acetate has shown efficacy in this group of patients[39]. The vaccine sipuleucel-T and the experimental therapy MDV3100 are also currently in late-stage trials. Given the different mechanism of action of all of these agents to cabazitaxel (and to each other), it seems likely that future use of these agents will complement one another in the treatment of this population. Due to the limited availability of data for these agents, further discussion is beyond the scope of this document.

Certain hormone therapies, including low dose corticosteroids and oestrogen analogies such as diethylstilboestrol, may be used after docetaxel chemotherapy, The clinical benefits of both treatment types are, however, unproven in this setting.[24,29] Further, these are more likely to be used in patients with poorer performance status who are ineligible for further chemotherapy, and as such are not appropriate comparators for cabazitaxel.

Cabazitaxel represents a new, effective option for second-line treatment in docetaxel-resistant patients. Figure 2-2 illustrates the potential place of cabazitaxel within a treatment algorithm for mHRPC. This is aligned with the most recent EAU guidelines, which recommend cabazitaxel as a potential second-line treatment, based on Grade A evidence.[30]

**Figure 2-2. Prostate cancer: current disease management**



### *2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.*

As discussed in Section 2.4, there is no clearly defined pathway for patients who have progressed following docetaxel. This indicates the paucity of available treatments and/or evidence. There are few guidelines specific to the management of mHRPC, and general guidelines do not include detailed sections on mHRPC management. Further, significant variations in daily practices are present among oncologists.[40] For patients eligible for chemotherapy, a combination of mitoxantrone plus prednisolone is an accepted palliative treatment.[41] The European Association of Urology (EAU) guidelines are followed by many European physicians; the latest version recommends considering cabazitaxel as second-line therapy, supported by Grade A evidence (the TROPIC trial).[30] Table 2-1 lists key European guidelines for the treatment of mHRPC.

Market research identified that ~55% of patients were eligible to receive cytotoxic chemotherapy in the second-line setting.[37] It is expected that the availability of effective, licensed second-line therapies will change clinical practice and increase the use of active second-line treatment – the fact that cytotoxic chemotherapies are used despite the lack of clear current evidence highlights the need for effective therapies in this setting.[42]

**Table 2-1. Key European guidelines for the treatment of mHRPC**

| Date | Title | Recommendation |
|---|---|---|
| National Comprehensive Cancer Network[43] | | |
| 2011 | *The 2011 NCCN clinical practice guidelines in oncology on prostate cancer* | Docetaxel in combination with prednisone is recommended as first-line chemotherapy for patients with mHRPC<br>Patients who have failed docetaxel-based chemotherapy should be encouraged to participate in clinical trials<br>Cabazitaxel with prednisone has been shown in a randomised Phase III study to prolong OS, PFS and PSA and radiological responses when compared with mitoxantrone and prednisone and is US FDA-approved in the post-docetaxel second-line setting |
| European Association of Urology[30] | | |
| 2011 | *EAU guidelines on prostate cancer* | Based on prospective randomised Phase III clinical trials, docetaxel in combination with prednisone represents the cytotoxic regimen of choice in men with mHRPC, resulting in a survival benefit of three months and a significant |

| | | |
|---|---|---|
| | | improvement of pain and QoL compared with mitoxantrone. Grade of recommendation A<br>According to the positive results of this prospective randomised clinical Phase III trial (level of evidence: 1), cabazitaxel should be considered as effective second-line treatment following docetaxel. Grade of recommendation A<br>Second-line docetaxel may be considered in patients previously responding to docetaxel. Grade of recommendation B |
| European Society of Medical Oncology[44] | | |
| 2009 | *Prostate cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up* | Docetaxel using a three-weekly schedule should be considered for symptomatic, castration refractory disease |
| NICE | | |
| 2002 | *Guidance on Cancer Services, Improving Outcomes for Urological Cancers: The Manual*[41] | NICE guidelines for the provision of services and treatments for patients with urological cancers |
| 2004 | *Atrasentan for hormone refractory prostate cancer* | Appraisal suspended |
| 2007 | *Technology Appraisal Guidance 101: Docetaxel for the treatment of hormone refractory metastatic prostate cancer*[6] | NICE has recommended the use of docetaxel, within its licensed indications, as a treatment option for men with mHRPC only if their Karnofsky performance status score is 60% or more |
| 2008 | *Clinical Guideline 58: Prostate Cancer Diagnosis and Treatment*[25] | NICE guidelines for the diagnosis and treatment of patients with prostate cancer |
| **Scottish Intercollegiate Guidelines Network (SIGN)** | | |
| None identified | | |
| **Scottish Medicines Consortium (SMC)** | | |
| No advice or forthcoming submissions (excepting a submission for cabazitaxel) for treatments for mHRPC identified | | |
| Key: FDA = US Food and Drug Administration; MDT = multidisciplinary team; mHRPC = metastatic hormone-refractory prostate cancer; NICE = National Institute for Health and Clinical Excellence; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; QoL = quality of life; SAE = serious adverse event | | |

## 2.5 Please identify the main comparator(s) and justify their selection.

The main comparator considered in this submission is mitoxantrone in combination with prednisolone (or prednisone), in line with the NICE scope.[9] Two Phase III randomised studies of mitoxantrone plus prednisone suggest that there is a palliative benefit from the addition of mitoxantrone to corticosteroids in the extent and duration of pain control in

previously untreated patients with mHRPC.[7,8] The combination of mitoxantrone plus predniso(lo)ne was initially approved and was used to provide palliation to previously untreated patients with mHRPC although it has not demonstrated a statistically significant benefit in overall survival.[31] Following the approval of docetaxel the combination of mitoxantrone plus prednisolone is frequently used for the treatment of patients who progressed during or following treatment with docetaxel-based regimens. In addition to TROPIC, mitoxantrone was chosen as a comparator in three other RCTs in second-line mHRPC. Thus, although unlicensed, mitoxantrone is judged to be the most relevant comparator for cabazitaxel.

The NICE scope specifies a second comparator of 'chemotherapy without cabazitaxel, for example 5-fluorouracil, cyclophosphamide and carboplatin/etoposide'. This acknowledges that other cytotoxic agents (other than mitoxantrone) might be used in second-line mHRPC in clinical practice. However, there is no clinical consensus on the choice of second-line cytotoxic agent, with variation between different centres and different clinicians. Thus, other than mitoxantrone, the frequency of use of any individual agent is low. For this reason, comparison against these agents is judged to be less relevant to UK clinical practice and thus to this appraisal. In addition, there are very limited data in this setting for any chemotherapy other than mitoxantrone – a systematic review of RCTs did not find any trials of these “other” agents in second-line mHRPC. The absence of RCT evidence means that the validity of comparisons against these agents would be limited. Because a robust assessment of these agents is unlikely, and since these agents cannot be considered part of the standard UK clinical practice, the second comparator specified in the scope is judged to be less pertinent to the decision problem.

In so far as a standard treatment can be defined for this patient population, only mitoxantrone plus prednisolone should be considered as the most appropriate comparator in the context of this submission.

## 2.6 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

As with other infusions of this type, cabazitaxel has been associated with infusion reactions (hypersensitivity). Premedication with antihistamines (such as chlorpheniramine), corticosteroids (typically dexamethasone) and $H_2$ antagonists (such as ranitidine) is recommended. If hypersensitivity is observed, infusions should be discontinued immediately and treated as indicated.

Consistent with British Society for Haematology (BSH),[45] European Organization for Research and Treatment of Cancer (EORTC),[46] and American Society of Clinical Oncology (ASCO) guidelines,[47] primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features that predispose them to increased complications from prolonged neutropenia. Similar guidance is provided in recommendations from the All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC).[48,49] Secondary prophylaxis should be considered in all patients at increased risk of recurrent neutropenic complications.

Nausea, vomiting and severe diarrhoea, at times, may occur. Patients should be treated with rehydration, antidiarrhoeal or anti-emetic medications as needed. Treatment delay or dosage reduction may be necessary if patients experience Grade ≥3 diarrhoea, or Grade 1 or 2 nausea with or without vomiting. Typically, patients will receive prophylactic anti-emetics (such as ondansetron) prior to each infusion.

## 2.7 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

The introduction of cabazitaxel is likely to have implications for NHS cancer day unit and pharmacy workloads, in terms of drug preparation and administration. Similar costs of preparation and administration are incurred by other IV chemotherapies used in the first- and second-line treatment of mHRPC. Therefore, the integration of cabazitaxel into chemotherapy units that currently treat mHRPC patients is not anticipated to add a major resource burden. There should be no implications for primary care resources.

A course of cabazitaxel comprises three-weekly infusions for up to ten weeks and daily prednisolone. The price of cabazitaxel is £3696 per vial.

Cabazitaxel concentrate solution for infusion requires two dilutions prior to administration with the supplied diluent, followed by dilution in either 0.9% sodium chloride solution or 5% dextrose solution. This should be carried out under aseptic conditions and is, therefore, likely to require pharmacy 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 £285 per administration according to NHS reference costs.[50]

Premedication costs will include:

- Oral antihistamine (chlorphenamine, dexchloropheniramine maleate, diphenhydramine or diphenhydramine-HCl)
- Corticosteroid (dexamethasone 8 mg or equivalent steroid); and $H_2$ antagonist (ranitidine 50 mg or equivalent $H_2$ antagonist)
- Anti-emetics (ondansetron, ondansetron-HCl, granisetron and granisetron-HCl). In some cases metoclopramide 10 mg three-times daily would be given for five days after each treatment.

G-CSF usage may be required for primary prophylaxis in patients with high-risk clinical features that predispose them to increased complications from prolonged neutropenia, and for secondary prophylaxis in all patients at increased risk of recurrent neutropenic complications.

According to clinical expertise, the majority of UK patients are medically, rather than surgically castrated. Therefore, the majority of patients will receive ongoing concomitant therapy with LHRH agonists. It is normal practice to continue these drugs until death. No extra outpatient visits are required for the administration of these drugs.

## 2.8 Does the technology require additional infrastructure to be put in place?

It is not anticipated that the introduction of cabazitaxel will require any service reorganisation.

# Section 3. Equity and equality

## 3.1 Identification of equity and equalities issues

### 3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

No issues relating to equity or equality have been identified.

### 3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

No issues relating to equity or equality have been identified.

### 3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

Not applicable as no issues were identified.

# Section 4. Statement of decision problem

| | Final scope issued by NICE[9] | Decision problem addressed in the submission |
|---|---|---|
| **Population** | Men who have mHRPC that has progressed following or during docetaxel-based treatment. | Men who have hormone refractory metastatic prostate cancer that has progressed following or during docetaxel-based treatment |
| **Intervention** | Cabazitaxel in combination with prednisolone | Cabazitaxel 25 mg/m$^2$ (every three weeks) plus prednisolone (or prednisone) 10 mg/day – up to a maximum of ten cycles |
| **Comparator(s)** | Mitoxantrone in combination with prednisolone<br>Chemotherapy without cabazitaxel (for example, 5-fluorouracil, cyclophosphamide and carboplatin/etoposide) | ***Comparators considered in this submission***<br>• Mitoxantrone in combination with prednisolone.<br>At present there is no approved second-line treatment for patients with docetaxel-resistant mHRPC. Mitoxantrone plus prednisolone is widely used in the UK for mHPRC patients who are considered fit for chemotherapy. The pivotal Phase III randomised study (TROPIC) provides a direct comparison of cabazitaxel with mitoxantrone.<br><br>***Comparators not considered in this submission***<br>• Chemotherapy without cabazitaxel (for example, 5-fluorouracil, cyclophosphamide and carboplatin/etoposide)<br>There are no RCTs of 5-fluorouracil, cyclophosphamide, carboplatin or etoposide in 2$^{nd}$-line mHRPC. The lack of evidence means comparison would be methodologically challenging and would be associated with considerable uncertainty. Further, the use of chemotherapy agents other than mitoxantrone is infrequent in the UK and therefore none of these individual agents can be considered as standard UK practice. |

| | | |
|---|---|---|
| **Outcomes** | The outcome measures to be considered included:<br>• Overall survival (OS)<br>• Progression-free survival (PFS)<br>• Response rate<br>• Prostate-specific antigen (PSA) level<br>• Adverse effects of treatment<br>• Health-related QoL | • Primary outcome: OS<br>• Secondary outcomes: PFS, TTP, overall response rate, PSA progression, pain response measures and safety.<br>Utility data (EQ-5D) is provided from the interim analysis of the cabazitaxel early access programme. |
| **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 (QALY).<br>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<br>Costs will be considered from an NHS and Personal Social Services perspective. | The cost-effectiveness of cabazitaxel is expressed as a cost per QALY.<br><br>The time horizon in the base case is the patient's lifetime<br><br>Costs are considered from an NHS and PSS perspective |

| | | |
|---|---|---|
| **Other considerations** | If evidence allows, consideration will be given to subgroups defined by:<br>• Baseline performance status<br>• Duration of prior docetaxel exposure<br>• Time since docetaxel treatment<br>Guidance will only be issued in accordance with the marketing authorisation | Clinical results for the primary outcome of OS include a number of pre-planned subgroups from the TROPIC trial including:<br>▪ Baseline performance status<br>▪ Duration of prior docetaxel exposure<br>▪ Time since docetaxel treatment<br>▪ Geographic region<br><br>The base-case in the economic evaluation considers European patients with an ECOG status of 0 -1, and who have previously received ≥ 225 mg/m$^2$ of docetaxel. This group is considered most relevant to patients who will receive cabazitaxel in UK clinical practice. In the UK, it is highly unlikely ECOG PS 2 patients would receive cabazitaxel and in line with NICE guidelines, it is expected all patients would have received sufficient exposure to docetaxel before consideration for second-line chemotherapy. Furthermore, because of differences in patient characteristics and treatment patterns between Europe, US, and the other countries included in TROPIC, the European data is considered most relevant to UK clinical practice.<br><br>As sensitivity analyses, we also present cost-effectiveness results for:<br>• Patients with ECOG status 0 -1 and who have previously received ≥ 225 mg/m$^2$ of docetaxel<br>• European patients<br>• The whole TROPIC population |
| **Special considerations, including issues related to equity or equality** | Guidance will only be issued in accordance with the marketing authorisation | End-of-life considerations are relevant to cabazitaxel. Cabazitaxel is indicated for a small population (estimated <2000 patients in England and Wales), with a life expectancy of ~12 months. In patients considered most representative of those likely to receive cabazitaxel in UK practice (European patients with ECOG 0 -1, who had already received ≥225 mg/m$^2$ docetaxel) cabazitaxel [redacted]<br><br>No additional issues relating to equity or equality were identified |

## Response to Kennedy Innovation Questions

### 1: Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Cabazitaxel is the first drug to provide a survival benefit in mHRPC patients who have progressed after docetaxel. Docetaxel is the gold standard for first-line mHRPC chemotherapy; however in many cases tumours eventually develop resistance to docetaxel. Cabazitaxel was specifically developed to overcome this resistance. As part of the cabazitaxel development programme, over 450 molecules were screened to identify a molecule with characteristics critical to overcoming taxane resistance. Preclinically, cabazitaxel has demonstrated activity in docetaxel-resistant cell lines and models (as well as docetaxel-sensitive models), suggesting cabazitaxel may be clinically active in tumours which have, or will become resistant to docetaxel. In the pivotal TROPIC trial, cabazitaxel was evaluated in patients who had progressed following first-line docetaxel. Cabazitaxel produced a statistically significant improvement in median overall survival of 2.4 months, and an improvement in mean overall survival of 4.2 months, an increase of ~ 30% in the life expectancy of this patient population. Until cabazitaxel, no drug had demonstrated a survival benefit in mHRPC patients progressing after docetaxel. We consider that the survival benefit provided by cabazitaxel, in a setting where no such benefit had previously been demonstrated, together with the potential for cabazitaxel to overcome the clinical problem of taxane resistance, represent a "step-change" in the management of mHRPC.

### 2: Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

We believe the QALY-value derived for cabazitaxel does not fully capture the benefits of cabazitaxel.

Whilst the QALY calculated using health state utilities and survival time allows a reasonable estimate of clinical benefit from cabazitaxel, it will however underestimate the psychological benefits that a new treatment, which increases survival, brings to patients who would otherwise have reached the end of proactive disease management. The positive experience for patients and their relatives of being able to continue to fight their disease, rather than palliate their condition in its final stages, is a significant and important benefit of cabazitaxel that is not captured directly by the EQ-5D tool, and consequently is not fully incorporated in the QALY measure.

- **3: Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.**

The cabazitaxel clinical development plan is presented in overview in the dossier, and further information on this could be provided if required by the committee in order to appreciate the innovative nature of cabazitaxel.

To understand the importance to patients and their families of actively challenging mHRPC in the second-line setting, and the psychological impact that the treatment with cabazitaxel can deliver, we consider the testimony of patients, family members and clinicians should be sought by the committee.

# Section 5. Clinical evidence

| Element of health technology assessment | Reference case | Section in 'Guide to the methods of technology appraisal' |
|---|---|---|
| Defining the decision problem | The scope developed by NICE | 5.2.5 and 5.2.6 |
| Comparator(s) | Therapies routinely used in the NHS, including technologies regarded as current best practice | 5.2.5 and 5.2.6 |
| Perspective costs | NHS and PSS | 5.2.7 to 5.2.10 |
| Perspective benefits | All health effects on individuals | 5.2.7 to 5.2.10 |
| Type of economic evaluation | Cost-effectiveness analysis | 5.2.11 and 5.2.12 |
| Synthesis of evidence on outcomes | Based on a systematic review | 5.3 |
| Measure of health effects | QALYs | 5.4 |
| Source of data for measurement of HRQL | Reported directly by patients and carers | 5.4 |
| Source of preference data for valuation of changes in HRQL | Representative sample of the public | 5.4 |
| Discount rate | An annual rate of 3.5% on both costs and health effects | 5.6 |
| Equity weighting | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | 5.12 |
| HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s) | | |

## 5.1 Identification of studies

### 5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

Three systematic reviews were conducted. 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 (mHRPC) (patients progressed after first-line docetaxel). This was done to identify any additional RCT evidence for comparators on the NICE scope that was 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 mHRPC (post-docetaxel). This was done to identify any non-randomised evidence for cabazitaxel or comparators on the NICE scope that could potentially be relevant to the decision problem.

**Systematic review of studies of cabazitaxel versus mitoxantrone**

A range of databases indexing published research were searched for studies about the clinical effectiveness and safety of cabazitaxel for men with mHRPC (defined as this or as metastatic castration-resistant prostate cancer [mCRPC]) who have progressed following treatment with docetaxel. Scoping searches indicated that the literature for cabazitaxel is very small, making it possible to conduct a highly sensitive search using only the drug name, drug development number and registry number. Searches were carried out in the following databases: MEDLINE, MEDLINE In-Process, EMBASE and the Cochrane Library in line with NICE methodological guidelines.[51] The searches were not limited by language or date range. Searches of regulatory organisation websites, trials registries and conference proceedings were also undertaken. The full cabazitaxel clinical study report was also provided by the manufacturer. Full details of the search strategies and the databases and resources searched are provided in Appendix 2, Section 9.2.

**Systematic review of all RCTs in mHRPC**

Similarly to the search above, MEDLINE, MEDLINE In-Process, EMBASE and the Cochrane Library were searched using terms for mHRPC (and mCRPC) and a validated search filter for RCTs. Searches were not limited by drug name. Conference proceedings were also

searched in line with NICE methodological guidelines.[51] Full details are provided in Appendix 4, Section 9.4.

**Systematic review of non-RCTs in mHRPC**

Medline, Embase and conference proceedings were searched to identify comparative or non-comparative observational studies and single-arm trials in mHRPC patients previously treated with docetaxel. Details of this search and study selection methods are provided in Appendix 6, Section 9.6.

## 5.2 Study selection

### 5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Two reviewers independently applied the predefined inclusion criteria to select studies for inclusion; disagreements were resolved by discussion. Study selection was performed in a two-step process; first, the title and abstracts were screened to exclude studies meeting exclusion criteria; second, the full texts were screened to ensure all included studies met the inclusion criteria. Table 5-1 summarises the inclusion criteria for the reviews.

**Table 5-1. Inclusion criteria used in search strategies**

| Review | Systematic review of studies of cabazitaxel versus mitoxantrone | Systematic review of all RCTs in second-line mHRPC | Systematic review of non-randomised studies in mHRPC |
|---|---|---|---|
| Population | Men with mHRPC or mCRPC who had progressed following or during docetaxel-based treatment | | |
| Intervention(s) | Cabazitaxel with prednisone or prednisolone | Any active intervention (not best supportive care) | Any active intervention (not best supportive care) |
| Comparator(s): | Any | Any | Any or none |
| Outcome(s) of interest: | OS, PFS, time to progression, overall response rate ORR, PSA response or progression, pain response or progression, Grade 3 or 4 AEs | | |
| Study design: | Phase II or III RCT or systematic review of Phase II or III RCTs; extension studies and cohort studies reporting AEs were also eligible for inclusion | | Non-randomised controlled studies, single-arm studies, case-control, cohort, cross-sectional studies |
| Language restrictions | There was no language restriction | English language only | |
| Publication timeframe: | Any date | 2000 – present (as the aim of these reviews was to provide a context for the cabazitaxel studies identified by the targeted systematic review, the date restriction was imposed for reasons of pragmatism, to focus on the most relevant, up-to-date literature. | |
| Publication status | Published, unpublished and grey literature (for example, conference abstracts) were eligible for inclusion | | |
| Exclusion criteria | Dosing studies were excluded, on the basis that they do not provide evidence of the effectiveness of cabazitaxel relative to relevant comparators | N/A | N/A |

Key: AE = adverse event; mCRPC = metastatic castration-resistant prostate cancer; mHRPC = metastatic hormone-resistant prostate cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; RCT = randomised controlled trial

### 5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

Studies were included or excluded on the basis of the criteria described in Table 5-1. The PRISMA flow diagrams show the number of studies included and excluded at each stage for each of the three reviews (Figure 5-1, Figure 5-2 and Figure 5-3).

**Figure 5-1. PRISMA flow diagram for systematic review of all cabazitaxel studies**

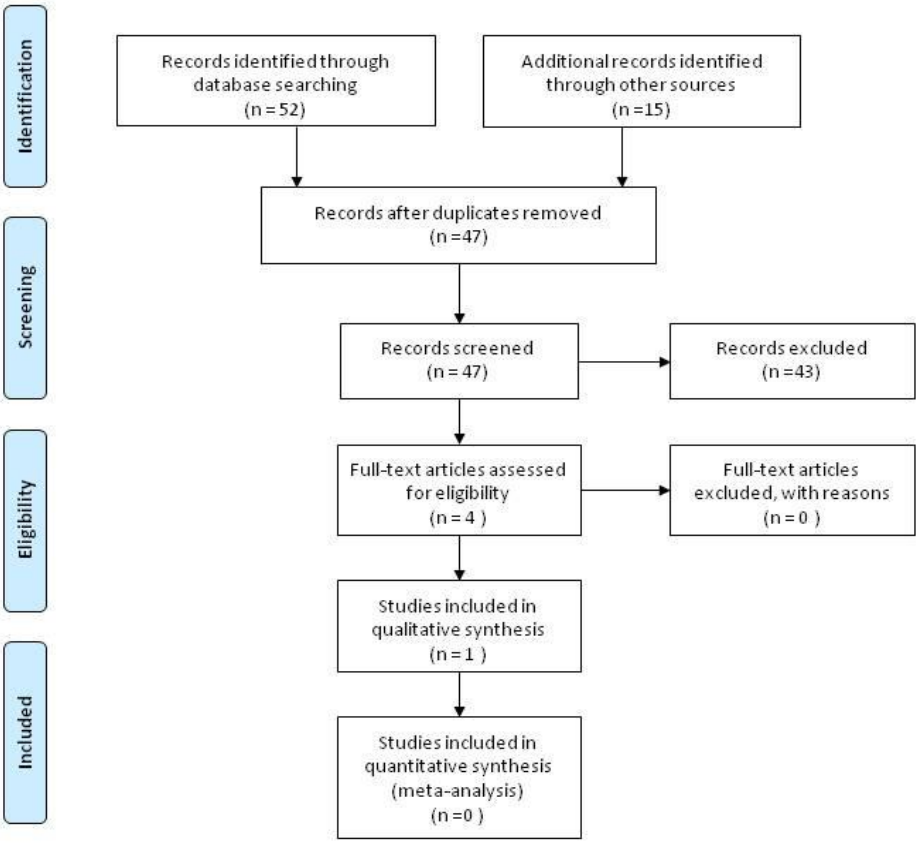


**Figure 5-2. PRISMA flow diagram for systematic review of all RCTs in second-line mHRPC**

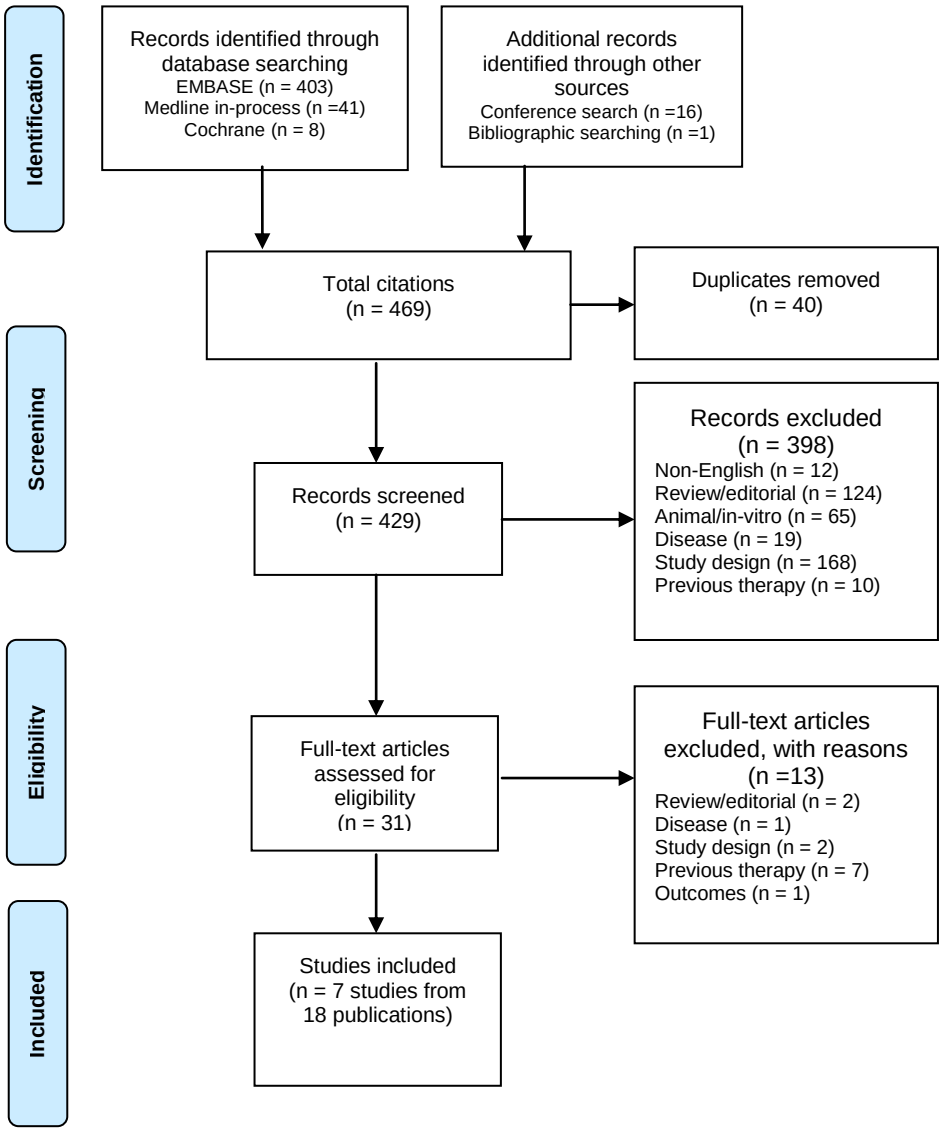
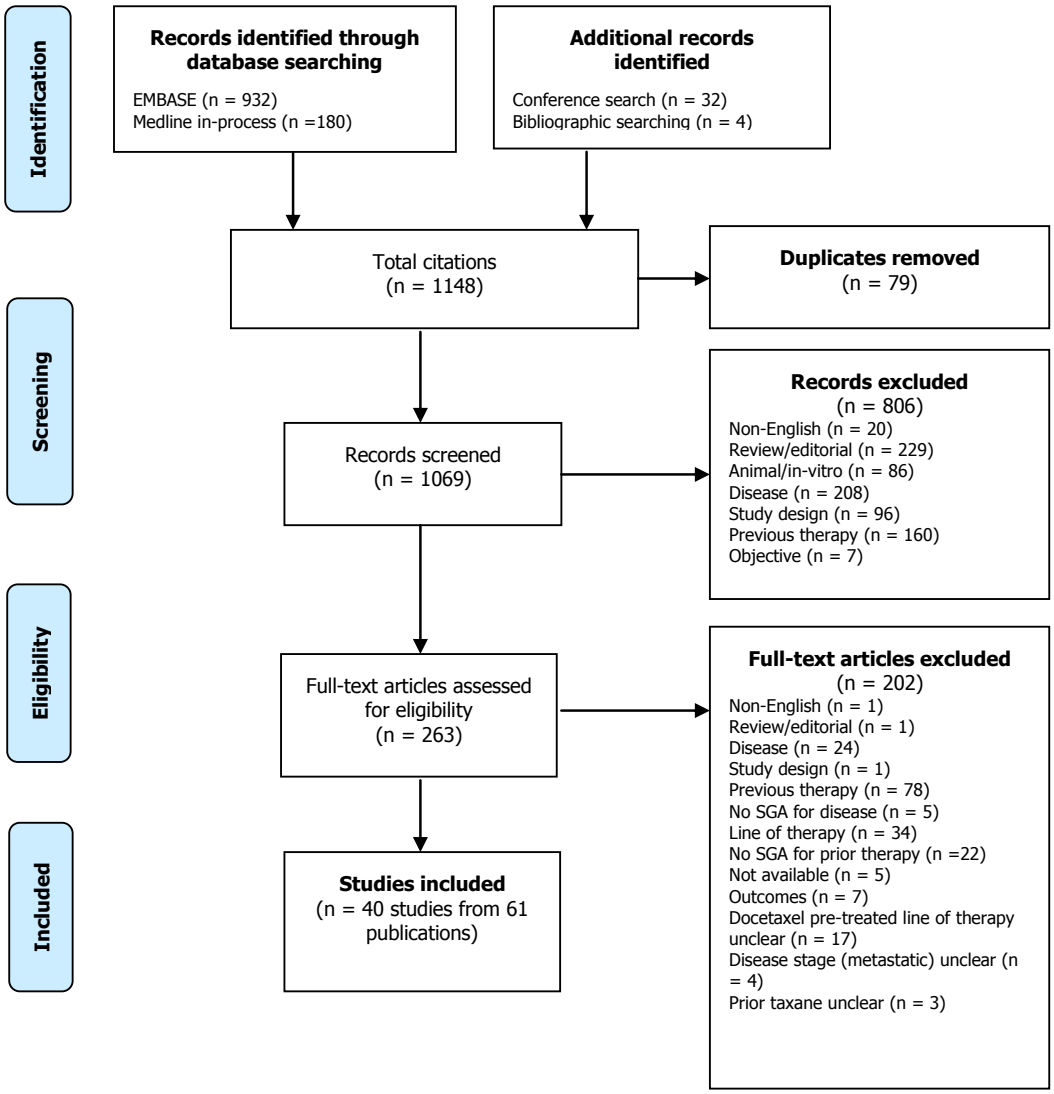


**Figure 5-3. PRISMA flow diagram for review of non-RCTs in second-line mHRPC**




### 5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

In the systematic review of studies of cabazitaxel, one RCT sponsored by sanofi-aventis, the TROPIC trial, met the criteria for inclusion. The data presented in this submission have been drawn from the following sources – four publications (abstract or journal article) and the unpublished clinical study report:

- de Bono JS *et al*. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet.* 2010; 376: 1147–1154.[10]
- A poster presented at American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium 2010 (San Francisco, CA): Sartor AO *et al*. Cabazitaxel or

mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results of a multinational Phase III trial (TROPIC).[52]

- A presentation at American Society of Clinical Oncology (ASCO) 2010 (Chicago, IL): de Bono JS *et al*. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results of a multinational Phase III trial (TROPIC).[53]
- A presentation at ASCO-GU 2011 (Orlando, FL): Oudard S *et al*. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Estimating mean overall survival (OS) for health economics analyses from a phase III trial (TROPIC).[11]
- The unpublished clinical study report.[54]

No other RCTs of cabazitaxel in the relevant patient group were identified. There are no earlier phase cabazitaxel trials in prostate cancer – the Phase II trial of cabazitaxel was in breast cancer and, therefore, was not relevant to the systematic review or the decision problem in this submission. The primary study reference is the published journal article from which data have been extracted for this appraisal; additional data were extracted from the unpublished clinical study report where necessary.

The broader systematic review of all RCTs in second-line mHRPC identified seven trials published in 18 publications (see Table 5-2). The review of non-randomised studies identified 40 studies published in 61 publications. A complete list is provided in section 9.6.8 (Appendix 6).

### Complete list of relevant RCTs

### 5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

TROPIC is the only identified RCT of cabazitaxel.

**Table 5-2. List of relevant RCTs**

| Trial no. (acronym) | Intervention | Comparator | Population | Primary study ref |
|---|---|---|---|---|
| EFC6193 (TROPIC) (NCT00417079) | Cabazitaxel plus prednisone or prednisolone | Mitoxantrone plus prednisone or prednisolone | Men with mHRPC and disease progression during or after treatment with a regimen containing docetaxel* | de Bono *et al*[10] |
| * The publication title referred to mCRPC; however, the licensed indication for cabazitaxel is mHRPC and for clarity this will be the terminology used throughout | | | | |

The systematic review of all RCTs in second-line mHRPC identified seven studies, one of which was TROPIC. The additional six studies are detailed in Table 5-3 below; none of them evaluate cabazitaxel. The study conclusion is included to provide an overview of the potential relevance of these studies to the decision problem (as discussed in section 5.2.6).

**Table 5-3. Studies identified by systematic review of all RCTs in second-line mHRPC (excluding TROPIC)**

| Trial no. (acronym) | Intervention | Comparator | Population | Study references | Study conclusion |
|---|---|---|---|---|---|
| COU-AA-301 | Abiraterone acetate plus prednisone | Prednisone | Men with mHRPC progressed after docetaxel | De Bono 2010[39] | Abiraterone produced a significant improvement in OS and PFS in comparison with prednisone alone |
| The SPARC trial | Satraplatin + prednisone | Prednisone | Men with mHRPC progressed after docetaxel | Sternberg 2009, Witjes 2009. Sartor 2008. Petrylak 2009. Sartor 2009[55-58] | Satraplatin did not improve OS, but did improve PFS, in comparison with prednisone |
| Saad 2009 | Docetaxel + prednisone + custirsen | Mitoxantrone + prednisone + custirsen | Men with mHRPC progressed after docetaxel | Saad 2009, Saad 2008[59] | 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 | Men with mHRPC progressed after docetaxel | De Bono 2010[60] | CNTO 328 plus mitoxantrone did not improve OS, and enrolment was terminated after an interim analysis |
| Fleming 2010, Fleming 2010 | Cetuximab + mitoxantrone + prednisone | Mitoxantrone + prednisone | Men with mHRPC progressed after docetaxel | Fleming 2010[61] | Cetuximab plus mitoxantrone did not improve survival compared with mitoxantone alone and is not recommended for further study |
| Rosenberg 2007 | Ixabepilone | Mitoxantrone + prednisone | Men with mHRPC progressed after docetaxel | Rosenberg 2007[62] | Ixabepilone and mitoxantrone plus prednisone showed similar modest activity in docetaxel-refractory mHRPC |

Key: mHRPC = metastatic hormone-refractory prostate cancer; OS = overall survival; PFS = progression-free survival

### 5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

The TROPIC trial is the only RCT of cabazitaxel and it compares cabazitaxel plus prednisolone directly with a comparator in the NICE scope; that is, mitoxantrone plus prednisolone in patients with mHRPC previously treated with a docetaxel-containing regimen.[10]

### 5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

No studies of cabazitaxel have been excluded from further discussion. The systematic review of cabazitaxel studies in second-line mHRPC identified only one study, which is discussed in detail below.

The broader systematic review of all second-line mHRPC RCTs identified seven studies, one of which was the TROPIC trial of cabazitaxel. The remaining six are not discussed further in the following sections because they do not provide data relevant to the decision problem. There are two comparators specified in the decision problem on the scope. With regards to the first, mitoxantrone, given the existence of a head-to-head study against mitoxantrone, indirect comparisons are not essential to address the decision problem. As there are only a few, small-scale trials with no other connections to cabazitaxel, there would be limited value in attempting a mixed-treatment comparison (as discussed further below in section 5.7). We have not compared cabazitaxel with the second comparator listed in the decision problem – 'chemotherapy without cabazitaxel'. This is due partly to the fact that it is not considered relevant to standard UK clinical practice (as discussed in section 2.6) and also due to the paucity of the evidence base, which would limit the validity of any comparisons performed. The limited evidence is demonstrated by the systematic review. As detailed in Table 5-3 above, there are few trials of chemotherapy other than mitoxantrone, and no trials of the example agents named in the scope. The other chemotherapies for which RCT data are available include satraplatin, which failed to demonstrate an OS benefit, docetaxel in combination with curtirsen (which is not relevant to the decision problem as discussed in section 2.6), and ixabepilone.

**List of relevant non-RCTs**

**5.2.7 Please provide details of any non-RCTs (for example, experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.**

The systematic review of non-RCTs identified 40 studies. These are detailed in Appendix 6 (section 9.6.8). None investigated cabazitaxel. Nine studies investigated mitoxantrone either as a single agent (with prednisone) or in combination. In the presence of a head-to-head study against mitoxantrone, these uncontrolled studies are not considered to add additional information pertinent to the decision problem. Thirteen investigated docetaxel rechallenge (either alone or in combination). Nineteen studies investigated other drugs, including pemetrexed, vorinostat, sunitinib, sorafenib, carboplatin plus etoposide, carboplatin plus 5-fluorouracil plus epirubicin, paclitaxel plus carboplatin plus estramustine, ketoconazole plus doxorubicin, cyclophosphamide plus dexamethasone, bevacizumab plus satraplatin plus prednisone, oxaliplatin plus capecitabine, cisplatin plus prednisone, paclitaxel poliglumex plus estradiol, and TPI287. These studies are the only published evidence available that could be used to address the second comparator of 'chemotherapy without cabazitaxel'. All studies are small (<50 patients) uncontrolled studies and, therefore, any comparison based on these would be methodologically challenging and associated with a high degree of uncertainty. We have, therefore, not compared against this second comparator, due to the limited validity of such a comparison.

## 5.3 Summary of methodology of relevant RCTs

**5.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.**

**TROPIC trial: Background and rationale**

Until now, no treatment has been shown to improve survival in mHRPC patients who have progressed after docetaxel. Therefore, there is a clear unmet need for effective treatments in this setting. Mitoxantrone is the most commonly used chemotherapy agent when patients have progressed after docetaxel. Cabazitaxel has antitumour activity in docetaxel-resistant

tumour models. Therefore, the TROPIC trial was undertaken to assess whether cabazitaxel plus prednisolone improved OS compared with mitoxantrone plus prednisolone in men with mHRPC that had progressed after docetaxel-based chemotherapy.[10,54]

### 5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

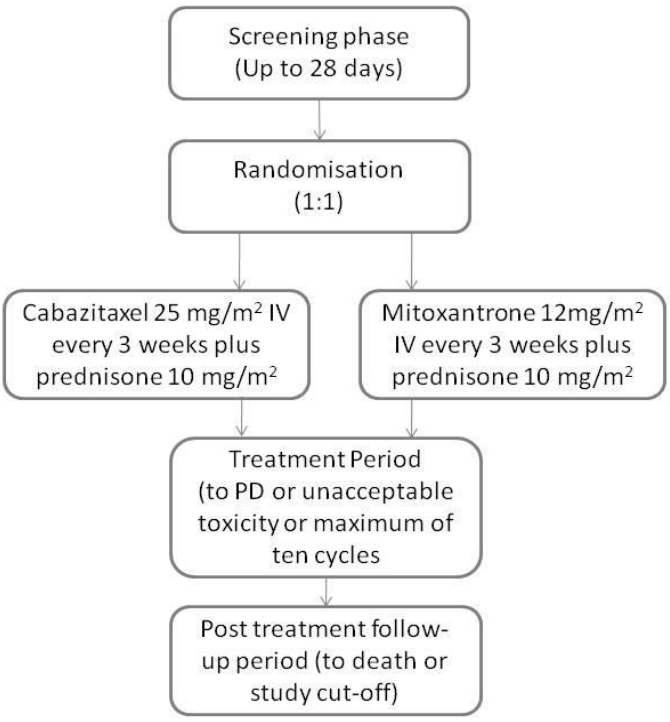
#### 5.3.2.1 Location

This was a multicentre 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)[10,54]. 402 (53%) patients were included from European countries. [redacted][10,54].

**Design**

The TROPIC trial was a Phase III, randomised, open label, multicentre, multinational, comparative study in patients with mHRPC previously treated with a docetaxel-containing regimen.[10]

**Figure 5-4. TROPIC trial: study design**




*Source: de Bono et al[10]*

#### 5.3.2.2 Duration of study

The first patient was enrolled on 2 January 2007 and the last patient completed (data cut-off date) on 25 September 2009 (approximately 2.5 years).[10]

#### 5.3.2.3 Randomisation

Patients were randomised to one of two treatment groups by the interactive voice response system (IVRS) ClinPhone[10], 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).[10]

A dynamic allocation method – method of minimisation – was used to avoid extreme imbalance of treatment assignment within a centre.[10,54]

#### 5.3.2.4 Method of blinding

Due to differences in administration between treatments this study was an open label study, so patients and treating physicians were not masked to treatment allocation.[10] 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.[10,54]

The study team was blinded to treatment assignments, except for those patients with SAEs reported to pharmacovigilance.[10] 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.[10,54]

The interim analyses were conducted and reviewed by the IDMC and the results not disclosed to the sponsor.[54]

#### 5.3.2.5 Intervention and comparator

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).[10]

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).[10]

Cycle length for both cabazitaxel and mitoxantrone was three weeks. Treatment was continued for a maximum of ten cycles.[10] The ten-cycle maximum was imposed due to the fact that mitoxantrone is associated with cardiotoxicity and that this is increased with cumulative exposure.[31]

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.

#### 5.3.2.6 Prior and concomitant medication

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.[10]

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.[10]

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.[10,54]

Patients were not allowed to take part in any other investigational trials while participating in the treatment phase of the trial.[10,54]

#### 5.3.2.7 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.[54]

#### 5.3.2.8 Duration of follow-up

Patients were followed until death to the cut-off date for analysis, 25 September 2009.[10]

Patients who progressed or started another anticancer therapy were followed up every three months for a maximum of two years.10,54 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.[10]

## Participants

### 5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

#### 5.3.3.1 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.[53,54]
- 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.[53,54]
    - 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.[53,54]

- 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.[53,54]
- Life expectancy >2 months.[53,54]
- 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).[53,54]
- Age ≥18 years.[53,54]
- 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 mHRPC 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.[63,64]

#### 5.3.3.2 Exclusion criteria

- Previous treatment with mitoxantrone.[53,54]
- 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)[53,54,64]
- Prior radiotherapy to ≥40% of bone marrow[53,54]
- Prior surgery, radiation, chemotherapy, or other anti-cancer therapy within four weeks prior to enrolment in the study.[53,54]
- Active Grade ≥2 peripheral neuropathy, stomatitis or other serious illness, including secondary cancer.[53,54]
- History of congestive heart failure, myocardial infarction within last six months, uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension.[53,54]
- History of severe hypersensitivity reaction (≥Grade 3) to polysorbate 80-containing drugs or prednisone.[53,54]
- Participation in another clinical trial with any investigational drug within 30 days prior to study enrolment.[53,54]
- 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.[53,54]

### 5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

The demographic characteristics of age, race, performance status (0, 1 versus 2), measurable disease, and extent of disease were well balanced between the treatment groups (see Table 5-4) with no statistically significant differences recorded. The majority of patients in each group had a normal ECG at baseline. Median LVEF results, whether by echocardiography or radionuclide ventriculography, were consistent across both groups.[10]

**Table 5-4. Characteristics of participants in the TROPIC trial across randomised groups – baseline and demographic characteristics (ITT population)**

| TROPIC trial<br>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 treatment | | |
| During | 104 (28% | 115 (30%) |
| <3 months from last dose | 181 (48%) | 158 (42%) |
| ≥3 months from last dose | 90 (24%) | 102 (27%) |
| Unknown | 2 (1%) | 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

Source: de Bono *et al*[10]

Overall, this was a patient group with severe disease who had received substantial prior treatment, as shown by the baseline characteristics.

The majority of patients received docetaxel as their first chemotherapy (87.8% cabazitaxel and 87.3% mitoxantrone). The median time from last docetaxel dose to randomisation was 4.1 months in the cabazitaxel arm and 3.7 months in the mitoxantrone arm.[54] Baseline haematological and biochemical parameters were similar between the treatment groups, with few abnormalities that were Grade ≥3.[54]

## Outcomes

**5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice).**

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

### 5.3.5.1 Primary outcomes

There was one primary outcome, 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.[10]

### 5.3.5.2 Secondary outcomes

- **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.[10]
- **Tumour response rate** (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 [complete response] = disappearance of all target lesions;
    - PR [partial response] = 30% decrease in the sum of the longest diameter of target lesions;

- PD [progressive disease] = 20% increase in the sum of the longest diameter of target lesions;
- SD [stable disease] = small changes that do not meet other criteria).
- Objective response had to be confirmed by repeat tumour imaging[10,54]

- **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.[10]
- **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).[10]
  - 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 5 ng/ml).[10]
- **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.[10]
- **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.[10]
- **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.[10]
- **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,[65] and summarised using Medical Dictionary for Regulatory Activities (MedDRA) version 12.0 terminology.[10,54] For each AE per patient and per cycle the worst NCI grade was used.[10]

## Statistical analysis and definition of study groups

### 5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

#### 5.3.6.1 Statistical analysis: populations analysed

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).[10,54] The primary analysis of the primary efficacy endpoint was performed using the ITT population.[10,54] The safety population was the same as the per protocol population and was used to summarise treatment compliance/administration and all clinical safety data.[53,54]

#### 5.3.6.2 Statistical analysis: primary and secondary endpoints

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 (see section 5.3.2.3).

The estimates of the hazard ratio 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.[10]

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.

#### 5.3.6.3 Statistical analysis: sample size

In previously untreated patients with metastatic prostate cancer, OS on mitoxantrone is 12 to 14 months.[66] 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.[10]

Assuming the median OS time in the comparator group was eight months, a total of at least 511 deaths in two treatment groups was 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.[10]

#### 5.3.6.4 Statistical analysis: handling of missing 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.[54]

### 5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post hoc.

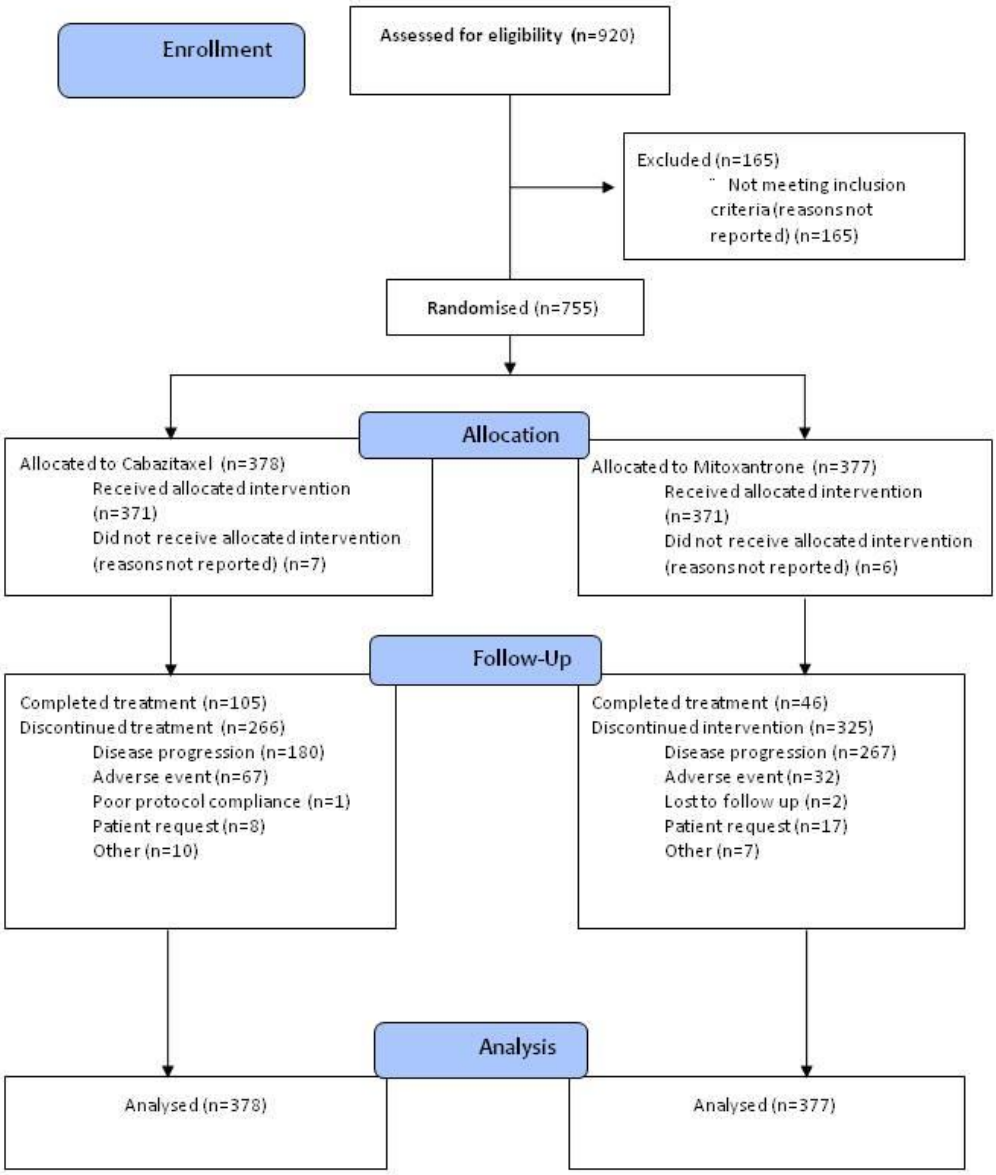
Pre-specified subgroup analyses of OS according to baseline characteristics were performed in the ITT population.[54] The following prognostic factors were considered: ECOG performance status, disease measurability, number of prior chemotherapy regimens, age, region, pain at baseline, PSA status, time from last docetaxel to randomisation, total docetaxel dose received, and time of progression from last docetaxel. Post-hoc, a number of additional subgroups were explored based on combinations of these factors. Three key subgroups are presented in the economic evaluation section:

- Patients with ECOG 0 – 1 who received ≥225 mg/m$^2$ docetaxel, based on European data. This group is presented as the base-case as it is considered the group most representative of patients who will receive cabazitaxel in UK practice.
- European patients.
- Patients with ECOG 0 – 1 who received ≥225 mg/m$^2$ docetaxel, based on the entire TROPIC population.

## Participant flow

### 5.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

**Figure 5-5. CONSORT participant flow diagram[10]**



## 5.4 Critical appraisal of relevant RCTs

### 5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

Critical appraisal of the TROPIC RCT was conducted by one reviewer and checked independently by a second reviewer. The complete quality assessment is presented in Appendix 3 (section 5.3).

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. This is unlikely to have introduced bias into the assessment of the primary outcome, OS, or objective assessments of tumour response or biochemical measurements such as PSA. The lack of blinding may, however, 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.[10]

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/m$^2$. 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.[54]

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[10] and usage was higher in the cabazitaxel arm due to the higher rate of neutropenia (39% versus 14% for usage from cycle 2 onwards). Anti-emetic prophylaxis was also given at the physicians' discretion in both treatment groups.[10]

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 5-5). 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.[10]

Scrutiny of the published journal article 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 5.3.6). Where available case analyses were conducted, the number of patients analysed in each group was clearly stated.[10]

### 5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

See Appendix 9.3.

### 5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Critical appraisals from the systematic review of all second-line mHRPC RCTs and the systematic review of non-RCTs are provided in Appendices 5 and 7 (section 9.5 and section 9.7).

## 5.5 Results of the relevant RCTs

The treatment received by the participants in the TROPIC trial is summarised in Table 5-5.[10]

**Table 5-5**. Treatment received in the TROPIC trial[10]

| 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) †<br>≥4 days<br>≤9 days<br>>9 days | <br>(7.9%)<br>110 (6.3%)<br>28 (1.6%) | <br>(9.3%)<br>157 (7.0%)<br>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
*Source: de Bono et al[10]*

### 5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.

#### 5.5.1.1 Primary outcome: overall survival

The median follow-up duration for both treatment groups combined was 12.8 months (interquartile range 8–16.9). At the cut-off date for analysis 234 deaths had occurred in the cabazitaxel group and 279 in the mitoxantrone group.

ITT analysis of the primary outcome showed an OS benefit in favour of cabazitaxel (see Table 5-6 and Figure 5-6). 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<0.0001), which is less than the target statistical significance level of 0.0452. The hazard ratio (HR) was 0.70 (95% CI, 0.59–0.83) in favour of cabazitaxel corresponding to a 30% reduction in risk of death.[10] An updated analysis was performed almost six months later, after 585 deaths had occurred, and has been presented at ASCO, but has not yet been published in a peer-reviewed publication. The updated analysis found identical median survival values with a HR of 0.72;[53] this submission uses the HR reported in the regulatory submissions and peer-reviewed *Lancet* publication[10]

[redacted]

**Table 5-6. Overall survival – ITT population**

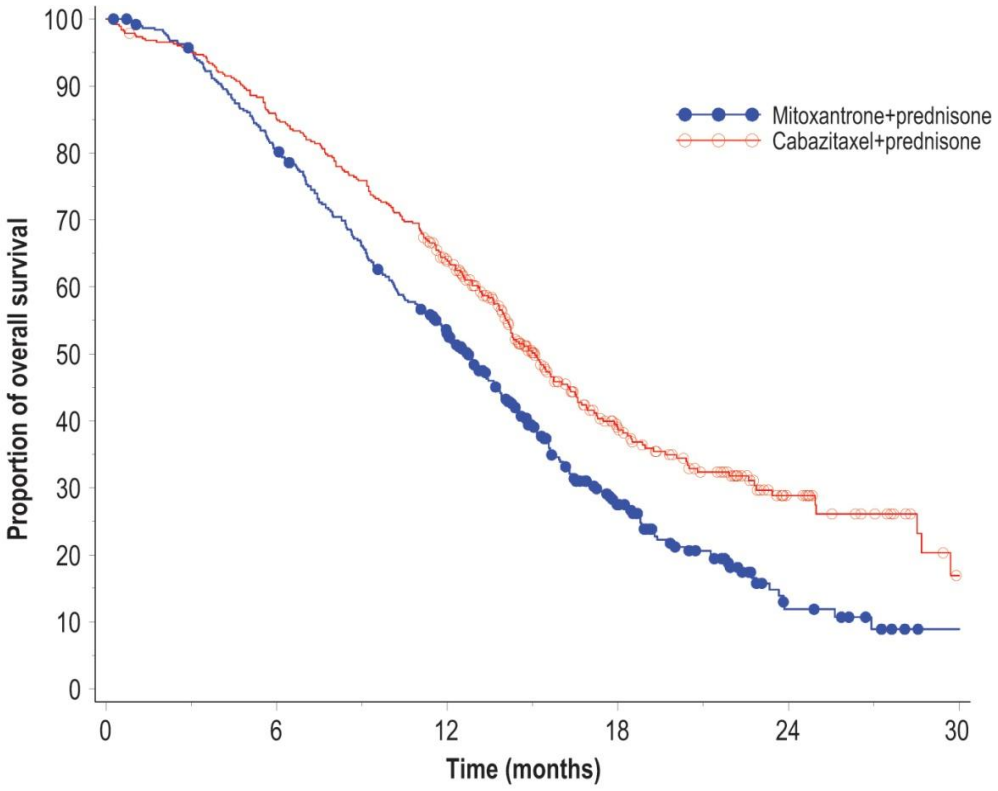
| | Mitoxantrone + prednisone (n=377) | Cabazitaxel + prednisone (n=378) |
|---|---|---|
| Number of patients with deaths (%) | 279 (74.0%) | 234 (61.9%) |
| Median survival in months (95%CI) | 12.7 (11.6–13.7) | 15.1 (14.1–16.3) |
| Hazard ratio (95% CI)* | 0.70 (0.59–0.83) | |
| P value† | <0.0001 | |

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
Source: de Bono et al[10]

Patients were censored in both arms (98 in the cabazitaxel group, 144 in the mitoxantrone group). Among them, three patients in the cabazitaxel group and seven patients in the mitoxantrone group were lost to follow-up before the study cut-off date.[54]

The Kaplan–Meier plots of OS are shown in Figure 5-6. 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 5-6. Overall survival – ITT population**




**Number at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Mitoxantrone+prednisone | 377 | 300 | 188 | 67 | 1 | 11 |
| Cabazitaxel+prednisone | 378 | 321 | 231 | 90 | 28 | 4 |

*Source: sanofi-aventis, data on file*[54]

In addition to the median OS data presented above, mean OS was estimated using patient level data from the TROPIC trial.[11] 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 Appendix 15 (section 9.15). Based on these extrapolations, mean OS was estimated as 14.0 months (95% CI, 13.1; 14.9) in the mitoxantrone arm versus 18.2 months (95% CI, 17.0; 19.4) in the cabazitaxel arm, a difference of 4.2 months (95% CI, 2.7; 5.7) in favour of cabazitaxel.

#### 5.5.1.1.1 Subgroup analyses

The following prognostic factors were considered in the preplanned subgroup analyses for overall survival: ECOG performance status, disease measurability, number of prior chemotherapy regimens, age, region, pain at baseline, PSA status, time from last docetaxel to randomisation, docetaxel dose and time of progression from last docetaxel. These are shown in the Forest plots Only two of the 26 subgroups presented showed HRs of around

1.0: patients with a prior docetaxel dose <225 mg/m$^2$ and 'other' countries. These are both small sample size subgroups (reflected in wide CIs).

Figure 5-7 and **Error! Reference source not found.**. There was a consistent trend for benefit in OS in favour of cabazitaxel across subgroups.

Only two of the 26 subgroups presented showed HRs of around 1.0: patients with a prior docetaxel dose <225 mg/m$^2$ and 'other' countries. These are both small sample size subgroups (reflected in wide CIs).

**Figure 5-7. Hazard ratio of overall survival (cabazitaxel and prednisone/prednisolone versus mitoxantrone and prednisone/prednisolone; ITT population)**

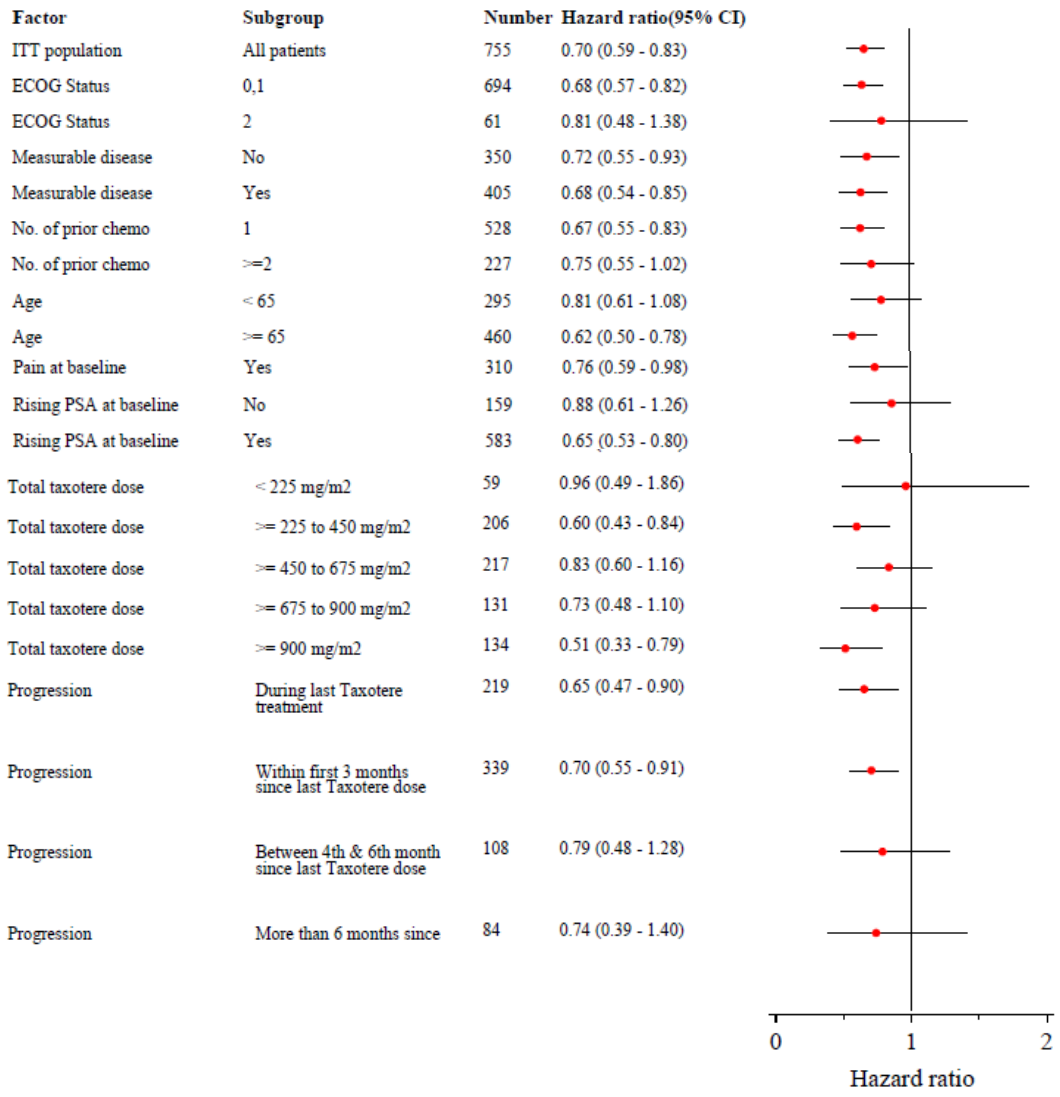
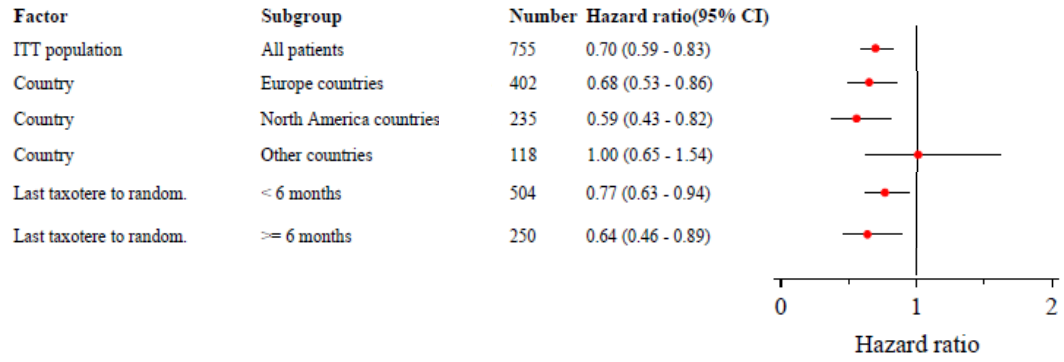


**Figure 5-8. Hazard ratio of overall survival (cabazitaxel and prednisone/prednisolone versus mitoxantrone and prednisone/prednisolone; ITT population)**




A number of post-hoc subgroup analyses were conducted to explore whether specific patient groups showed particular benefit from cabazitaxel. All post-hoc analyses were based on combinations of factors explored in the pre-planned analyses. Three subgroups are considered in the economic evaluation section:

- European patients with ECOG status 0–1 who had received ≥225 mg/m$^2$ docetaxel
- Patients with ECOG status 0–1 who had received ≥225 mg/m$^2$ docetaxel
- European patients

The first of these is presented as the base-case in the economic evaluation section, because it is considered most relevant to UK clinical practice. As detailed in 5.3.2.1, TROPIC was a global trial and included a number of countries where treatment patterns differ from UK clinical practice. Such differences could be expected to affect the treatment outcomes of cabazitaxel and indeed differences were seen in the HR and in AE rates by geographic region[10]. Therefore, the benefits demonstrated in the European region are considered most likely to represent the benefits expected in UK practice. The criterion that patients had received at least 225 mg docetaxel was added as a protocol amendment to TROPIC; in the UK, NICE guidance recommends docetaxel as first-line chemotherapy for mHRPC and thus it is unlikely patients would be considered for second-line chemotherapy before receiving

sufficient exposure to the NICE-recommended first-line treatment. Finally, input from clinicians indicates that it is extremely unlikely that in the UK, patients with an ECOG status of 2 would be considered for cabazitaxel treatment. In summary, the subgroup most representative of patients in the UK who would receive cabazitaxel is the European group of patients with ECOG status 0 -1 and who had received ≥225 mg/m$^2$ docetaxel. This group constitutes 45% of the entire TROPIC population, and has a median OS difference of [redacted] months and a mean OS difference of [redacted] months.

The other subgroups (the "all-region" patient group with ECOG status 0–1 who had received ≥225 mg/m$^2$ docetaxel, and the subgroup of European patients with no further qualification) are presented as sensitivity analyses in the economic section alongside the entire TROPIC population. In these, median OS difference was [redacted] and [redacted] months respectively, and the mean OS difference was [redacted] and [redacted] months respectively.
Results are presented in detail in section 6.3.6.

#### 5.5.1.1.2 Secondary outcome: progression-free survival

PFS was a composite endpoint, defined as the time between randomisation and the 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 (see Table 5-7). The difference in overall PFS was statistically significant in favour of the cabazitaxel group (p<0.0001). The HR was 0.74 (95% CI, 0.64 –0.86) in favour of cabazitaxel, corresponding to a 26% reduction in risk of progression (see Table 5-7). The Kaplan–Meier plots for PFS are presented in Figure 5-9.[10] 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 5-8, 40–50% of progression events were due to PSA progression, with symptom deterioration recorded in 2-4% of patients. The interpretation of PFS is discussed further in section 5.10.2.1 and should be considered when interpreting the median PFS values in TROPIC.[67]

**Table 5-7. Progression-free survival**

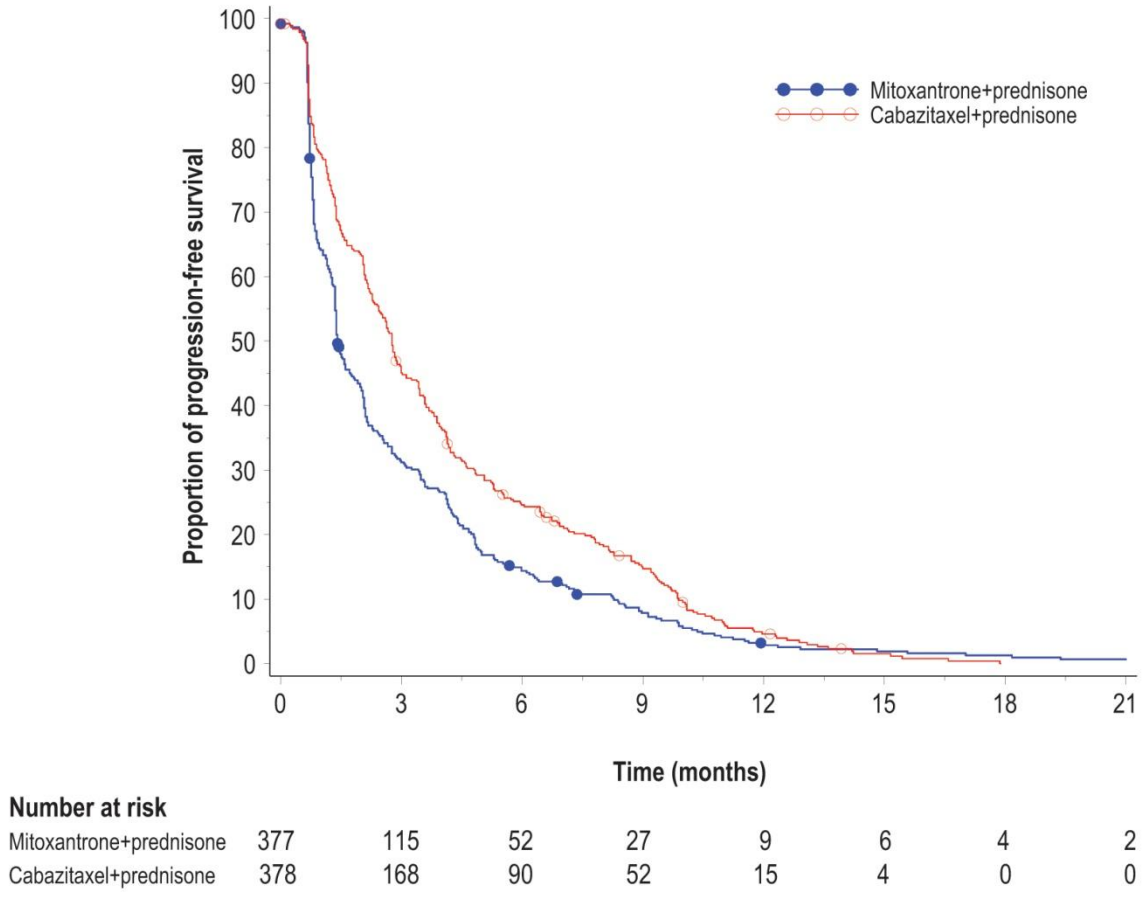
| | **Mitoxantrone + prednisone (n=377)** | **Cabazitaxel + prednisone (n=378)** |
|---|---|---|
| Number of patients with PFS events (%) | 367 (97.3%) | 364 (96.3%) |
| Median PFS in months (95%CI) | 1.4 (1.4–1.7) | 2.8 (2.4–3.0) |
| Hazard ratio (95% CI) | 0.74 (0.64–0.86) | |
| p value | <0.0001 | |

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: de Bono et al[10]

**Table 5-8. Descriptive analysis of progression-free events**

| | Mitoxantrone + prednisone (n=377) | Cabazitaxel + prednisone (n=378) |
|---|---|---|
| Number of patients with PFS events (%) | 367 (97.3%) | 364 (96.3%) |
| Death | 29 (7.7%) | 38 (10.1%) |
| Tumour progression | 68 (18.0%) | 67 (17.7%) |
| PSA progression | 186 (49.3%) | 163 (43.1%) |
| Pain progression | 70 (18.6%) | 86 (22.8%) |
| Symptom deterioration | 14 (3.7%) | 10 (2.6%) |
| Number of patients censored (%) (data censored at last available assessment) | 10 (2.7%) | 14 (3.7%) |
| Key: PSA = prostate-specific antigen; PFS = progression-free survival | | |

**Figure 5-9. Kaplan–Meier curves of PFS – ITT population**




*Source: de Bono et al*[10]

#### 5.5.1.1.3 Secondary outcome: tumour response rate (objective response)

Overall response rate (ORR) was evaluated only in patients with measurable disease (201 cabazitaxel patients [53.2%], 204 mitoxantrone patients [54.1%]). The ORR among evaluable patients was 14.4% in the cabazitaxel group and 4.4% in the mitoxantrone group,

which was statistically significant in favour of cabazitaxel (p=0.0005) (see Table 5-9). All responses were confirmed partial responses.[10]

**Table 5-9. Summary of overall response, patients with measurable disease[10]**

| | Mitoxantrone + prednisone (n=204) | Cabazitaxel + prednisone (n=201) | Mitoxantrone + prednisone vs. cabazitaxel + prednisone p-value |
|---|---|---|---|
| Number of OR (CR or PR) | 9 (4.4%) | 29 (14.4%) | 0.0005† |
| (95% CI)* | (1.6% to 7.2%) | (9.6% to 19.3%) | |
| Number of OR | | | |
| CR | 0 | 0 | |
| PR | 9 (4.4%) | 29 (14.4%) | |
| SD | 88 (43.1%) | 95 (47.3%) | |
| PD | 70 (34.3%) | 49 (24.4%) | |
| Not evaluable/ missing data | 37 (18.1%) | 28 (13.9%) | |

Key: CI = confidence interval; CR = complete response; OR = overall response; PD = progressive disease; PR = partial response; SD = stable disease
*Estimated by normal approximation
†Comparing frequency distribution based on Chi square test
Records with missing values for factors were excluded from statistical analyses
Source: de Bono et al[10]

Time to tumour progression (TTP) was defined as the number of months from the date of randomisation to evidence of PD based on tumour measurements (RECIST criteria). Patients without PD were censored at their last tumour assessment. The median TTP was 8.8 months in the cabazitaxel group and 5.4 months in the mitoxantrone group. TTP was statistically significantly longer in favour of cabazitaxel (p<0.0001 [HR 0.61; 95% CI, 0.49–0.76]) (see Figure 5-10)[10,54]

[redacted]

[redacted]

#### 5.5.1.2 Secondary outcome: PSA progression and response

Median time to PSA progression was 6.4 months in the cabazitaxel group and 3.1 months for the mitoxantrone group. Time to PSA progression was significantly longer in the cabazitaxel group (p=0.001 [HR 0.75; 95% CI, 0.63–0.90]) (see Figure 5-11).[10,54] Sensitivity analyses to allow for skipped or delayed visits showed similar results.[54]

[redacted]

[redacted]

PSA response was evaluated in patients with a baseline PSA >20 ng/ml (329 [87%] cabazitaxel patients, 325 [86%] mitoxantrone patients).[10] The PSA response rate was 39.2% in the cabazitaxel group compared with 17.8% in the mitoxantrone group and was statistically significant in favour of cabazitaxel (p=0.0002).[10]

#### 5.5.1.3 Secondary outcome: pain progression and response

There was no statistically significant difference in pain response between the treatment arms (9.2% cabazitaxel [95% CI: 4.9, 13.5] versus 7.7% mitoxantrone [95% CI: 3.7, 11.8]) (p=0.63).

There was no statistically significant difference between treatment arms in time to pain progression (TTPP) (p=0.5192 [HR 0.91; 95% CI, 0.69–1.19]) (see Figure 5-12).[10,54] Median TTPP was 11.1 months in the cabazitaxel arm and was not reached in the mitoxantrone arm. A key limitation of the TROPIC trial is that it did not capture HRQoL as an outcome. When considering the relative impact of cabazitaxel and mitoxantrone on HRQoL, the results for pain outcomes may be relevant, because pain has an important influence on overall HRQoL. The fact that TROPIC showed no significant difference in pain response and TTPP between

cabazitaxel and mitoxantrone, a drug that is mainly used for its palliative benefits.on pain, suggests that cabazitaxel may be similar to mitoxantrone in at least this aspect of QoL.

[redacted]

[redacted]

## 5.6 Meta-analysis

Not applicable, as there is only one study available that compares cabazitaxel with mitoxantrone.

## 5.7 Indirect and mixed treatment comparisons

The NICE scope specifies two comparators. Firstly, mitoxantrone plus prednisolone, which is the standard chemotherapy for patients progressing after docetaxel in mHRPC. As there is head-to-head data against mitoxantrone, the decision problem can be addressed without indirect comparison. Of the RCTs identified by a systematic review of all second-line mHRPC treatments, two other trials in addition to TROPIC evaluated mitoxantrone in combination with predniso(lo)ne. These were small (86 and 115 patients) and compared mitoxantrone with ixabepilone, and mitoxantrone plus cetuximab with mitoxantrone alone respectively.[61,62] Only the ixabepilone study reported OS data. Because there are no other

connections to cabazitaxel, the trial network is not an obvious candidate for a mixed-treatment comparison.

The second comparator in the scope is 'chemotherapy without cabazitaxel, for example 5-fluorouracil, cyclophosphamide and carboplatin/etoposide'. The systematic review of all second-line mHRPC RCTs found seven trials in total, which investigated five separate chemotherapy agents. These were cabazitaxel, mitoxantrone, docetaxel, ixabepilone and satraplatin. Satraplatin failed to improve survival, ixabepilone is not reported to be used at all in UK practice, and docetaxel rechallenge is not a suitable comparator for an agent designed to overcome docetaxel resistance, and is not recommended by NICE beyond the first-line setting. The review did not identify any trials with the agents named above as chemotherapies (5-fluorouracil, cyclophosphamide, carboplatin/etoposide) (see Appendix for details). Therefore, none of these RCTs are considered relevant to addressing the comparison with the second comparator in the scope. As discussed in section 5.2.7, the systematic review of non-RCTs identified 32 studies of 'other' chemotherapies. However, all of these were small, (<50 patients) uncontrolled studies, and, therefore, it is considered that any attempt to perform an indirect comparison based on these would be of limited validity. Because of this, and because (as discussed in section 2.6) these are not considered representative of UK clinical practice, this second comparator has not been compared to within the submission.

## 5.8 Non-RCT evidence

### 5.8.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.

As discussed in section 5.2.7, a systematic review of non-RCTs was performed. None of these studies are considered relevant to the decision problem, or are discussed further, and, therefore, we have not reported the details of these studies here. A summary is provided in Appendix 6, section 9.6.8. Quality assessment of the studies is provided in Appendix 7.

## 5.9 Adverse events

### 5.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

No studies were identified that investigated safety as the primary outcome. The TROPIC trial is, therefore, the primary source of safety data for cabazitaxel. Details of the AEs for this study are given in Section 5.9.2.

### 5.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

The most common AEs (Grade ≥3 events occurring in ≥1% of patients in either treatment group) are summarised in Table 5-10. 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).[10]

The most important AE associated with cabazitaxel is neutropenia, due to the potential for serious clinical complications. Neutropenia is an expected side-effect of taxane chemotherapy and is not necessarily a major clinical problem to manage. However, complications of neutropenia such as neutropenic sepsis and febrile neutropenia are serious clinical events. As can be seen in the table, patients treated with cabazitaxel had higher rates of neutropenia, and higher rates of infections and febrile neutropenia.

The clinical consequences of neutropenia were the most frequent cause of 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. Following this, no new neutropenic 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. [redacted]

Logistic regression analysis of neutropenia and diarrhoea incidence (all grades) suggested differences ($p<0.1$) in event rates by age (higher rates in patients aged ≥75 years), previous radiotherapy (higher rates in patients who had previous radiotherapy), and geographical region. The rate in Europe was 16.1%, which is lower than that in North America (25.7%) and in the other countries (35.1%). There were no differences in subgroups defined by race, baseline liver function, baseline renal function, ECOG performance status, or prior chemotherapy.[10,54]

Gastrointestinal disorders of all types (Grade ≥3) were more common in the cabazitaxel group (12.4% cabazitaxel, 1.6% mitoxantrone).[54] Notably, Grade ≥3 diarrhoea was more common on cabazitaxel (6.2%) compared with mitoxantrone (0.3%). The rate of Grade ≥3 nausea and vomiting was 3% on cabazitaxel and 0.3% on mitoxantrone.[10]

**Table 5-10. Adverse events reported in patients who received at least one dose of study treatment*[10]**

| Adverse event* | Mitoxantrone (n=371)† | | Cabazitaxel (n=371)† | | Relative risk (95% CI) | | Risk difference (95% CI) | |
|---|---|---|---|---|---|---|---|---|
| | All grades | Grade ≥3‡ | All grades | Grade ≥3‡ | All grades | Grade ≥3‡ | All grades | Grade ≥3‡ |
| Haematological§ | | | | | | | | |
| Neutropenia | 325 (88%) | 215 (58%) | 347 (94%) | 303 (82%) | 1.07 (1.02–1.12) | 1.41 (1.28–1.56) | 0.06 (0.02–0.10) | 0.24 (0.17–0.30) |
| Febrile neutropenia | – | 5 (1%) | – | 28 (8%) | | 5.60 (2.19–14.34) | | 0.06 (0.03–0.09) |
| Leukopenia | 343 (92%) | 157 (42%) | 355 (96%) | 253 (68%) | 1.03 (1.00–1.07) | 1.61 (1.40–1.85) | 0.03 (-0.002–0.07) | 0.26 (0.19–0.33) |
| Anaemia | 302 (81%) | 18 (5%) | 361 (97%) | 39 (11%) | 1.20 (1.14–1.26) | 2.17 (1.26–3.72) | 0.16 (0.12–0.20) | 0.06 (0.02–0.10) |
| Thrombocytopenia | 160 (43%) | 6 (2%) | 176 (47%) | 15 (4%) | 1.10 (0.94–1.29) | 2.50 (0.98–6.37) | 0.04 (-0.03–0.11) | 0.02 (-0.0002–0.05) |
| Non-haematological | | | | | | | | |
| Diarrhoea | 39 (11%) | 1 (<1%) | 173 (47%) | 23 (6%) | 4.44 (3.23–6.09) | 23 (3.12–169.43) | 0.36 (0.42–0.29) | 0.059 (0.04–0.09) |
| Fatigue | 102 (27%) | 11 (3%) | 136 (37%) | 18 (5%) | 1.33 (1.08–1.65) | 1.64 (0.78–3.42) | 0.09 (0.02–0.16) | 0.02 (-0.01–0.05) |
| Asthenia | 46 (12%) | 9 (2%) | 76 (20%) | 17 (5%) | 1.65 (1.18–2.31) | 1.89 (0.85–4.18) | 0.08 (0.03–0.13) | 0.02 (-0.006–0.05) |
| Back pain | 45 (12%) | 11 (3%) | 60 (16%) | 14 (4%) | 1.33 (0.93–1.91) | 1.27 (0.59–2.77) | 0.04 (-0.01–0.09) | 0.008 (-0.02–0.04) |
| Nausea | 85 (23%) | 1 (<1%) | 127 (34%) | 7 (2%) | 1.49 (1.18–1.89) | 7.00 (0.87–56.61) | 0.11 (0.05–0.18) | 0.02 (0.0004–0.04) |
| Vomiting | 38 (10%) | 0 | 84 (23%) | 7 (2%) | 2.21 (1.55–3.15) | - | 0.12(0.07–0.18) | 0.02 (0.005–0.04) |
| Haematuria | 14 (4%) | 2 (1%) | 62 (17%) | 7 (2%) | 4.43 (2.53–7.77) | 3.50 (0.73–16.74) | 0.13 (0.09–0.17) | 0.01 (-0.004–0.03) |
| Abdominal pain | 13 (4%) | 0 | 43 (12%) | 7 (2%) | 3.31 (1.81–6.05) | - | 0.08 (0.04–0.12) | 0.02 (0.005–0.04) |
| Pain in extremity | 27 (7%) | 4 (1%) | 30 (8%) | 6 (2%) | 1.11 (0.67–1.83) | 1.50 (0.43–5.27) | 0.008 (-0.03–0.05) | 0.005 (-0.01–0.03) |
| Dyspnoea | 17 (5%) | 3 (1%) | 44 (12%) | 5 (1%) | 2.59 (1.51–4.45) | 1.67 (0.40–6.92) | 0.07 (0.03–0.11) | 0.005 (-0.01–0.02) |
| Constipation | 57 (15%) | 2 (1%) | 76 (20%) | 4 (1%) | 1.33 (0.98–1.82) | 2.00 (0.37–10.85) | 0.05 (-0.004–0.11) | 0.0054 (-0.01–0.02) |
| Pyrexia | 23 (6%) | 1 (<1%) | 45 (12%) | 4 (1%) | 1.96 (1.21–3.17) | 4.00 (0.45–35.62) | 0.06 (0.02–0.10) | 0.008 (-0.006–0.02) |
| Arthralgia | 31 (8%) | 4 (1%) | 39 (11%) | 4 (1%) | 1.26 (0.80–1.97) | - | 0.02 (-0.02–0.06) | 0 (-0.018–0.018) |
| UTI | 11 (3%) | 3 (1%) | 27 (7%) | 4 (1%) | 2.45 (1.24–4.87) | 1.33 (0.30–5.92) | 0.04 (0.01–0.08) | 0.003 (-0.01–0.02) |
| Pain | 18 (5%) | 7 (2%) | 20 (5%) | 4 (1%) | 1.11 (0.60–2.07) | 0.57 (0.17–1.94) | 0.005 (-0.03–0.04) | -0.008 (-0.03–0.01) |
| Bone pain | 19 (5%) | 9 (2%) | 19 (5%) | 3 (1%) | 1 (0.54–1.86) | 0.33 (0.09–1.22) | 0.00 (-0.03–0.03) | -0.02 (-0.04–0.003) |

* Grade ≥3 events occurring in ≥1% of patients in either treatment group

† Safety outcomes were assessed in patients who received at least one dose of study treatment

‡ National Cancer Institute Common Terminology Criteria for adverse event

§ Data for haematological adverse events were based on laboratory assessments

With regard to the elderly, 240 of the 371 patients treated with cabazitaxel were ≥65 years of age. The following AEs occurred at rates ≥5% higher in patients aged ≥65 years compared with younger patients: fatigue (40.4% versus 29.8%), neutropenia (24.2% versus 17.6%) asthenia (23.8% versus 14.5%), pyrexia (14.6% versus 7.6%), dizziness (10.0% versus 4.6%), urinary tract infection (9.6% versus 3.1%) and dehydration (6.7% versus 1.5%). The incidence rates of Grade ≥3 neutropenia based on laboratory abnormalities (86.3% versus 73.3%), clinically complicated neutropenia (23.8% versus 16.8%) and febrile neutropenia (8.3% versus 6.1%) were higher in patients aged ≥65 years compared with younger patients.[1]

The number of deaths among patients who received at least one dose of study drug are summarised in Table 5-11. 18 (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[10 54]

**Table 5-11. Deaths due to AEs other than disease progression reported in the TROPIC trial**

| Outcome | Mitoxantrone + prednisone (n=371)* | Cabazitaxel + prednisone (n=371)* |
|---|---|---|
| Total deaths during the study | 275 (74%) | 227 (61%) |
| Total deaths ≤30 days after last dose of study drug | 9 (2.4%) | 18 (4.8%) |
| Causes of death ≤30 days after last dose of study drug | | |
| Disease progression | 6 (2%)† | 0 |
| Deaths due to AEs | 3 | 18 |
| Neutropenia and clinical consequences / sepsis | 1 | 7 |
| Cardiac | 0 | 5 |
| Dyspnoea‡ | 1 | 0 |
| Dehydration / electrolyte imbalance | 0 | 1 |
| Renal failure | 0 | 3 |
| Cerebral haemorrhage | 0 | 1 |
| Unknown cause | 0 | 1 |
| Motor vehicle accident | 1 | 0 |
| Deaths >30 days after last dose of study drug | 266 (72%) | 209 (56%) |

* Assessed in patients who received at least one dose of study treatment; † Includes three patients whose death was reported as an adverse event coded as disease progression; ‡ Dyspnoea was reported as the adverse event leading to death, but the investigator regarded the death as related to disease progression
Key : AE = adverse event
*Source: de Bono et al[10]*

In the TROPIC trial patients in the cabazitaxel group received more cycles of study treatment (median number of cycles: six) compared with patients in the mitoxantrone group (median number of cycles: four). In the cabazitaxel group, 9.8% of cycles were administered with a dose reduction of ≥20% and and 2% of cycles were delayed by >9 days compared with 5.1% of cycles dose reduced and 2% cycles delayed, respectively, in the mitoxantrone group.[10,54]

### 5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Cabazitaxel is a taxane chemotherapy. As such, it was expected that it would have a harsher side-effect profile than mitoxantrone, which is typically a very well-tolerated palliative chemotherapy. The most common AEs observed in the cabazitaxel group were neutropenia and its complications (febrile neutropenia and infections), asthenic conditions (asthenia and fatigue), and gastrointestinal toxicity (diarrhoea, nausea and vomiting) (see Table 5-10). These are common to the taxanes as a class and were expected to be associated with cabazitaxel use. These AEs are manageable by patient education, close monitoring for development of neutropenia, prompt administration of corrective therapy such as hydration, use of antibiotics, and/or G-CSF use as per ASCO guidelines.[47] UK physicians have experience with other drugs, such as docetaxel, with similar side-effects, and have experience managing these side-effects.

Patients considered to be at high risk should be considered for primary prophylactic G-CSF.

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.[2] This reflects the fact that the side-effects of cabazitaxel are predictable and manageable. Further, the higher risk of AEs is outweighted 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.

## 5.10 Interpretation of clinical evidence

### 5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Prior to TROPIC, no drug had demonstrated a significant improvement in OS in second-line mHRPC. The TROPIC trial compared cabazitaxel with mitoxantrone, which is the most commonly used active treatment following progression after docetaxel. The results from the TROPIC trial show that cabazitaxel offers a significant and meaningful OS improvement over mitoxantrone in the second-line treatment of mHRPC patients previously treated with docetaxel. Median survival for patients in the cabazitaxel group was 15.1 months in comparison with 12.7 months in the mitoxantrone group ($p<0.0001$), with a HR of 0.70 (95% CI: 0.59, 0.83) corresponding to a 30% reduction in risk of death.[10] The mean OS improvement of 4.2 months represents a 30% increase in the mean survival expected from the most commonly used second-line treatment mitoxantrone (details of mean survival calculation presented in Appendix 15). In the subgroup presented as the base-case in the

economic evaluation, the median OS benefit was [redacted] months, with a HR of [redacted] corresponding to a [redacted] reduction in the risk of death, and the mean OS benefit was [redacted] months. The survival benefits of cabazitaxel are prolonged – that is, the OS curves remain divergent.

[redacted]

PFS, defined as the time between randomisation and disease progression (defined as confirmed rise in PSA, radiological, symptomatic deterioration, or pain progression, whichever happened first) or death (due to any cause) was also statistically significantly longer in the cabazitaxel group compared with the mitoxantrone group (P<0.0001, hazard ratio = 0.74 [95% CI: 0.64, 0.86], and median PFS was 2.8 months versus 1.4 months).[10] The most common progression event was PSA progression (~50%), followed by pain progression and tumour progression (both accounting for ~20% of events) (see **Table 5-8** for details). As discussed in the limitations section below, there are challenges in defining PFS In prostate cancer. This has two key consequences. First, it is common in prostate cancer trials to observe a relatively short PFS duration, as seen here. Second, PFS is not a clear surrogate for OS. Notwithstanding these challenges, PFS in the cabazitaxel was double that in the mitoxantrone group.

Other secondary endpoints also supported the benefit shown in the primary endpoint, including response rates for PSA and tumour assessments by RECIST, as well as TTP and time to PSA progression.

Pain is an important outcome in mHRPC – many patients experience considerable pain, mainly due to bone metastases. Effective alleviation of pain is a critical goal of mHRPC treatment and the effects of mitoxantrone on pain outcomes is the main reason why mitoxantrone has been extensively used as a palliative agent in mHRPC. In the TROPIC trial, response rates for pain and TTPP did not show statistically significant differences.[10]

This suggests that the survival benefit of cabazitaxel is not counteracted by poorer symptom control.

The analysis of safety data found the safety profile to be predictable and manageable, even in heavily pretreated patients.[2] The most frequent AEs observed in the cabazitaxel group were neutropenia and its complications (febrile neutropenia and infections), asthenic conditions (asthenia and fatigue) and gastrointestinal toxicity (diarrhoea and vomiting). The intended cabazitaxel dose was delivered as indicated by the highest median relative dose intensity (96.1%). There was a high proportion of heavily pretreated patients with

measurable disease with poor prognosis in the TROPIC trial. These factors, alongside infiltration of bone marrow by tumour and previous treatment, could account for the rates of neutropenia and febrile neutropenia in the control group of the study, which were higher than those observed in first-line trials (such as TAX327).[31] The extensive monitoring in this trial (weekly testing during Cycle 1) is also likely to have contributed to the high rates of neutropenia detected. However, despite the compromised bone marrow reserve of this patient population, more than 75% of patients received more than 90% of the planned dose intensity.[10]

In section 6.4.3 we present interim results from the UK early access programme (EAP) for cabazitaxel, which is evaluating utility via the EQ-5D. An important limitation of this is that it is a non-comparative study, so it is not possible to compare the impact of cabazitaxel on utility with that of mitoxantrone. [redacted] This suggests that cabazitaxel is not associated with a significant negative effect on utility, and may even improve utility possibly through stabilising disease and controlling symptoms. This picture is consistent with anecdotal evidence from clinicians treating patients with cabazitaxel (see Appendix 17).

Cabazitaxel is the first treatment to demonstrate improved OS and provide a meaningful therapeutic option for patients with mHRPC previously treated with a docetaxel-containing regimen who have progressed during or following treatment with a docetaxel-based regimen. These results are even more notable given that an active control was used as a comparator in the study design.

### 5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

#### 5.10.2.1 Strengths

The TROPIC trial directly compared cabazitaxel with mitoxantrone, an active comparator that is the most common treatment for the patient population under consideration. The primary outcome was OS, which is clinically relevant and not susceptible to bias or limitations in assessment.

TROPIC was a large (755 patients) multicentre trial. With regard to internal validity, the study was well conducted and adequately powered. Analysis of time-to-event efficacy outcomes, including the primary outcome, was conducted on the ITT population. 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.[54]

The results of this study show a statistically and clinically meaningful prolongation in OS as measured by both median[10] and mean OS. 4.2 months mean OS difference represents an increase in survival of approximately 30% for this patient group. In the patient group considered most representative of UK patients likely to receive cabazitaxel, the mean OS difference was [redacted] The primary outcome was further supported by statistically significant improvements observed for PFS, response rate for PSA and response rates by RECIST, TTP and time to PSA progression. Improved efficacy was balanced with a predictable and manageable AE profile for an agent in this class.[10] Analyses across subgroups and sensitivity analyses showed the data to be consistent with the overall group.[10,54]

**Limitations**

TROPIC is the only RCT of cabazitaxel in prostate cancer, as is commonly the case with oncology agents. TROPIC was an open label study; although this is unlikely to bias assessment of OS, or objective assessments of tumour response, there is potential for ascertainment bias in the subjective assessment of PPI and symptomatic progression. As these were components of the composite endpoint for PFS this may have introduced some bias into the interpretation of PFS. However, these accounted for 23% of progression events, thus the likely impact of this was relatively small. Clinical (not laboratory) assessment of AEs may have been biased by the open label nature of the trial.

Secondary endpoints such as PFS, tumour response rate and tumour progression have limitations in the assessment of treatment efficacy among patients with non-measurable disease due to interobserver bias and variability. A large proportion of patients with mHRPC do not have measurable disease as prostate cancer typically metastasises to the bones (45% of patients in the TROPIC trial). It would have been inappropriate to have excluded patients without measurable disease as the trial population would have been unrepresentative.[10,54] The lack of a standard definition for PFS in mHRPC trials has proved problematic. This 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,[68] 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.

In the TROPIC trial cabazitaxel was directly compared with an active comparator, mitoxantrone. However, although mitoxantrone plus prednisolone is unlicensed for the indication under review, it is the most commonly used therapy in this patient population in current clinical practice. Mitoxantrone has been shown to improve symptom control among patients with mHRPC who have not received prior chemotherapy and is licensed in this indication by the US FDA.[69] However, the impact of mitoxantrone on survival is unclear – mitoxantrone has not been shown to improve survival compared with corticosteroids alone in any indication. In the systematic review of all second-line mHRPC treatments, only one trial other than TROPIC reported OS for mitoxantrone in combination with prednisolone and this study did not report a significant difference with the comparator (ixabepilone).[62]

A limitation to studies of novel agents after docetaxel treatment is the absence of a standard definition for docetaxel resistance. Standardised definitions are needed to improve the early identification of disease progression and docetaxel-resistant disease. The definition of disease progression for patients with mHRPC remains challenging and is often based on combinations of measures such as rising serum PSA concentrations, new or enlarging radiological lesions or appearance of symptoms.[63,64] On the basis of emerging guidelines recommending the delivery of 12 weeks of treatment before adjustment of therapy for mHRPC,[64] an amendment was made to the trial protocol after 59 patients had been enrolled to exclude patients previously receiving a cumulative docetaxel dose lower than 225 mg/m².

TROPIC was an international trial, including countries in North America, Europe, and other regions. While it is a strength of TROPIC that the effectiveness of cabazitaxel was evaluated in many different countries, it is recognised that different countries show considerable variation in treatment practice which may have affected the clinical benefits and harms observed with cabazitaxel. For example, in TROPIC, analysis of the incidence of neutropenia and diarrhoea by subgroup suggested differences in geographical region[10], and in the group of non-north American, non-European countries the HR was 1.0. For this reason, in the economic section, the base-case utilises data from the European region, which is considered more representative of UK patients than the data from the North America region or the other included countries.

QoL data were not collected in the trial. However, EQ-5D data have been collected from UK patients included in the cabazitaxel EAP. An interim analysis is presented in this submission (see section 6.4.3), although this does not provide comparative data. In the absence of comparative QoL data, results for pain, which is an important factor influencing QoL, show no significant differences between cabazitaxel and mitoxantrone. Additional evidence that may be relevant to cabazitaxel is the QoL (FACT-P) data from the TAX327 trial of docetaxel

compared with mitoxantrone (that is, compares mitoxantrone with another taxane drug). This showed an improvement over time on first-line treatment, with no significant differences between docetaxel and mitoxantrone (docetaxel scores being slightly higher).[70]

### 5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The decision problem focuses on a comparison of cabazitaxel with two specified comparators, in a patient population with mHRPC that has progressed following docetaxel.

The TROPIC trial directly compares cabazitaxel with the main comparator specified in the NICE scope, mitoxantrone (both with prednisolone), in men with mHRPC who have progressed after docetaxel. Mitoxantrone is the most relevant comparator for cabazitaxel as it is the main chemotherapy agent used in NHS practice in patients who have progressed after docetaxel. The NICE scope also states that chemotherapy in general (for example, 5-fluorouracil, cyclophosphamide or carboplatin/etoposide) should be considered as a comparator. However, none of these agents or any other chemotherapy drug than mitoxantrone or docetaxel retreatment is used with any frequency in NHS practice, reflecting the lack of effective treatments in second-line mHRPC. Furthermore, there are no RCTs of any of these agents to date in second-line mHRPC (see details of the systematic review in Appendix 9.2), making comparison difficult. In the absence of RCT evidence, information from non-randomised studies may be relevant; however, a systematic review of non-RCTs found very limited evidence for any agents other than mitoxantrone and docetaxel retreatment (see section 5.2.7). Due to the limited evidence, any comparison would be associated with limited validity and because of this and the limited use of other chemotherapies, we have focused on mitoxantrone as the only relevant comparator to cabazitaxel.

Recently, a number of novel agents have been trialled in second-line mHRPC. Data have shown that the novel androgen biosynthesis inhibitor abiraterone acetate is effective in this group of patients.[39] The product is not yet licensed for use in the UK. Given the different mechanism of action to cabazitaxel, it seems likely that future use of abiraterone and cabazitaxel will complement one another in the treatment of this population. However, due to the limited availability of abiraterone data at this time, further discussion is beyond the scope of this document.

With regard to patient population, this submission presents an evaluation of the clinical effectiveness and cost-effectiveness of cabazitaxel in its licensed indication of mHRPC

patients who have progressed following docetaxel. In the economic evaluation, in order to consider the cost-effectiveness of cabazitaxel from the perspective of the UK NHS, we have based the evaluation on a patient population considered the most representative of patients likely to receive cabazitaxel in UK clinical practice. This is, European patients with an ECOG performance status 0 – 1 and who have received at least 225 mg of docetaxel. We have used European data from TROPIC, because European treatment patterns and patient characteristics are more likely to be similar to UK patterns than those in the US or other non-European countries. Clinical opinion indicates it is extremely unlikely that ECOG PS 2 patients would be considered for cabazitaxel in the UK (and indeed only 61 patients in TROPIC had ECOG PS 2). In line with NICE guidance, it is expected all UK patients considered for cabazitaxel would have received a sufficient exposure to docetaxel before consideration for second-line chemotherapy. The criterion for patients to have received at least 225 mg of docetaxel was added as a protocol amendment in TROPIC and only 59 patients in TROPIC did not meet this criterion. The cost-effectiveness of cabazitaxel in the TROPIC population as a whole, and in the subgroup of patients with ECOG 0 -1 and who have received at least 225 mg docetaxel is presented as a sensitivity analysis.

The decision problem scope specifies a number of outcomes, including OS, PFS, response rate and PSA level, and AEs. All of these outcomes were directly assessed in TROPIC. The primary endpoint, OS, is unequivocally the most relevant clinical outcome in oncology. Improvement in OS is the primary unmet need in second-line mHRPC – until TROPIC, no drug had demonstrated a survival benefit in this setting.

TROPIC did not assess QoL.To address the limitations of the TROPIC data in terms of accurately assessing the QoL impact of cabazitaxel, EQ-5D data are being collected from the cabazitaxel EAP in the UK. Results of the interim analysis are presented in 6.4.3 and the values from this prospective study are used in the economic model.

Overall, it is expected that the benefits observed in the TROPIC trial would also be observed in clinical practice in the UK, due to the fact that:

- TROPIC was a well-conducted trial
- The European patients in TROPIC were representative of UK patients in terms of baseline characteristics and treatment history
- Outcomes assessed in TROPIC such as OS and tumour response rate are not easily susceptible to bias (other outcomes which may be more susceptible to bias show a similar trend to OS)

- Treatment practice among European patients in TROPIC (for example, concomitant medication use) is representative of UK practice.

In conclusion, cabazitaxel is the first treatment to demonstrate improved OS and provide a meaningful therapeutic option for patients with mHRPC, who have progressed during or following treatment with a docetaxel-based regimen. The TROPIC trial provides evidence directly relevant to the decision problem of the value of cabazitaxel in second-line mHRPC.[10]

### 5.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Cabazitaxel has received marketing authorisation for patients with mHRPC who have progressed following docetaxel with an ECOG performance status of 0–2. The mHRPC patients in the TROPIC trial are reflective of the proposed indication statement.[71] The dosing schedule used in the TROPIC trial is consistent with the dosing schedule detailed in the summary of product characteristics,[1] consisting of 25 mg/m$^2$ (Day 1) intravenous infusion over 60 minutes every three weeks, and prednisone 10 mg orally given daily.[1] Treatment duration is to be until disease progression, death, unacceptable toxicity or a maximum of ten cycles (three weeks per cycle [30 weeks]).[1]

It is expected that cabazitaxel will be used in the UK due to the clear unmet need and lack of alternative effective therapies. An audit of five centres in the UK showed that [redacted] of patients in these centres received cytotoxic chemotherapy as second-line treatment.[42] It is expected that clinicians would consider such patients potentially eligible for cabazitaxel. It is not expected that all patients who have progressed after docetaxel would receive cabazitaxel – rather, cabazitaxel will be used in a subset of patients with good performance status who are able and willing to tolerate further chemotherapy, and of whom the patients included in TROPIC are representative. In terms of performance status, it is expected that cabazitaxel will be used almost exclusively in patients with ECOG status 0-1 in the UK. This is reflective of TROPIC, where the majority of patients (>91% in both arms) in TROPIC had ECOG status 0–1. It is also expected that, in line with NICE guidance, UK patients would receive exposure to at least 3 cycles (225 mg/m$^2$) of docetaxel before being considered for second-line chemotherapy. Again, this is reflective of TROPIC, where this criterion was introduced as a protocol amendment, and where >92% patients had in fact received at least this

exposure to docetaxel. To ensure results reflect as possible the likely cost-effectiveness of cabazitaxel in the UK, the base-case economic evaluation considers patients with ECOG status 0 -1 and who had received at least 225 mg/m$^2$.of docetaxel.

The TROPIC trial was a multinational study in 26 countries, including countries in North and South America, Asia and Africa, where treatment practice and patient characteristics differ somewhat from the UK and the rest of Europe. These differences may impact on the clinical benefits realised with cabazitaxel. Data from TROPIC show that there were differences in efficacy and AE rates by geographic region[10]. Therefore, in the base-case cost-effectiveness section we have used European data as being most representative of the clinical benefits and harms expected in UK patients. European patients constituted just over 53% of the total TROPIC population, [redacted] The HR in the European population was 0.68 (95% CI, 0.54 – 0.85) (see Forest plot in 5.5.1.1).

Overall, the results of TROPIC are considered to be clinically meaningful and relevant to UK practice. In the economic evaluation we have presented an analysis which is based on European patients and which excludes patients unlikely to be considered for cabazitaxel in UK practice, which uses UK-specific prospectively collected EQ-5D data, and UK-specific retrospectively collected resource use data. Therefore, we believe that, as far as is possible, this accurately reflects the cost-effectiveness of cabazitaxel in the UK.

# Section 6. Cost-effectiveness

## 6.1 Published cost-effectiveness evaluations

***Identification of studies***

### 6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness data from published literature and unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

A range of databases indexing published research were searched for studies of the cost-effectiveness of cabazitaxel in men with mHRPC who have progressed following treatment with docetaxel. The databases searched included: MEDLINE, MEDLINE In-Process, EMBASE, EconLit and the NHS Economic Evaluation database (NHS EED). The strategy did not use an economic search filter as scoping searches had indicated that the literature for cabazitaxel is very small. Searching only for cabazitaxel as a drug name, drug development number and registry number ensured a sensitive search. No date or language limits were applied. Full details of the search strategies, databases and resources searched are provided in section 9.10, Appendix 10.

### 6.1.2 Description of identified studies

The systematic literature search identified no published economic evaluations that met the inclusion criteria.

### 6.1.3 Quality assessment

No economic evaluations of cabazitaxel were identified.

## 6.2 De novo analysis

***Patients***

### 6.2.1 What patient group(s) is (are) included in the economic evaluation?

The patient group considered in the base-case is men with mHRPC previously treated with a docetaxel-containing regimen, with ECOG PS 0 -1 and who have received at least 225 mg/m$^2$ docetaxel. The base-case uses data from the European patient population from TROPIC.

This patient population is considered most representative of the patients who will receive cabazitaxel in the UK. In terms of performance status, it is expected that cabazitaxel will be used almost exclusively in patients with ECOG status 0-1 in the UK. It is also expected that, in line with NICE guidance, UK patients would receive exposure to at least 3 cycles (225 mg/m$^2$) of docetaxel before being considered for second-line chemotherapy. The TROPIC trial was a multinational study in 26 countries, including countries in North and South America, Asia and Africa, where treatment practice and patient characteristics are likely to differ somewhat from the UK and the rest of Europe. Therefore, in the base-case cost-effectiveness section we have used European data as being most representative of the clinical benefits and harms expected in UK patients.

Three further patient groups are presented in the subgroup analyses section. These are:

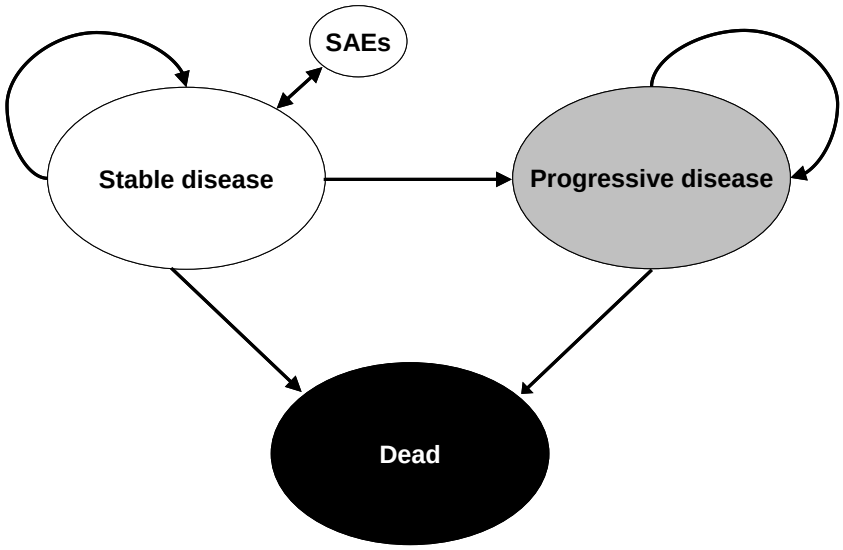
- Patients with ECOG PS 0 -1 and who had received at least 225 mg/m$^2$ docetaxel (from the entire TROPIC population)
- European patients
- The entire TROPIC population

***Model structure***

### 6.2.2 Provide a diagrammatic representation of the model you have chosen

A Markov model was used, to represent the progressive nature of the disease. A model diagram is provided below. Patients start in the stable disease state at the first cycle of treatment. Once patients progress, they move to the 'progressive disease' state. Finally, patients can die from all causes, and at any time. The cycle length in the model is three weeks, reflecting the timing of treatment cycles.

**Figure 6-1. Schematic model structure**




### 6.2.3 Justify the chosen structure in line with the clinical pathway of care identified in section 2.4

With regard to the pathway of care defined in section 2.4, the model starts at the initation of second-line mHRPC therapy. The model structure is typical in modelling metastatic cancers, and has been used in many previous NICE submissions. It captures the progressive nature of the disease, and reflects the main outputs produced by the pivotal source of evidence (the TROPIC trial).

### 6.2.4 Define what the health states in the model are meant to capture

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; that is, 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 three health states used in the model are meant to capture the three most important health states in mHRPC (and cancer in general). These are:

- Stable disease (patients on second-line treatment who have not yet progressed)
- Progressive disease (patients who have progressed following second-line mHRPC therapy)
- Death.

### 6.2.5 How does the model structure capture the main aspects of the condition of patients and clinicians as defined in section 2. What was the underlying disease progression implemented in the model or what treatment was assumed to reflect underlying disease progression? Cross reference to section 2.1

All patients begin in the ‘stable disease’ health state at the first cycle of treatment and are treated with cabazitaxel or mitoxantrone.

Patients can move from the stable disease state to the progressive disease and from both of these states to death. The definition of ‘progression’ matches that used in the TROPIC trial (see section 5.3.5.2).

These health states reflect the most important goals of mHRPC treatment (that is, stabilising disease and delaying progression, and improving survival) and the key outputs from the TROPIC trial.

The model structure (see Figure 6-1) shows that patients are able to move from the stable disease state to either the progressive disease state or to death. The arrow looping back to the stable disease state means that it is also possible to remain in that health state. Similarly, patients in the progressive disease health state can remain in that health state or progress to death. Thus, once a patient has progressed while on initial therapy, they are not able to return to the stable disease health state. Finally, death is an absorbing state, which means that it is not possible to leave it once it has been reached. As this is a cohort model, patients are not followed individually.

Costs are assigned for each Markov health state in the model, as well as health utilities for estimation of QALYs.

Within each of these health states, it is possible that there are subgroups that may have differences in resource use and QoL. For example, in the stable disease state, it is possible that there may be a difference between patients who are responding to treatment (under the definition of responders in the TROPIC trial) and those who are not responding but not also progressing. However, as tumour response rate (by RECIST) was only evaluated in patients with measurable disease, it would have been problematic to implement this difference in the model.

Moreover, there is a possibility that there will be subgroups of patients that have not progressed according to the definitions of progression used in the TROPIC trial (by tumour-, PSA-, or pain progression), but that have experienced SAEs. These patients will, therefore, constitute a group of patients in the stable disease state that acquire higher costs and lower

utility. However, including AEs as separate states would make the model overly complex and computationally excessive. Therefore, they have been taken into consideration by assigning a cost and utility reduction in each cycle for Grade ≥3 AEs. Key assumptions and the rationale for these are shown in Table 6-1.

**Table 6-1. Model features**

| Factor | Chosen values | Justification | Reference |
|---|---|---|---|
| Time horizon | Lifetime; 15 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 mHRPC 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 measured in QALYs; if not, what was used? | Yes, health effects measured in QALYs | As recommended in the Reference Case. | NICE MTA method guide |
| Discount of 3.5% for utilities and costs | Costs and benefits were discounted at 3.5%. | As recommended by the UK Treasury. Discount rates were varied in the sensitivity analysis. | 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: mHRPC = metastatic hormone-refractory prostate cancer; NHS = National Health Service; PSS = Personal Social Services; QALYs = quality-adjusted life years

*Technology*

### 6.2.6 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The model compares cabazitaxel with mitoxantrone, which is the first comparator in the NICE scope. Both are implemented in the model in the dose used in the TROPIC trial, as per the cabazitaxel licence and usual practice for mitoxantrone (mitoxantrone is unlicensed for this indication).

The model arms 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.

The average BSA of patients included in the TROPIC trial was 2.01 $m^2$ and this is used in the base-case. A BSA of 1.9 $m^2$, estimated by UK clinicians, is applied in a scenario analysis.

### 6.2.7 Please note that the following question refers to clinical continuation rules and not patient access schemes.

**Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.**

- **The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).**
- **The robustness and plausibility of the endpoint on which the rule is based.**
- **Whether the 'response' criteria defined in the rule can be reasonably achieved.**
- **The appropriateness and robustness of the time at which response is measured.**
- **Whether the rule can be incorporated into routine clinical practice.**

- **Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.**
- **Issues with respect to withdrawal of treatment from non-responders and other equity considerations.**

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 therapy.

## 6.3 Clinical parameters and variables

### 6.3.1 Please demonstrate how the clinical data were implemented into the model.

The efficacy and safety of cabazitaxel and mitoxantrone in the model are based directly on the TROPIC trial data.[10,54] The primary endpoint of TROPIC was OS; PFS was a secondary endpoint. PFS data were used to determine the probability of patients remaining in the stable disease state (that is, not progressed on second-line treatment), while OS data were used to determine the probability of death. PFS is defined as in TROPIC as the first occurrence of any of the following events: tumour progression as determined by the RECIST criteria (for measurable disease), PSA progression, pain progression or death due to any cause (as reported in section 5.5.1.1.2).

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. This reflects the TROPIC protocol, in which treatment in both groups was continued until disease progression, unacceptable toxicity, death, or for a maximum of up to ten cycles. Patients who received mitoxantrone were not able to cross over to cabazitaxel, while patients who were initially assigned to cabazitaxel were able to cross over to receive mitoxantrone. As mitoxantrone is usually considered to only have a palliative effect there was no need to account for any crossover effect on survival data when designing the model. Following progression, it is assumed that a proportion of patients will receive post-second-line chemotherapy, with the remainder receiving BSC. 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 audit of five major UK cancer centres. It is assumed that post-second-line treatment has no efficacy and, therefore, does not affect survival or utility; the impact is purely due to cost of treatment. This assumption was

necessary due to the lack of data on the efficacy of post-second-line treatment and is valid because this benefit should already have been accounted for through the OS data. Post-second-line treatment is only received for a relatively short duration (as shown by both TROPIC and the UK audit) and the cost of these drugs is therefore 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 audit, and expert opinion on frequency of hospice care provision (hospice care was not available from the hospital-based patient records captured in the audit).

### Adverse events

As mentioned in section 6.2.5, Grade ≥3 AEs are incorporated into this model as costs and disutilities rather than separate events or states. That is, 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, not after patients progressed.

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.

Fifteen AEs were included in the model. These are listed in Table 6- in section 6.3.6 below together with AE rates in patients who experienced these events in each arm of the TROPIC trial. These AEs were chosen on the ground 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.

### 6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide transition matrix, details of the transformation of clinical outcomes or other details here

PFS data were used to determine the probability of patients remaining in the stable disease state (that is, not progressed on second-line treatment), while OS data were used to determine the probability of death. Therefore, no transformation of clinical outcomes was required. For both OS and PFS, parametric functions were fitted to the actual trial event rates and used to extrapolate beyond the trial cut-off date.

#### Overall survival

Extrapolation of the TROPIC-derived survival curve using parametric distributions (exponential, Weibull, lognormal, loglogistic and Gompertz distributions) was performed and the goodness of fit tested, as described in Appendix 15, section 9.15. For the cabazitaxel arm, the Weibull distribution provided the best fit as evaluated by all three methods. For the mitoxantrone arm, the Weibull distribution provided a better fit than the other distributions, taking into account both the AIC and BIC criteria, and the graphical method fit to the tail of the survival curve. Parameters were estimated based on a timescale in months.

To estimate the probability of death in each cycle of the model, the following formula was used:

$$Prob(death) = 1 - exp(-\lambda t\sigma) / exp(-\lambda(t-1)\sigma)$$

where $t$ represents time and σ and λ represent the shape and scale parameters, respectively.

The actual Kaplan–Meier survival data are implemented in the model base-case. The Kaplan–Meier data cannot be used over the whole timeframe, however, as the follow-up time was limited. The Kaplan–Meier data for OS were used up to around two years post-baseline (111 weeks). Thereafter, the parametric Weibull survival curves were used to extrapolate the Kaplan–Meier data. Using parametric functions for the entire curve (that is, smoothed curves instead of trial data) is implemented as a scenario analysis.

#### Progression-free survival

The Lognormal distribution provided the best fit to PFS data for the mitoxantrone arm, whereas the Weibull distribution provided the best fit for the cabazitaxel arm. The Lognormal distribution was employed in the model base-case for the mitoxantrone PFS data, while the Weibull distribution can be chosen as a sensitivity analysis.

To estimate the probability of staying in the stable disease (SD) health state in each cycle of the model, the following formula was used:

$$SDstayProb = exp(-\lambda t\sigma)/\ exp(-\lambda(t-1)\sigma)$$

where *t* represents time and σ and λ represent the shape and scale parameters, respectively.

As with OS, the actual Kaplan–Meier survival data are implemented in the model base-case up until the time when the small number of patients makes the curve erratic and unreliable. Thereafter, the parametric functions are used to extrapolate the Kaplan–Meier data. Using parametric functions for the entire curve (that is, smoothed curves instead of trial data) is implemented as a scenario analysis.

### 6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, explain why it has been excluded

Probabilities for both progression and death are time-dependent. Incorporation of time-dependence is standard for survival modelling in oncology and is accounted for within the parametric functions used to determine the transition probabilities within the model.

### 6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Intermediate markers were not used, since PFS and OS were drawn directly from the trial.

### 6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

- **The criteria for selecting the experts**
- **The number of experts approached**
- **The number of experts who participated**
- **Declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought**
- **The background information provided and its consistency with the totality of the evidence provided in the submission**

[1] 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.

- **The method used to collect the opinions**
- **The medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **The questions asked**
- **Whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

As part of model development, an advisory board was held with four oncologists on 30 November 2009. Criteria for selection was that they specialised in prostate cancer, that they were UK-based (from different parts of the UK) and that they were 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. The estimates of resource use have now been largely superseded by a UK-based restrospective audit of five major cancer centres, which provides the resource use data used in the model (discussed below in section 6.5.4).

In terms of clinical inputs, input from experts was used to estimate the UK-specific value for the BSA to be 1.9 $m^2$ (applied in a sensitivity analysis). 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.

***Summary of selected values***

### 6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below

Table 6-2 shows key variables in the model for the base-case population. Median OS and PFS values are not used in the model but are included to provide aid understanding of overall efficacy in this population. It should be noted that mean OS and PFS inputs represent those from parametric functions fitted to the Kaplan-Meier data and implemented over the entire survival curve. However, in the model, the actual Kaplan–Meier survival data are implemented in the model base-case with extrapolation only used for the period in which Kaplan-Meier data are unreliable due to limitations in follow-up.

AEs are listed separately in Table 6-3. Due to the extensive costings in the model, these are outlined in detail in 6.5 and are not itemised here.

**Table 6-2. List of variables used in model, for base-case population (European patients with ECOG 0 -1 and received ≥225 mg docetaxel (as used in model base-case)**

| Variable | Mitoxantrone + prednisolone | | | Cabazitaxel + prednisolone | | | Comparison | | | Source | Section |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Number dead / N (%)** | **Median survival (95% C.I.)** | **Mean survival** | **Number dead /N (%)** | **Median survival (95% C.I.)** | **Mean survival** | **Hazard Ratio (HR)** | **Median differene** | **Mean difference** | | |
| **OS** | 117/159 (73.6%) | [redacted] | [redacted] | 109/181 (60.2%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | TROPIC; Weibull curves fit to K-M data to calculate mean | 6.3.2 |
| **PFS** | 156/ 159 (98.1%) | [redacted] | [redacted] | 177/ 181 (97.8%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | TROPIC; Parametric curves fit to K-M data to calculate mean (Weibull for cabazitaxel, lognormal for mitoxantrone) | 6.3.2 |
| Utility | Stable disease | [redacted] | | [redacted] | [redacted] | | - | | | Cabazitaxel EAP | 6.4.3 |
| | Progressive disease | [redacted] | | [redacted] | [redacted] | | - | | | Decrement from Sullivan 2007 applied to EAP SD value | 6.4.6, 6.4.9 |
| | Disutilities due to AEs | Various – detailed in section 6.4.3 | | Disutilities due to AEs | Various – detailed in section 6.4.3 | | - | | | Literature | 6.4.8 – 6.4.9 |
| Drug acquisition costs | | | | | | | | | | British National Formulary[72] | 6.5.6 |
| Other costs | | | | | | | | | | NHS Reference Costs, British National Formulary, PSSRU Unit Costs, published literature[50,72,73] | 6.5.6 |

**Table 6-3. AE rates (even/t patient) in TROPIC (European data from patients with ECOG 0 -1 and received ≥225 mg docetaxel (as used in model base-case)**

| AE (Grade ≥3) | AE rates | |
|---|---|---|
| | Mitoxantrone arm | Cabazitaxel arm |
| Neutropenia | [redacted] | [redacted] |
| Febrile neutropenia | [redacted] | [redacted] |
| Diarrhoea | [redacted] | [redacted] |
| Fatigue | [redacted] | [redacted] |
| Asthenia (weakness) | [redacted] | [redacted] |
| Leukopenia | [redacted] | [redacted] |
| Back pain | [redacted] | [redacted] |
| Anaemia | [redacted] | [redacted] |
| Thrombocytopenia | [redacted] | [redacted] |
| Pulmonary embolism | [redacted] | [redacted] |
| Dehydration | [redacted] | [redacted] |
| Nausea / vomiting | [redacted] | [redacted] |
| Bone pain | [redacted] | [redacted] |
| Deep vein thrombosis | [redacted] | [redacted] |
| Neuropathy | [redacted] | [redacted] |
| Key: AE = adverse event | | |

### 6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

For follow up beyond the trial duration, OS and PFS outcomes were extrapolated using survival curves, as described in Section 6.3.2. This is a common approach to survival modelling. Appendix 15 details the tests applied to test the goodness-of-fit of the survival curves, and presents the graphs of curve-fittings.

### 6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

**Table 6-2. Assumptions and justifications**

| 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 | Reflects clinical management of mHRPC patients in TROPIC and in the UK |

| Assumption | Justification |
|---|---|
| patients receiving BSC alone). | |
| 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 some/ all of these benefits. |
| Utility values do not change over time as long as the patient remains in the same health state. | Reflect available utility data (discussed further below) |

## 6.4 Measurement and valuation of health effects

### *Patient experience*

### 6.4.1 Outline the aspects of the condition that most affect patients' quality of life

Although early-stage disease may be asymptomatic, metastatic prostate cancer is associated with a range of symptoms that substantially affect QoL (Section 2.1). Symptoms include lymphoedema, weight loss, pain, and SREs associated with bone metastases.[21] Pain associated with bone metastases is considered one of the most important factors affecting QoL in mHRPC. The patient's QoL is also likely to be directly affected by various other factors, including fatigue and anxiety. Mitoxantrone is used and was licensed in the first-line setting principally for its palliative benefits, including its impact on pain,[69] illustrating the importance of effective symptom control in mHRPC.

In addition to the impact of the disease, AEs and general fatigue/ malaise associated with chemotherapy are also likely to affect QoL. However, the use of active chemotherapy 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.

### 6.4.2 Describe how a patient's HRQoL is likely to change over the course of the condition

There is limited published data available to describe HRQoL in mHRPC over time. The usual approach taken to modelling metastatic cancer is to assume lower QoL in the progressed disease state compared with the stable disease state and this is the approach taken here. However, in reality, this is unlikely to be a stepwise transition as it is likely that a number of factors will affect HRQoL, including presence of painful bone metastases, efficacy of pain control, receipt and type of chemotherapy, and disease history. Thus, there may be considerable variation between patients. Overall, however, it is expected that HRQoL would remain reasonably constant while patients are in the stable state and receiving regular chemotherapy, and that HRQoL would decrease towards the last months of life, when

patients have very advanced, progressing cancer. This is consistent with the modelling approach taken and is supported by the literature (described below in section 6.4.12).

### 6.4.3 HRQoL data derived from clinical trials

**If HRQoL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQoL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.**

- **Method of elicitation.**
- **Method of valuation.**
- **Point when measurements were made.**
- **Consistency with reference case.**
- **Appropriateness for cost-effectiveness analysis.**
- **Results with confidence intervals.**

No HRQoL data were collected in the TROPIC trial.

The EAP for cabazitaxel (CABAZ-C-05331) is evaluating utility in patients treated with cabazitaxel. The EAP is an open label, single-arm trial of cabazitaxel. It is recruiting globally but only the UK is collecting utility data.[74] As of 20 May 2011, nine UK sites were active, with a further three initiated. Seventy-seven patients have been consented, with 63 treated. An interim analysis based on a cut-off date of 29 April 2011 and including [redacted] was conducted for this submission (see Appendix 14 for more detail).

Utility is assessed via the EQ-5D questionnaire and via visual analogue scale (VAS) estimation. EQ-5D and VAS are administered at baseline, Day 1 of Cycle 2, Cycle 4, Cycle 6, Cycle 8, Cycle 10 and within 30 days of last treatment. Utility values were derived from these according to UK value sets.

The EAP provides utility data for UK patients treated with cabazitaxel and prospectively followed up, via the EQ-5D questionnaire. These data are therefore considered to be consistent with the reference case.

There are two key limitations to the EAP utility data. First, the EAP is non-comparative and, therefore, does not allow comparison of the QoL impact of cabazitaxel with that of mitoxantrone. It is therefore assumed in the model that patients experience the same utility regardless of the treatment administered, provided that they are in the same disease state. There are two ways in which this may not be the case: first, cabazitaxel results in a higher rate of AEs than mitoxantrone, and second, as a more active treatment, cabazitaxel may

have a greater effect on disease control. The potential for treatment to adversely affect utility is assumed to be fully accounted for through the incorporation of AE-related disutilities in the model. The effect of treatment on disease control is assumed to be accounted for through the impact of treatment on disease progression and probability of transitioning from stable to progressed state.

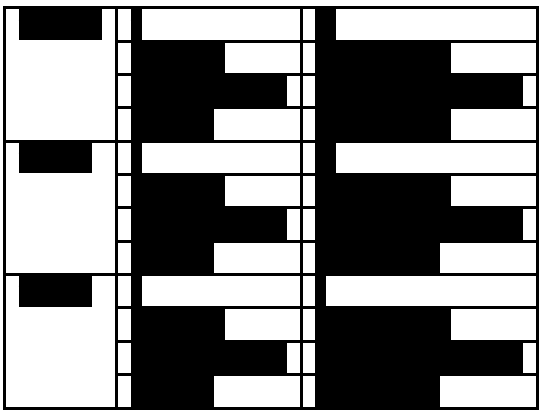
The second limitation is that the interim analysis presented here only has data available for the stable disease state. Only two patients had progressed at the interim analysis, and therefore the data for the progressed state is unreliable. For this reason, we have used the utility data for the stable disease state only, and then applied a decrement for moving from the stable to the progressed disease state based on the literature.

In August, a further interim analysis will be performed and the analysis/ report updated as appropriate.

**Results**

Results from the EAP are presented below. At baseline, patients had progressed following first-line treatment and had not yet received cabazitaxel; that is, they had progressive disease. The baseline value is similar to the baseline value for UK patients identified in the literature (see section 6.4.7). The results show that mean utility improves modestly from baseline to Cycle 2. This suggests that, at the very least, there is not a detrimental effect of cabazitaxel on utility, and that cabazitaxel may have a positive impact on utility through its effectiveness in stabilising the disease and controlling symptoms. This is consistent with anecdotal evidence from clinicians treating patients with cabazitaxel (see Appendix 17).

**Table 6-3. Utility results from EAP**



### 6.4.4 Mapping

**If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.**

- **Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.**
- **Details of the methodology used.**
- **Details of validation of the mapping technique.**

Mapping was not undertaken, because QoL data were not collected in the trial. Pain data were collected in TROPIC and it is possible to map pain data to utility. However, this approach would not capture the aspects of QoL driven by factors other than pain (for example, fatigue). Therefore, such an analysis is likely to show similar results to the 'raw' pain data from TROPIC; namely, no significant difference between cabazitaxel and mitoxantrone. For this reason, it was considered that this would not add significant evidence to the answer to the decision problem and it was, therefore, not conducted.

### HRQoL studies

### 6.4.5 Please provide a systematic search of HRQoL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

### Identification of studies

A range of databases indexing published research were searched for studies of the HRQoL of mHRPC. 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. An important consideration with such a search is managing the trade-off between the retrieval of large numbers of irrelevant records and the risk of missing relevant studies. However, even text word searching in the titles and abstracts of database records will not necessarily find relevant records if the utilities terms are not mentioned in the title or abstract. The databases searched included the NICE minimum required: MEDLINE, MEDLINE In-Process, EMBASE, EconLit and the NHS Economic Evaluation database (NHS EED). No date or language limits were applied. Full details of the search strategies, databases and resources searched are provided in section 9.12, Appendix 12.

Studies were considered relevant if they reported both:

- mHRPC having progressed after first-line docetaxel or metastatic prostate cancer during the last 12 months of life
- EQ-5D measures of HRQoL.

In total, the search identified 59 reports that required full document review to ascertain whether they met the inclusion criteria. Of these, 57 reports were rejected for inclusion for the following reasons:

- Five were commentaries and did not provide HRQoL data
- Twenty-three were about early or locally advanced prostate cancer
- Twenty-nine did not provide EQ-5D data.

### 6.4.6 Details of the studies in which HRQoL is measured.

Two studies were identified which met the inclusion criteria: Sandblom (2004) and Sullivan (2007).[76,77] Table 6-4 and Table 6-5 provide a summary of the information from these papers.

**Table 6-4. Study details, population in which health effects were measured and utility details from Sandblom *et al*[76]**

| **Study details** | |
|---|---|
| Study | Sandblom G, Carlsson P, Sennfalt K, Varenhorst E. A population-based study of pain and quality of life during the year before death in men with prostate cancer**.** *British Journal of Cancer* 2004; **90:** 1163–1168. |
| Interventions and comparators | The study was non-interventional and focused on measuring how pain and QoL changed for men during their last year of life with prostate cancer. The treatment of patients in the cohort was described, with the majority treated with watchful waiting or treatment with palliative intent. Analysis by specific treatment was not provided. |
| Study design | An HRQoL, pain and demographic questionnaire distributed to men with prostate cancer in Sweden with the goal of determining how HRQoL changes towards the end of life. |
| **Population in which health effects were measured** | |
| Country | Sweden. |
| Recruitment | All men with prostate cancer identified from National Tumour Register cross-referenced with National Population Register. Men had to be aged under 100 and diagnosed fewer than 30 years ago. All men identified were sent a letter explaining the study and an HRQoL questionnaire. |
| Sample size | 1,442 (166 died within 12 months). |
| Response rates | 86%. |
| Mean age | 80 (of those who died in 12 months) |
| Disease stage | While the disease stage at diagnosis was recorded (including whether it was metastatic) for each patient in the study, a breakdown of the study sample by stage of disease was not provided. In the analysis, the impact of tumour stage at diagnosis (either 'localised' or 'advanced') on EQ-5D scores was analysed. |
| Severity of prostate cancer | Analysis by advanced or localised cancer. |

| | |
|---|---|
| Appropriateness of health states given condition and treatment pathway | As focus was on death within 12 months, QoL measured within 12 months before death is relevant. |
| Method of elicitation | Patients completed a preference-based questionnaire. |
| Method of valuation | EQ-5D index. |
| Perspective of utility states | Patient. |
| High anchor detail | Not provided, but as EQ-5D was used it may be assumed to be one year in perfect health. |
| Utility values reported | EQ-5D scores were reported at the time the questionnaire was completed. Scores were separated out in a graph by those men who died 0–4 months, 4–8 months, 8–12 months and 12–16 months after completion of the questionnaire. A table provides EQ-5D for responders who died within 12 months of completing the questionnaire die to prostate cancer or other causes. |
| Mapping | Not undertaken. |
| Uncertainty around values | Not relevant. |
| Consistency with reference case | Not relevant. |
| Appropriateness for cost-effectiveness analysis | Not relevant. |
| Results with confidence intervals | EQ-5D are mean scores at the start of the study for patients who died within 12 months.<br>For the 66 patients who died of prostate cancer: EQ-5D score: 0.538 ± 0.077<br>For the 100 patients who died of other causes:<br>EQ-5D score: 0.564 ± ± 0.067<br>Graphs are provided for EQ-5D and VAS data and show relatively constant utility up to the last 8 months of life, with a drop of approximately 0.03 on moving into the last 8 months, and a drop of approximately 0.14 on moving from the last 8 to the last 4 months before death. |
| Appropriateness of the study for cost-effectiveness analysis | Although a useful study, it is challenging to translate into use in a cost-effectiveness analysis. The study is not specific to mHRPC and it also does not provide utility for states analogous to 'stable' and 'progressed', which is what is required for modelling purposes. In addition, the study reports that for the majority of patients included, the treatment approach was watchful waiting or treatment with palliative intent. Utility estimated from such a patient group receiving such a treatment approach is not directly applicable to patients suitable for and receiving active treatment with cabazitaxel or mitoxantrone.<br>The graphs showing utility over time are broadly supportive of the utility changes in the model, as they show a decreased utility in the last 8 months of life, which would generally correspond to the time spent in the progressed state in the model. The utility decrement shown is applied as the decrement between stable and progressive disease in a sensitivity analysis on the model. |

**Table 6-5. Study details, population in which health effects were measured and utility details from Sullivan *et al*[77]**

| **Study details** | |
|---|---|
| Study | Sullivan PW, Mulani PM, Fishman M, Sleep D. Quality of life findings from a multicenter, multinational, observational study of patients with metastatic hormone-refractory prostate cancer. *Quality of Life Research* 2007; **16:** 571–575. |
| Interventions and comparators | The study was non-interventional. However, results were |

| | |
|---|---|
| | discussed in terms of treatment arm. |
| Study design | Observational, multicentre (37 sites), multinational (7 countries) prospective cohort study. Several HRQL questionnaires were issued to men with mHRPC at diagnosis and 3, 6 and 9 months after diagnosis. The purpose was to explore how QoL of patients with mHRPC deteriorated over time. |
| **Population in which health effects were measured.** | |
| Country | Australia, Canada, France, Germany, Italy, UK and USA. |
| Recruitment | Not reported in detail. Men had to be aged over 19 years with a diagnosis of symptomatic M1 mHRPC by TNM staging criteria. |
| Sample size | 280. |
| Response rates | 56% completed to nine months. 30% died before nine months. |
| Mean age | 72 (total); 73 (UK). |
| Disease stage | Symptomatic M1 mHRPC diagnosed by TNM staging criteria. |
| Severity of prostate cancer | Advanced. |
| Appropriateness of health states given condition and treatment pathway | Health states are not explicit states, but the study reports changes over time. |
| Method of elicitation | Preference-based questionnaire but it is not clear whether patients or clinicians completed it. |
| Method of valuation | EQ-5D. |
| Perspective of utility states | Patient. |
| High anchor detail | Not provided, but as EQ-5D was used it is assumed to be one year in perfect health. |
| Utility values reported | EQ-5D scores at the time the questionnaire completed and 3, 6 and 9 months after first completion. EQ-5D baseline scores are provided in a table but scores at 3, 6 and 9 months are only provided as a graph of change from baseline. |
| Mapping | Not undertaken. |
| Uncertainty around values | Not relevant. |
| Consistency with reference case | Not relevant. |
| Appropriateness for cost-effectiveness analysis | Not relevant. |
| Results with confidence intervals | Mean EQ-5D score at baseline (confidence intervals not reported):<br>All countries: 0.635<br>UK: 0.715<br><br>Graphically, it is shown that there is a decrement of approximately 0.07 in the EQ-5D between baseline and measurements at 3 months, 6 months and 9 months. This was taken as an average because the values at 3, 6 and 9 months are similar and because the graph shows a smaller decrement at 6 months compared with the 3-month and 9-month timepoints, which is assumed to be a measurement artefact. |

| | |
|---|---|
| Appropriateness of the study for cost-effectiveness analysis | The study includes mHRPC patients and provides data specifically for UK patients.<br>The study provides utility data for baseline and for 3, 6 and 9 months after baseline. There was no requirement for patients to have stable disease at baseline and therefore the baseline value is likely to represent patients with both stable and progressive disease. The study provides information on the average utility decrement from baseline to 3, 6 and 9 months. Based on the PFS duration from TROPIC (1.8 and 2.4 months for mitoxantrone and cabazitaxel respectively), it is assumed most patients would have progressed by these timepoints, and that the decrement in the study is due to disease progression. Therefore the average decrement from baseline to these timepoints is used in the model to represent the decrease in utility on moving from the stable to progressive disease states. |

### 6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The [redacted] is similar to the baseline value identified in the Sullivan 2007 study for UK patients (0.715).

Only the EAP provides data for 'true' stable disease; that is, for patients whose disease is currently controlled by treatment. Thus, it is difficult to compare to the values identified in the literature. The EAP is thus considered to be the best data source for estimating the utility of patients whose disease is stable and who are receiving active treatment. It is also the only source of utility data in the specific cabazitaxel target population.

It is challenging to accurately estimate utility in the progressive disease state. More mature data from the EAP are likely to be the best source of information. In the absence of these data, we have used information from the literature. Sullivan 2007 provides an estimate of the utility decrement at 3, 6 and 9 months from baseline (with similar values shown for all of the post-baseline timepoints) in men with mHRPC.[77] We assume that this is due to disease progression from baseline and, therefore, use this decrement in the cost-effectiveness analysis base case as the decrement on moving from stable to progressed disease.

The Sandblom study provides an estimate of utility at 16–12, 12–8, 8–4, and in the last four months before death, in men with prostate cancer (not specifically mHRPC).[76] Utility is relatively constant up till eight months before death, after which it decreases. As a sensitivity analysis, we apply a decrement calculated from the decrease in utility observed between 16 and eight months before death and in the last eight months before death, as these time periods correspond roughly to the time periods spent in stable and progressed disease as measured in TROPIC and used in the model.

### 6.4.8 Describe how adverse events have an impact on HRQoL

AEs will impact on HRQoL and, as discussed in section 5.9, cabazitaxel has a higher AE rate than mitoxantrone. Therefore, it is important to account for the disutility associated with AEs. The disutility value associated with experiencing an AE presented in the model was found in secondary literature,[78-84] in the absence of utility data from TROPIC. 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 Section 6.4.9.

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.[78] 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*[82] and Treasure *et al*[83] and the disutility of deep vein thrombosis was taken from Gould *et al*.[82]

The disutility associated with febrile neutropenia, fatigue and nausea/vomiting were averages of disutilities retrieved from the studies by Nafees *et al*[78] and Lloyd *et al*.[79] 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*.[81]

The disutility values associated with anaemia were taken from a study of standard gamble interviews in members of the general public.[80] 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.[84]

### 6.4.9 Quality of life data used in cost-effectiveness analysis

**Summarise the values chosen for cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.**

**Table 6-6. Cost-effectiveness analysis**

| State | Utility value | Confidence interval | Reference in submission | Justification |
|---|---|---|---|---|
| Stable disease | [redacted] | [redacted] | [redacted] | The EAP is the only data source to provide data for patients with true stable disease (ie disease controlled by treatment); furthermore, it is specific to UK patients on cabazitaxel. It is therefore judged to be the most appropriate data source |
| Progressive disease | [redacted] | Not available | Sullivan *et al* (2007)[77] Sandblom *et al* (2004)[76] | No sources provide data specifically for utility in progressive disease. As described in section 6.4.7, Sullivan 2007 provides an estimate of the utility decrement at various timepoints from baseline in men with mHRPC. We assume that this decrement is due to disease progression from baseline and apply this as the decrement on moving from stable to progressed disease. This decrement is estimated from the graph as 0.070, [redacted]<br><br>In a sensitivity analysis we apply a decrement estimated from Sandblom 2004. This study shows a decline in utility between the period 16–8 months before death and the 8 months immediately before death. This decrease was estimated as 0.085, based on an average of the utility estimated from the graph for the two time periods within the last 8 months. [redacted] |
| Dead | 0.000 | | Assumption | Standard approach |
| Neutropenia | -0.090 | Not available | Nafees *et al* (2008)[78] | Only available evidence |
| Febrile neutropenia | -0.120 | Not available | Lloyd *et al* (2006) and Nafees *et al* (2008)[78,79] | Average of the two available studies. |
| Diarrhoea | -0.047 | Not available | Nafees *et al* (2008)[78] | Only available evidence |
| Fatigue | -0.094 | Not available | Lloyd *et al* (2006) and Nafees *et al* (2008)[78,79] | Average of the two available studies |
| Asthenia (weakness) | -0.094 | Not available | Assumption | No data available – assumed to be equal to fatigue |
| Leucopenia | -0.090 | Not available | Assumption | No specific data available – assumed to be equal to neutropenia |
| Back pain | -0.069 | Not available | Doyle *et al* (2008)[81] | Only available evidence |
| Anaemia | -0.125 | Not available | Lloyd *et al* (2008)[80] | Only available evidence |

| State | Utility value | Confidence interval | Reference in submission | Justification |
|---|---|---|---|---|
| Thrombocytopenia | -0.090 | Not available | Assumption | No specific data available – assumed to be equal to neutropenia |
| Pulmonary embolism | -0.145 | Not available | Gould *et al* (1999) and Treasure *et al* (2009)[82,83] | Average of the two available studies |
| Dehydration | -0.151 | Not available | Lloyd *et al* (2006)[79] | Based on clinical expert opinion that stomatitis cases are often filed under dehydration |
| Nausea/vomiting | -0.076 | Not available | Lloyd *et al* (2006) and Nafees *et al* (2008)[78,79] | Average of the two available studies |
| Bone pain | -0.069 | Not available | Doyle *et al* (2008)[81] | Only available evidence |
| Deep vein thrombosis | -0.160 | Not available | Gould *et al* (1999)[82] | Only available evidence |
| Neuropathy | -0.116 | Not available | Lewis *et al* (2010)[84] | Only available evidence |

### 6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[2]:

- **The criteria for selecting the experts**
- **The number of experts approached**
- **The number of experts who participated**
- **Declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought**
- **The background information provided and its consistency with the totality of the evidence provided in the submission**
- **The method used to collect the opinions**
- **The medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **The questions asked**
- **Whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

Not applicable.

### 6.4.11 Define what a patient experiences in the health states in terms of HRQoL. Is it constant or does it cover potential variances?

In the model, we assume HRQoL is constant within the same health state, except when disutilities due to AEs are incurred.

Clinically, it is likely that this pattern will be seen in the stable disease state; when patients have disease controlled by treatment, it is likely their utility will stay relatively constant except if treatment-related AEs occur. Progressive disease will lead to decreased utility due to the worsening symptoms of the disease. 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, this assumption in the model may underestimate the health benefits of both treatments. However, given the available data, it was not possible to identify an alternative way of modeling this.

[2] 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.

### 6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No health effects identified in the literature or clinical trials were excluded from the model.

### 6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

No, QoL was assigned specifically to each health state.

### 6.4.14 Please clarify whether HRQoL is assumed to be constant over time. If not, provide details of how HRQoL changes with time.

HRQoL was assumed to be constant *within each health state*. The utility value for the stable disease state [redacted] is applied throughout the duration for which patients are in the stable disease state. Then, the utility on progression is calculated by applying the 0.070 decrement estimated from the Sullivan 2007 paper, to give a utility for the progressed state of [redacted] This is constant throughout the progressed disease state. Then, because patients progress through the health states, the *average* HRQoL will worsen over time. In addition, within each health state, there is some variation in HRQoL, due to disutilities due to 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.

### 6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

In the case of disutilities where more than one study providing disutility data was found, values from the studies were averaged, as described in section 6.4.7.

## 6.5 Resource identification, measurement and valuation

### 6.5.1 NHS costs

**Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.**

At present, as described in section 2.1, there is no standard of care recommended in clinical guidelines in the UK or elsewhere for mHRPC patients who have progressed after treatment with docetaxel. As there is no gold standard treatment for second-line mHRPC in the UK, clinical management is accepted to be multimodal rather than sequential and patients can receive a combination of palliative treatments.[6]

### 6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Because the treatment is likely to have a number of consequences on the resource use of patients, it is appropriate to consider NHS reference costs in this analysis.

### 6.5.3 Resource identification, measurement and valuation studies

**Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:**

- **Country of study**
- **Date of study**
- **Applicability to uk clinical practice**
- **Cost valuations used in study**
- **Costs for use in economic analysis**
- **Technology costs.**

There are limited published data available on resource use in second-line mHRPC, as indicated by initial scoping searches. Therefore, rather than undertaking an exhaustive literature review, 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 mHRPC on or after 1 June 2007 and for whom

records were available. [redacted] 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, section 9.14.

It is considered that these data are the most robust source available for resource use information for second-line mHRPC in UK clinical practice. Costings from standard sources (such as NHS reference costs, *BNF* drug costs) were applied to these resource use estimates in the model.

**NB: In this document we refer to this project as an audit, as this is a simpler description and more intuitively understandable. However, it is more correctly referred to as a series of 5 service evaluations.**

### 6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- **The criteria for selecting the experts**
- **The number of experts approached**
- **The number of experts who participated**
- **Declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought**
- **The background information provided and its consistency with the totality of the evidence provided in the submission**
- **The method used to collect the opinions**
- **The medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **The questions asked**
- **Whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

As described above, an advisory board was held with four oncologists on 30 November 2009. This sought input on UK-specific resource use data. The estimates of resource use have now been largely superseded by a UK-based restrospective audit of five major cancer centres, which provides the resource use data used in the model. However, some data were not available from the audit study and so clinician estimates are still used for the rates of use of liver function test, PSA test and ECG, and the rates of secondary G-CSF prophylaxis. In

[3] 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.

addition, clinicians made estimates around palliative care requirements in the last month of life. This was necessary as the audit was based on hospital records and did not estimate accurately palliative care received elsewhere (e.g. in a hospice), although data on inpatient hospitalisations occurring in the last month of life were available from the audit and were used.

### 6.5.5 Intervention and comparators' cost

**Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.**

**Table 6-7. Unit costs associated with the technology in the economic model**

| Items | Cabazitaxel | Ref. in submission | Mitoxantrone | Ref. in submission |
|---|---|---|---|---|
| Drug cost (unit) | £3,696 per vial | 1.10 | £100 per vial | 1.10 |
| Mean cost of technology treatment | £3,696 per cycle | 6.5.6 | £187.14 per cycle | 6.5.6 |
| Administration cost | £285.95 per cycle | 6.5.6 | £285.95 per cycle | 6.5.6 |
| Premedications | £88.58 per cycle | 6.5.6 | £36.53 per cycle | 6.5.6 |
| Concomitant medications | £75.61 per cycle | 6.5.6 | £75.61 per cycle | 6.5.6 |
| Adverse event management costs (total) | £487 (total) | 6.5.7 | £178 (total) | 6.5.7 |
| Additional costs (tests, hospitalisations) | per cycle | 6.5.6 | per cycle | 6.5.6 |
| Progressive disease : active treatment | per cycle | 6.5.6 | per cycle | 6.5.6 |
| Progressive disease: BSC treatment cost | per cycle | 6.5.6 | per cycle | 6.5.6 |
| Progressive disease: additional costs (tests, hospitalisations etc) | per cycle | 6.5.6 | per cycle | 6.5.6 |
| End of life costs (per month) | per cycle | 6.5.6 | per cycle | 6.5.6 |

### 6.5.6 Health state cost

**Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.**

**Stable disease state**

Costs in the stable disease state comprise acquisition costs for active treatment, acquisition costs for premedications 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 6-8, and unit costs in Table 6-9. Adverse event costs are summarised separately in section 6.5.8.

Drug acquisition costs were sourced from the *BNF;*[72] the cost of cabazitaxel was supplied by the manufacturer. The base case assumes no vial sharing; that is, some element of wastage occurs for cabazitaxel and mitoxantrone. This is explored in a sensitivity analysis. It is assumed no cabazitaxel patients would require more than one vial. However, with mitoxantrone, it is likely some patients will require more than one vial; the cost is therefore adjusted for this. For mitoxantrone in this analysis, and in the sensitivity analysis based on vial sharing, dose is adjusted according to the mean dose intensity received in TROPIC ([redacted] for cabazitaxel and mitoxantrone respectively).

Assumptions around pre- and concomitant medications are summarised in Table 6-8 below. The most complex is G-CSF prophylaxis, which is discussed separately below the tables.

In the stable disease state, costs for active treatment, premedications 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.

**Table 6-8. 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 | 1 vial of 60 mg per 3 weekly cycle plus daily 10 mg prednisolone | Based on dose of 25 mg/m$^2$, BSA of 2.01m$^2$ as in TROPIC, and assumption of no vial-sharing |
| Comparator: mitoxantrone | 1 or 2 vials of 20 mg plus daily 10 mg prednisolone | Based on dose of 12 mg/m$^2$, BSA of 2.01m$^2$ as in TROPIC, and assumption of no vial sharing |
| Premedications – cabazitaxel arm | 100% patients receive premedication with antihistamine, H2-antagonist, anti-emetic, and corticosteroid once per 3-week cycle<br>25% patients receive primary prophylaxis with G-CSF per cycle | Mandated premedication regimen<br>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%), H2 antagonist (25%), anti-emetics (100%), corticosteroids (56%), G-CSF as primary prophylaxis (10%) per cycle. | Data from TROPIC for treatments received<br>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) |
| Resource use general to both arms | | |
| 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 |
| Outpatient care: visits to clinical oncologist | [redacted] | UK treatment audit |
| Outpatient care: visits to urologist | [redacted] | UK treatment audit |
| Inpatient care: oncology ward | [redacted] | UK treatment audit |
| Inpatient care: general ward | [redacted] | UK treatment audit |
| Imaging: CT scan | [redacted] | UK treatment audit |
| Imaging: MRI | [redacted] | UK treatment audit |
| Imaging: bone scan | [redacted] | UK treatment audit |
| Imaging: ultrasound | [redacted] | UK treatment audit |
| Imaging: X-ray | [redacted] | UK treatment audit |
| Lab tests: complete blood count | [redacted] | UK treatment audit |
| Chemistry panel | [redacted] | UK treatment audit |
| Liver function test | [redacted] | UK treatment audit |
| PSA | [redacted] | UK treatment audit |
| ECG | [redacted] | UK treatment audit |
| Echocardiogram | [redacted] | UK treatment audit |

**Table 6-9. 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) – *BNF*[72] |
| Cabazitaxel | £61.60 | Mg | Cost per 60 mg vial: £3696.00 |
| Premedication | | | |
| Antihistamines | 0.18 | Mg | Based on cost for chlorphenamine - *BNF*[72] |
| $H_2$ inhibitors | 0.01 | Mg | Based on cost for ranitidine – *BNF*[72] |
| Anti-emetics | 0.62 | Mg | Based on cost for ondansetron – *BNF*[72] |
| Corticosteroids | 0.07 | Mg | Based on cost for dexamethasone – *BNF*[72] |
| G-CSF | 195.20 | Mg | Based on cost for filgrastim - *BNF*[72] |
| Concomitant medication | | | |
| Prednisolone | 0.01 | Mg | *BNF*[72] |
| Goserelin | 16.25 | Mg | *BNF*[72] (based on price of Novgos) |
| Leuprorelin | 20.06 | Mg | *BNF*[72] (basedon price of Prostap) |
| Chemotherapy administration | | | |
| Chemotherapy administration | 285 | Per administration | National Schedule of Reference Costs (2009–10) – NHS Trusts HRG data - Deliver subsequent elements of a Chemotherapy cycle SB15Z[50] |
| Pharmacist time | 28 | Per administration | PSSRU (2010), Hospital pharmacist, Table 13.6, Cost per hour[73] |
| Supportive care costs | | | |
| Outpatient care: visits to clinical oncologist | 129 | Per visit | National Schedule of Reference Costs (2009–10) – NHS Trusts Consultant Led: Follow Up Attendance Non-Admitted Face to Face[50]<br>370: Medical Oncology |
| Outpatient care: visits to urologist | 88 | Per visit | National Schedule of Reference Costs (2009–10) – NHS Trusts Consultant Led: Follow Up Attendance Non-Admitted Face to Face[50]<br>101: Urology |
| Inpatient care: oncology ward | 359 | Per 24 h | National Schedule of Reference Costs (2009–10) – NHS Trusts Non-Elective Inpatient (Short Stay) HRG Data – average of LB06D, E, and G; hospitalisation for kidney, urinary tract and prostate neoplasms |
| Inpatient care: general ward | 359 | Per 24 h | National Schedule of Reference Costs (2009–10) – NHS Trusts Non-Elective Inpatient (Short Stay) HRG Data – average of LB06D, E, and G; hospitalisation for kidney, urinary tract and prostate neoplasms |
| Imaging: CT scan | 112 | Per scan | National Schedule of Reference Costs (2009–2010) – NHS Trusts Diagnostic Imaging: Outpatient[50]<br>RA10Z: Computerised Tomography Scan, one area, pre and post contrast |
| Imaging: MRI | 239 | Per scan | National Schedule of Reference Costs (2009–2010) – NHS Trusts Diagnostic Imaging: Outpatient[50]<br>RA03Z: Magnetic Resonance Imaging Scan, one area, pre and post contrast |
| Imaging: bone scan | 180 | Per scan | National Schedule of Reference Costs (2009–2010) – NHS Trusts Diagnostic Imaging: Outpatient[50]<br>RA36Z: Nuclear Medicine - category 2 |

| | | | |
|---|---|---|---|
| Imaging: ultrasound | 63 | Per scan | National Schedule of Reference Costs (2009–2010) – NHS Trusts Diagnostic Imaging: Outpatient[50]<br>Mean of:<br>RA23Z: Ultrasound Scan less than 20 minutes<br>RA24Z: Ultrasound Scan more than 20 minutes |
| Imaging: X-ray | 180 | Per scan | National Schedule of Reference Costs (2009–2010) – NHS Trusts Diagnostic Imaging: Outpatient[50]<br>RA36Z: Nuclear Medicine - category 2 |
| Lab tests: complete blood count | 3 | Per test | National Schedule of Reference Costs (2009–10) – NHS Trusts Direct Access: Pathology Services[50]<br>DAP823: Haematology [Excluding Anti-Coagulant Services] |
| Chemistry panel | 1 | Per test | National Schedule of Reference Costs (2009–10) – NHS Trusts Direct Access: Pathology Services[50]<br>DAP841: Biochemistry |
| Liver function test | 5 | Per test | National Schedule of Reference Costs (2009–10) – NHS Trusts Direct Access: Pathology Services[50]<br>DAP841: Biochemistry<br>Multiplied by number of tests required = 5 |
| PSA | 1 | Per test | National Schedule of Reference Costs (2009–10) – NHS Trusts Direct Access: Pathology Services[50]<br>DAP841: Biochemistry |
| ECG | 32 | Per test | National Schedule of Reference Costs (2009–10) – NHS Trusts Direct Access: Pathology Services[50]<br>DA13: Electrocardiogram |
| Echocardiogram | 78 | Per test | National Schedule of Reference Costs (2009–10) – NHS Trusts Diagnostic Imaging: Direct Access: RA60Z[50] |

**G-CSF prophylaxis**

The model reflects the ASCO guidelines on G-CSF prophylactic treatment, which were implemented in the TROPIC trial.[47] These guidelines are internationally accepted and are also recommended for use in the UK.[85-88] In the base-case scenario, 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. [redacted]. 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 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 (Vogel *et al*).[89] 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.*[89] 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.

Although the ASCO guidelines advise that secondary prophylaxis is only recommended for patients who did not receive it as primary prophylaxis,[47] 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 because the UK clinical expert panel estimated the proportion of patients receiving G-CSF as secondary prophylaxis irrespective of any known proportions of primary prophylaxis, and this was not possible to implement in the model retrospectively. This implies that the proportion of patients receiving G-CSF as secondary prophylaxis may be overestimated in the model, but this can be regarded as a conservative assumption.

**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 6-12 and unit costs for items not already covered within the stable disease state are shown in Table 6-13.

**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 [redacted] 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. 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 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 6-10 represent the proportion of patients in each arm receiving the respective types of chemotherapeutic agents post-second-line.

**Table 6-10. Frequency of post-second-line chemo for the base-case population**

| Treatment | Frequency | |
|---|---|---|
| | **Cabazitaxel (n=142)** | **Mitoxantrone (n=142)** |
| Carboplatin | [redacted] | [redacted] |
| Cyclophosphamide | [redacted] | [redacted] |
| Docetaxel | [redacted] | [redacted] |
| Estramustine | [redacted] | [redacted] |
| Etoposide | [redacted] | [redacted] |
| Mitoxantrone | [redacted] | [redacted] |
| Paclitaxel | [redacted] | [redacted] |
| Vinorelbine | [redacted] | [redacted] |
| Cisplatin | [redacted] | [redacted] |
| Gemcitabine | [redacted] | [redacted] |

The UK-specific post-second-line treatment mix is presented in Table 6-11. It should be noted that carboplatin was used in a mixture of regimens, with no one regimen used in more than one patient.

**Table 6-11. The treatments that constitute the UK-specific post-second-line treatment mix[42]**

| Treatment | Frequency (n) | Source |
|---|---|---|
| | Mitoxantrone and cabazitaxel arm | |
| Docetaxel | [redacted] | [redacted] |
| Mitoxantrone | [redacted] | [redacted] |
| Carboplatin-based regimens | [redacted] | [redacted] |

### 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 mHRPC. 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 audit.[42] 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.

[redacted]

[redacted]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.

**Table 6-12. Resource use estimates for progressive disease state[42]**

| Resource use item | Resource use estimate per 3 weekly cycle | Source/justification |
|---|---|---|
| Post-second-line chemotherapy mix | As detailed in Table 6-10 and Table 6-11 | TROPIC and UK audit |
| BSC treatment: analgesics | [redacted] – assumed 50-50 split between diclofenac and co-codamol | UK treatment audit |
| BSC treatment: palliative radiotherapy | [redacted] – assumed 50-50 split between strontium-89 and external beam radiotherapy | UK treatment audit |
| BSC treatment: corticosteroids | [redacted] – assumed 50-50 split between prednisolone and dexamethasone | UK treatment audit |
| BSC treatment: bisphosphonates | [redacted] – assumed all patients receive zoledronate | UK treatment audit |
| 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 |
| Outpatient care: visits to clinical oncologist | [redacted] | UK treatment audit |
| Outpatient care: visits to urologist | [redacted] | UK treatment audit |
| Inpatient care: oncology ward | [redacted] | UK treatment audit |
| Inpatient care: general ward | [redacted] | UK treatment audit |
| Inpatient care: urology ward | [redacted] | UK treatment audit |
| Imaging: CT scan | [redacted] | UK treatment audit |
| Imaging: MRI | [redacted] | UK treatment audit |
| Imaging: bone scan | [redacted] | UK treatment audit |
| Imaging: ultrasound | [redacted] | UK treatment audit |
| Imaging: X-ray | [redacted] | UK treatment audit |
| Lab tests: complete blood count | [redacted] | UK treatment audit |

| | | |
|---|---|---|
| Chemistry panel | [redacted] | UK treatment audit |
| Liver function test | [redacted] | UK treatment audit |
| PSA | [redacted] | UK treatment audit |
| ECG | [redacted] | UK treatment audit |
| Echocardiogram | [redacted] | UK treatment audit |
| **End-of-life resource use** | | |
| Hospice care | Required by 20% patients, average 2 stays per month, average length of stay 5 days | Expert estimate |
| Palliative care at home | Required by 50% of patients, 6 visits per month, 80% nurse, 20% GP | Expert estimate |
| Palliative outpatient visits | Required by 50% patients, average of 0.8 visits per month | Expert estimate |
| Palliative inpatient stays | [redacted] | UK treatment audit |

**Table 6-13. Unit costs for progressive disease cost items**

| Cost | Cost/unit | Unit | Comment |
|---|---|---|---|
| **BSC** | | | |
| Analgesics – co-codamol | 0.04 | Tablet | Cost per tablet 30/500 – *BNF*[72] |
| Analgesics – diclofenac | 0.0003 | Tablet | Cost per tablet – *BNF*[72] |
| Strontium-89 | 97 | Dose | Per dose<br>NHS National Schedule of Reference Costs 2009-2010[50]<br><br>NHS Trusts Radiotherapy Treatment: Outpatient<br>SC29Z: Other Radiotherapy Treatment |
| External beam radiation | 112 | Fraction | Per fraction<br>NHS National Schedule of Reference Costs 2009-2010[50]<br><br>NHS Trusts Radiotherapy Treatment: Outpatient<br>SC22Z: Deliver a fraction of treatment on a megavoltage machine |
| Bisphosphonate – zoledronic acid | 45.83 | mg | *BNF*[72] |
| **Post-second-line chemotherapy mix drugs** | | | |
| Etoposide | 0.12 | mg | *BNF*[72] |
| Estramustine | 1.71 | Tablet | *BNF*[72] |
| Cyclophosphamide | 0.01 | mg | *BNF*[72] |
| Paclitaxel | 2.23 | mg | *BNF*[72] |
| Vinorelbine (tartrate) | 2.90 | mg | *BNF*[72] |
| Carboplatin | 0.44 | mg | *BNF*[72] |
| Cisplatin | 0.59 | mg | *BNF*[72] |
| Gemcitabine | 0.16 | mg | *BNF*[72] |
| Docetaxel | 6.68 | mg | *BNF*[72] |
| **Palliative care** | | | |

| | | | |
|---|---|---|---|
| Palliative homecare (nurse) | 27 | Per home visit | PSSRU 2010, Cost of Community Nurse per home visit[73] |
| Palliative homecare (GP) | 120 | Per home visit | PSSRU (2010), Cost of GP per home visit lasting 23.4 minutes including travel time[73] |
| Palliative hospital outpatients visits | 254 | Per visit | National Schedule of Reference Costs (2009–10) – NHS Trusts Specialist Palliative Care: Outpatient[50] SD04A: Medical Specialist Palliative Care Attendance 19 years and over |
| Hospital inpatient | 359 | Per 24 h | National Schedule of Reference Costs (2009–10) – NHS Trusts Non-Elective Inpatient (Short Stay) HRG Data – average of LB06D, E, and G; hospitalisation for kidney, urinary tract and prostate neoplasms |

### 6.5.7 Adverse event cost

**Summarise the costs for each adverse event listed in section 5.9 including the cost of therapies identified in 2.7. Cross ref and provide rationale for the choice of values used in CE model.**

Costs for drugs used to treat AEs were retrieved from the *BNF* (see Table 6-14 below).[72] 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 6-14.[50]

**Table 6-14. Cost for drugs used to treat AEs**

| AE treatment drug | Cost/unit | Unit | Comment |
|---|---|---|---|
| Gentamicin | £0.04 | Mg | |
| Teicoplanin | £0.02 | Mg | |
| Imodium | £0.02 | Mg | |
| Blood transfusion | £136 | Unit | Per unit |
| Platelet transfusion | £225 | Pool | Per pool |
| Intravenous drip | £60 | Day | Per day |
| Warfarin | £0.03 | Mg | |
| Domperidone | £0.0019 | Mg | |
| Metoclopramide | £0.004 | Mg | |
| Cyclizine | £0.001 | Mg | |
| Amitryptiline | £0.004 | Mg | |

**Table 6-15. Costs of adverse events**

| Reason for hospitalisation | Unit cost (per 24 h) | Average length of stay (days) | HRG currency code |
|---|---|---|---|
| Neutropenia | £471 | 4.65 | SA08F |
| Febrile neutropenia | £772 | 5.40 | PA45Z |
| Diarrhoea | £363 | 4.32 | Average: FZ43A, B, C |
| Fatigue | £461 | 1.61 | Average: AA31Z, DZ38Z |
| Asthenia (weakness) | £461 | 1.61 | Average: AA31Z, DZ38Z |
| Leucopenia | £471 | 4.65 | SA08F |
| Back pain | £401 | 9.55 | Average: HD36A, B, C |
| Anaemia | £452 | 6.46 | Average: SA04C, E, F |
| Thrombocytopenia | £549 | 5.88 | Average: SA12D, F |
| Pulmonary embolism | £437 | 6.32 | Average: DZ09A, B, C |
| Dehydration | £404 | 7.37 | Average: KC02A, B, C |
| Nausea / vomiting | £363 | 4.32 | Average: FZ43A, B, C |
| Bone pain | £401 | 9.55 | Average: HD36A, B, C |
| Deep vein thrombosis | £387 | 4.65 | EB11Z |
| Neuropathy | £521 | 2.77 | PA01B |

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 (see Table 6-16 below). The average length of stay for each hospitalisation episode was based on HRG data, using appropriate currency codes.[50]

**Table 6-16. Hospitalisation rates by severe adverse event**

| Severe adverse event (Grade ≥3) | Rate of hospitalisation |
|---|---|
| Neutropenia | [redacted] |
| Febrile neutropenia | [redacted] |
| Diarrhoea | [redacted] |
| Fatigue | [redacted] |
| Asthenia (weakness) | [redacted] |
| Leucopenia | [redacted] |
| Back pain | [redacted] |
| Anaemia | [redacted] |
| Thrombocytopenia | [redacted] |
| Pulmonary embolism | [redacted] |
| Dehydration | [redacted] |
| Nausea | [redacted] |
| Bone pain | [redacted] |
| Deep vein thrombosis | [redacted] |
| Neuropathy | [redacted] |

### 6.5.8 Miscellaneous costs

**Describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.**

It is believed all costs have been covered above.

## 6.6 Sensitivity analysis

### 6.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

A number of model assumptions are investigated through scenario analyses. These are detailed below. Some of these reflect alternative choices in parameter inputs rather than alternative structures but are most appropriately investigated through scenario analyses. The deterministic one-way sensitivity analysis in section 6.6.2 investigates the relative impact of changes in various parameters on results.

**Table 6-17. Scenario analyses conducted**

| Aspect of model structure | Base-case | Scenario analysis | Rationale |
|---|---|---|---|
| OS/PFS input data | Kaplan–Meier data used directly; parametric functions used purely for extrapolation beyond trial cut-off date | Fitted curves used throughout | It is of interest to the impact on results of using smoothed curves throughout |
| Mitoxantrone PFS function | Lognormal function fitted to mitoxantrone PFS | Weibull function fitted to mitoxantrone PFS | Weibull implemented to match functions implemented for both drugs' OS and cabazitaxel PFS |
| Post-second-line treatment mix (% pts receiving BSC and % split among post-second-line treatments) | From TROPIC | From UK audit data | Base-case reflects follow-up sequence of trial patients most closely; scenario analysis reflects UK practice most closely |
| Vial sharing | No vial sharing; wastage | No wastage | To evaluate the impact of wastage on results |
| BSA | 2.01 $m^2$ as in TROPIC | 1.9 $m^2$ as estimated by UK experts | To evaluate the impact of drug costings based on likely UK patients |
| AE disutilities | Included | Not included | To evaluate the impact of AE-related disutilities on overall cost-effectiveness |
| G-CSF usage | Primary prophylaxis rate as in TROPIC | [redacted] | To evaluate the impact on cost-effectiveness if UK practice on G-CSF prophylaxis does not change in line with the introduction of cabazitaxel |
| Utility | Decrement from Sullivan paper applied to derive PD utility | Decrement from Sandblom paper applied to derive PD utility | To evaluate the impact of an alternative assumption about utility on results |
| Progressive disease costs | Applied on per cycle basis in both arms | Assumed equal costs between both arms | Ongoing per cycle costs for progressive disease penalise cabazitaxel because it prolongs survival and hence accrues greater costs. It is of interest to examine the ICER in a scenario where longer survival is not associated with additional cost. |

### 6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

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 6-18. One-way sensitivity analyses implemented in the model**

| One-way sensitivity analysis variable | Variation | Rationale |
|---|---|---|
| Cost of cabazitaxel | [redacted] | Expected to be major cost driver |
| Cost of mitoxantrone | [redacted] | Important to investigate as comparator arm |
| State utility values | ±20% | To investigate the relative impact of utility values (both SD and PD) on results |
| Time horizon | 1, 2, 3, 5 and 10 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 |
| State costs | ±50% | To investigate the relative impact of state costs on results |
| Proportion G-CSF primary prophylaxis | 0, 20, 40, 60, 80 and 100% proportions applied | Variations in G-CSF usage may occur in 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

### 6.6.3 Was probabilistic sensitivitiy analysis undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

To account for the uncertainty of the underlying parameter estimates, second-order stochastic sensitivity analysis was performed.

The uncertainty of the parameters of the Weibull and lognormal survival distributions for PFS and OS were studied through the variance-covariance matrix. As both the Weibull and the lognormal distributions are two-parameter distributions, it is important to capture not only the variance related to the estimation of the parameters, but also their covariance. The covariance is obtained from the variance-covariance matrix, which can be estimated with standard statistical packages when survival analysis is performed. In the PSA, the covariance between the parameters in the survival distribution is calculated using a

mathematical technique called Cholesky decomposition. The correlated random variables, y, are then calculated as y = x + Tz, where T is the Cholesky decomposition matrix, z is a vector of independent standard normal random variables and x is the vector of estimated mean values for the parameters in the survival distributions.

The utility parameters included in the PSA were assumed to follow a beta distribution. The beta distribution is a suitable choice for probabilities and utilities, because it is bounded between 0 and 1. All proportions, such as the share of patients receiving a certain type of treatment, were also assumed to follow a beta distribution. The body surface area was assumed to follow a beta distribution with the smallest (1.34 $m^2$) and largest (2.84 $m^2$) body surface areas observed in TROPIC as lower and upper bounds, and 2.01 $m^2$ as the most probable value. This distribution is not bounded between 0 and 1 as in the standard beta distribution. However, the beta distribution can be adapted to any interval [$\alpha$,$\beta$] by using the linear transformation X' = $\alpha$ + ($\beta$ – $\alpha$) * X.

The standard error (SE) was used for exploring the uncertainty around the estimate of the mean. The SE for utilities was calculated from EAP data. The SE for disutilities, proportions and relative risks was taken from the literature or was based on modelling assumptions. For rates and proportions where no other data were available, SE was estimated according to the formula for calculating the standard error of a proportion:

$$SE = \sqrt{\frac{p(1-p)}{n}}$$

where *p* is the yearly proportion according to the advisory board and *n* is the number of patients in the study arm.

For proportions estimated by the expert panel, there were no data on the number of patients. Then the assumption from the Beta-Pert method was used, that is, the standard error was estimated as SE = (maximum value – minimum value)/6, with the maximum and minimum values estimated as 25% higher and lower than the mean, respectively.

The parameters $\alpha$ and $\beta$ in the beta distribution were estimated from the means and standard errors of the variables included in the PSA. The mean $\mu$ and variance $\sigma^2$ of a beta distribution depend on $\alpha$ and $\beta$ according to the following formulae:

$$\mu = \frac{\alpha}{\alpha + \beta}$$

$$\sigma^2 = \frac{\alpha\beta}{(\alpha + \beta)^2(\alpha + \beta + 1)}$$

These formulae can be used for the estimation of the appropriate beta distribution for each of the variables included in the PSA, based on the mean and variance.

The resource use variables were based on the lognormal distribution, which is appropriate as resource use data are typically skewed. The standard error for the length of stay due to AEs was estimated based on the relative uncertainty in the quartile estimations for costs in the NHS data. The uncertainty in costs is thus assumed mainly to represent the uncertainty in resource use. The unit costs were not included in the PSA because these were generally based on fixed costs, such pharmaceutical costs or costs from price lists.

The underlying distributions of all variables included in the PSA are summarised in Table 6-19.

**Table 6-19. Distribution of variables**

| Variable | Distribution | Standard error |
|---|---|---|
| Weibull survival curve | Weibull | From TROPIC |
| Lognormal survival curve | Lognormal | From TROPIC |
| Utility values | Beta | From EAP |
| Disutility of AEs | Beta | Only Doyle *et al* reported the SE for the disutility for an AE.[81] This SE was assumed to be representative of the uncertainty for other AEs as well |
| Proportion of patients receiving certain type of care | Beta | SE was estimated from TROPIC data for the proportion of patients requiring inpatient care due to AEs. For other proportions the SE was estimated based on a maximum and minimum values 25% higher and lower than the mean, respectively |
| Resource use | Lognormal | The SE for length of stay due to AEs was estimated based on the relative uncertainty in the quartile estimations for costs in the NHS data. For resources not included in the NHS data, we assumed that these would have an uncertainty estimated based on a maximum and minimum values 25% higher and lower than the mean, respectively |
| Relative risks | Lognormal | The SE was estimated from data presented in Vogel *et al*[89] |
| BSA | Beta | The SE was estimated from data in the TROPIC trial |
| Key: AE = adverse event; BSA = body surface area; SD = standard deviation; SE = standard error | | |

## 6.7 Results

**Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.**

- **Link between clinical- and cost-effectiveness results.**
- **Costs, QALYs and incremental cost per QALY.**

- **Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.**
- **A statement as to whether the results are based on a PSA.**
- **Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.**
- **Scatter plots on cost-effectiveness quadrants.**
- **A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability**

### 6.7.1 Clinical outcomes from the model

**For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.**

The model is based on OS and PFS data from TROPIC. TROPIC provides estimates of the **median** OS and PFS, but estimates of the **mean** OS and PFS are required to evaluate cost-effectiveness. To calculate mean OS and PFS, parametric functions were fitted to TROPIC data and extrapolated to provide complete follow-up (as described in Appendix 15).

The median OS and PFS from TROPIC, the median OS and PFS as estimated in the model (based on the proportion of patients dying and the proportion in the stable disease state) and the mean OS and PFS estimated through fitting parametric functions to TROPIC data are provided in Table 6-20and Table 6-21. These are provided for the model base-case, that is, European patients with ECOG 0 -1 and who had previously received ≥225 mg/m$^2$ docetaxel. There is a good match between the median values reported in the trial and the median values obtained from the model.

**Table 6-20. Summary of model results compared with clinical data (cabazitaxel)**

| Outcome | Median from TROPIC trial (months) | Median from model (months) | Mean value (from Weibull fit to OS and PFS data) |
|---|---|---|---|
| Progression-free survival | [redacted] | [redacted] | [redacted] |
| Overall survival | [redacted] | [redacted] | [redacted] |

**Table 6-21. Summary of model results compared with clinical data (mitoxantrone)**

| Outcome | Median from TROPIC trial (months) | Median from model (months) | Mean value (from Weibull fit to OS and lognormal fit to PFS data) |
|---|---|---|---|
| Progression-free survival | [redacted] | [redacted] | [redacted] |
| Overall survival | [redacted] | [redacted] | [redacted] |

In the model, the calculated survival (in terms of life-years and progression-free life years) differs slightly from the mean OS and PFS reported in Table 6-20 and Table 6-21 above. This is due to 3 key reasons:

- The model has a cycle length of 3 weeks, and therefore probabilities of survival and staying in the progression-free state are calculated on a 3-weekly basis
- In the base-case, the model uses the raw Kaplan-Meier curves for the period for which these are available and reliable, with extrapolation only used for the period beyond this. By contrast, the mean values reported above are calculated based on use of the fitted curves for the entire duration.
- Costs and outcomes are discounted at a rate of 3.5%.

### 6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

**Figure 6-2. Cohort trace (cabazitaxel)**

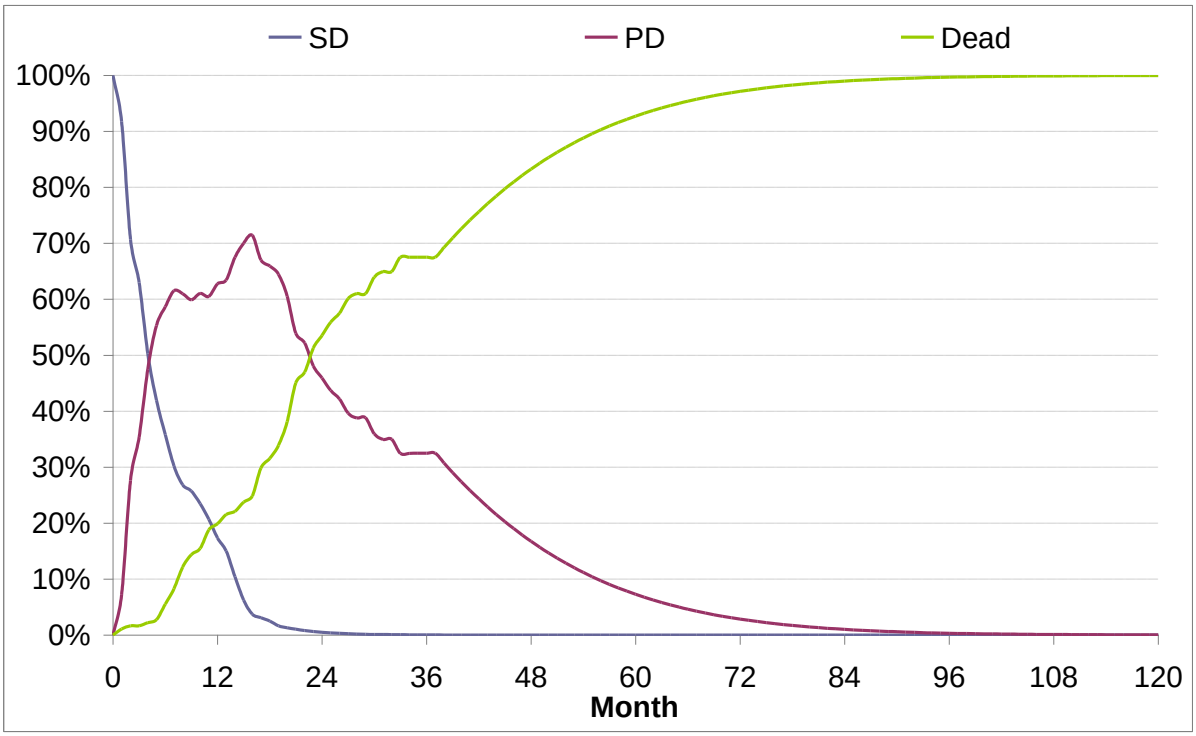
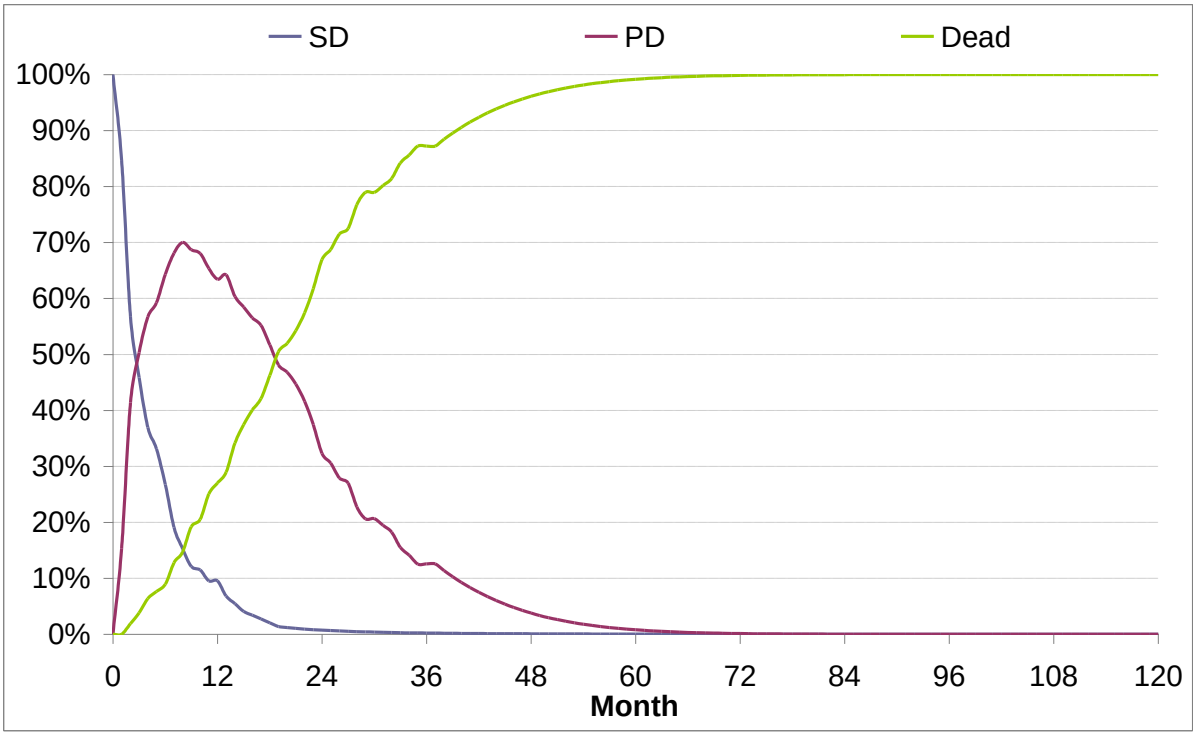



**Figure 6-3. Cohort trace (mitoxantrone)**



### 6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

**Figure 6-4. Cumulative QALYs (cabazitaxel)**

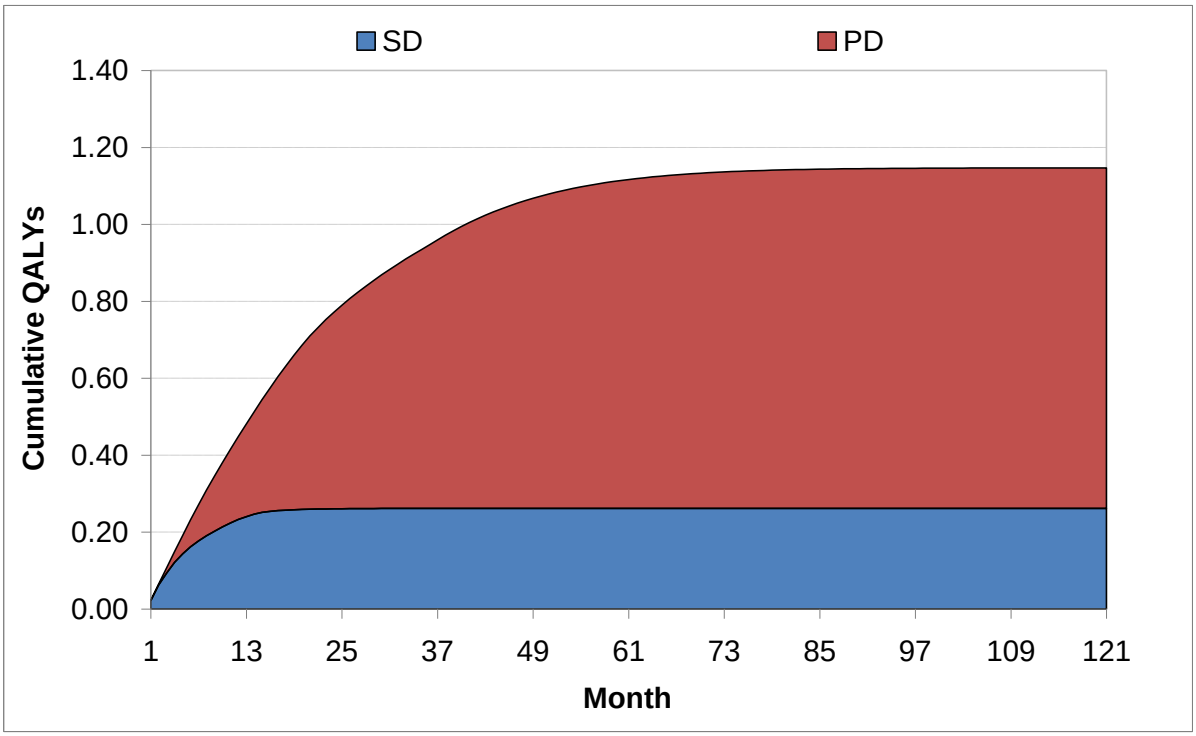
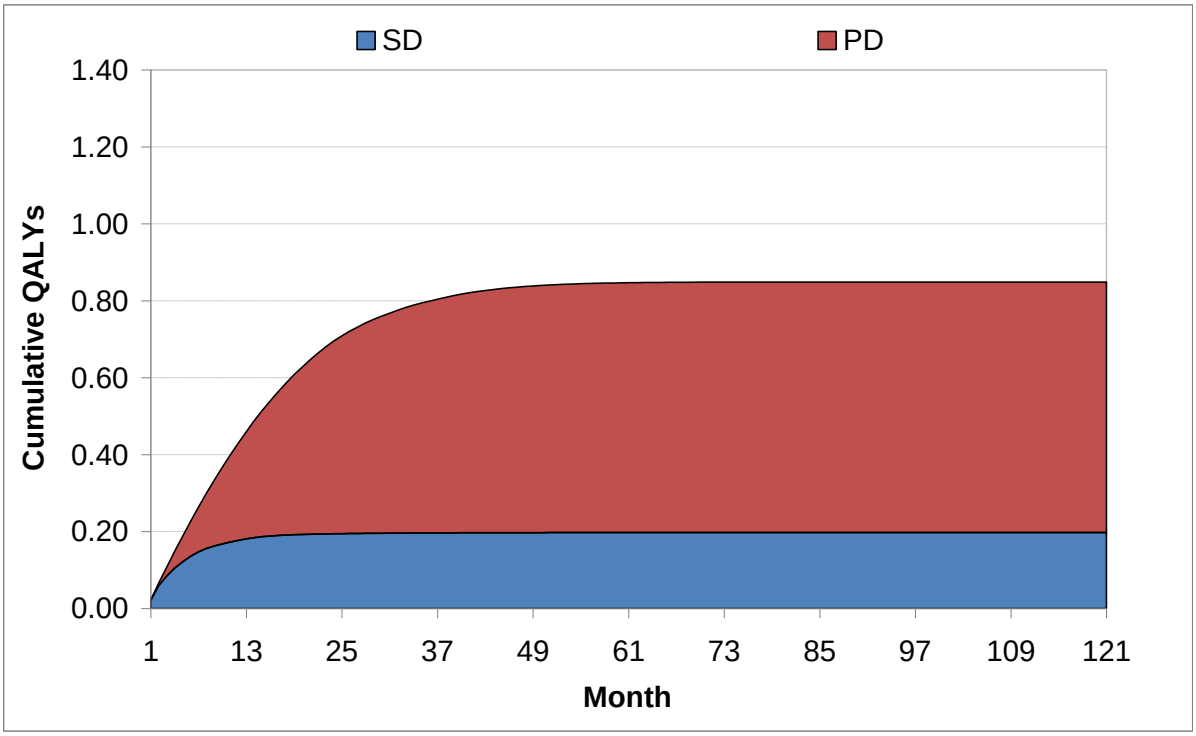


**Figure 6-5. Cumulative QALYs (mitoxantrone)**




### 6.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

**Table 6-22. Model outputs by clinical outcomes (cabazitaxel)**

| Outcome | LY | QALY | Cost (£) |
|---|---|---|---|
| Progression-free survival | 0.339 | 0.262 | [redacted] |
| Post-progression survival | 1.245 | 0.885 | [redacted] |
| Overall survival | 1.584 | 1.147 | 35,372 |
| Key: LY = life year; QALY = quality-adjusted life year | | | |

**Table 6-23. Model outputs by clinical outcomes (mitoxantrone)**

| Outcome | LY | QALY | Cost (£) |
|---|---|---|---|
| Progression-free survival | 0.256 | 0.198 | [redacted] |
| Post-progression survival | 0.915 | 0.651 | [redacted] |
| Overall survival | 1.171 | 0.849 | 13,047 |
| Key: LY = life year; QALY = quality-adjusted life year | | | |

## 6.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

**Table 6-24. Summary of QALY gain by health state**

| Health state | Cabazitaxel | Mitoxantrone | Increment | Absolute increment | % absolute increment |
|---|---|---|---|---|---|
| Stable | 0.262 | 0.198 | 0.064 | 0.064 | 21% |
| Progressed | 0.885 | 0.651 | 0.234 | 0.234 | 79% |
| Total | 1.147 | 0.849 | 0.298 | 0.298 | 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 | | | | | |

**Table 6-25. Summary of costs by health state**

| Health state | Cabazitaxel | Mitoxantrone | Increment | Absolute increment | % absolute increment |
|---|---|---|---|---|---|
| Stable | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Progressed | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total | 35,372 | 13,047 | 22,325 | 22,326 | 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 | | | | | |

## 6.7.6 Base-case analysis

**Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.**

**Table 6-26. Base-case results**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| Mitoxantrone | 13,047 | 1.171 | 0.849 | - | - | - | | |
| Cabazitaxel | 35,372 | 1.584 | 1.147 | 22,325 | 0.413 | 0.298 | 74,908 | 74,908 |
| Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life year | | | | | | | | |

### 6.7.7 Sensitivity analyses

**Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.**

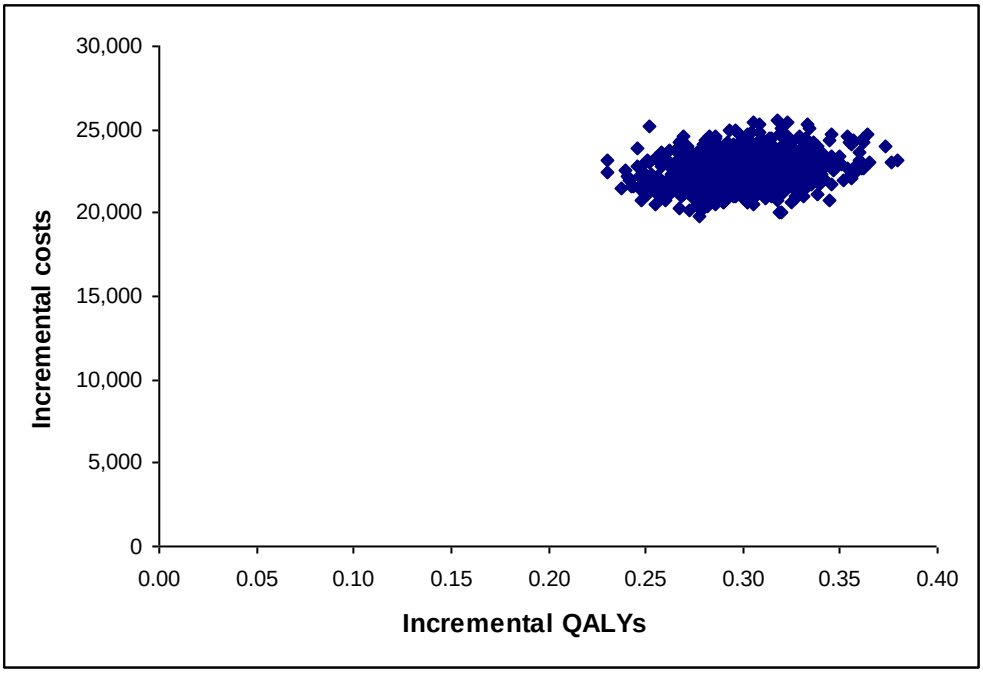
**Table 6-27. Deterministic sensitivity analysis results**

| Analysis | ΔCost | ΔQALY | ΔLYG | ICER (QALY) | ICER (LYG) |
|---|---|---|---|---|---|
| **Base case** | **£22,325** | **0.30** | **0.41** | **£74,908** | **£54,051** |
| | | | | | |
| [redacted] | | | | | |
| | | | | | |
| **Utilities** | | | | | |
| AE disutilities excluded | £22,325 | 0.30 | 0.41 | £74,536 | £54,051 |
| SD utility +20% | £22,325 | 0.31 | 0.41 | £71,764 | £54,051 |
| SD utility -20% | £22,325 | 0.28 | 0.41 | £78,341 | £54,051 |
| PD utility +20% | £22,325 | 0.34 | 0.41 | £64,733 | £54,051 |
| PD utility -20% | £22,325 | 0.25 | 0.41 | £88,878 | £54,051 |
| | | | | | |
| **Time horizon** | | | | | |
| 1 year | £19,699 | 0.05 | 0.06 | £425,106 | £335,268 |
| 2 years | £20,418 | 0.12 | 0.16 | £168,895 | £124,732 |
| 3 years | £21,520 | 0.23 | 0.32 | £93,882 | £68,059 |
| 5 years | £22,279 | 0.29 | 0.41 | £75,694 | £54,629 |
| 10 years | £22,325 | 0.30 | 0.41 | £74,908 | £54,051 |
| | | | | | |
| **Discount rates** | | | | | |
| Costs: 0%, Effects: 0% | £22,695 | 0.32 | 0.45 | £70,705 | £50,974 |
| Costs: 3.5%, Effects: 0% | £22,346 | 0.32 | 0.45 | £69,618 | £50,190 |
| Costs: 0%, Effects: 3.5% | £22,674 | 0.30 | 0.41 | £76,078 | £54,896 |
| Costs: 6%, Effects: 6% | £22,076 | 0.28 | 0.39 | £78,038 | £56,346 |
| | | | | | |
| **State costs** | | | | | |
| Caba & Mitox drug & adm cost -50% | £12,501 | 0.30 | 0.41 | £41,945 | £30,266 |
| Caba & Mitox post 2nd line (drugs & adm) cost -50% | £22,231 | 0.30 | 0.41 | £74,592 | £53,823 |
| Caba & Mitox other costs SD -50% | £22,150 | 0.30 | 0.41 | £74,320 | £53,626 |
| Caba & Mitox other costs PD -50% | £21,411 | 0.30 | 0.41 | £71,840 | £51,837 |
| AE costs -50% | £22,171 | 0.30 | 0.41 | £74,389 | £53,677 |
| | | | | | |
| **Proportion with G-CSF as primary prophylaxis** | | | | | |
| Caba & Mitox: 0% | £22,146 | 0.30 | 0.41 | £74,387 | £53,616 |
| Caba & Mitox: 20% | £22,128 | 0.30 | 0.41 | £74,268 | £53,574 |
| Caba & Mitox: 40% | £22,111 | 0.30 | 0.41 | £74,150 | £53,533 |
| Caba & Mitox: 60% | £22,094 | 0.30 | 0.41 | £74,031 | £53,491 |
| Caba & Mitox: 80% | £22,077 | 0.30 | 0.41 | £73,913 | £53,450 |
| Caba & Mitox: 100% | £22,060 | 0.30 | 0.41 | £73,795 | £53,408 |

### 6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

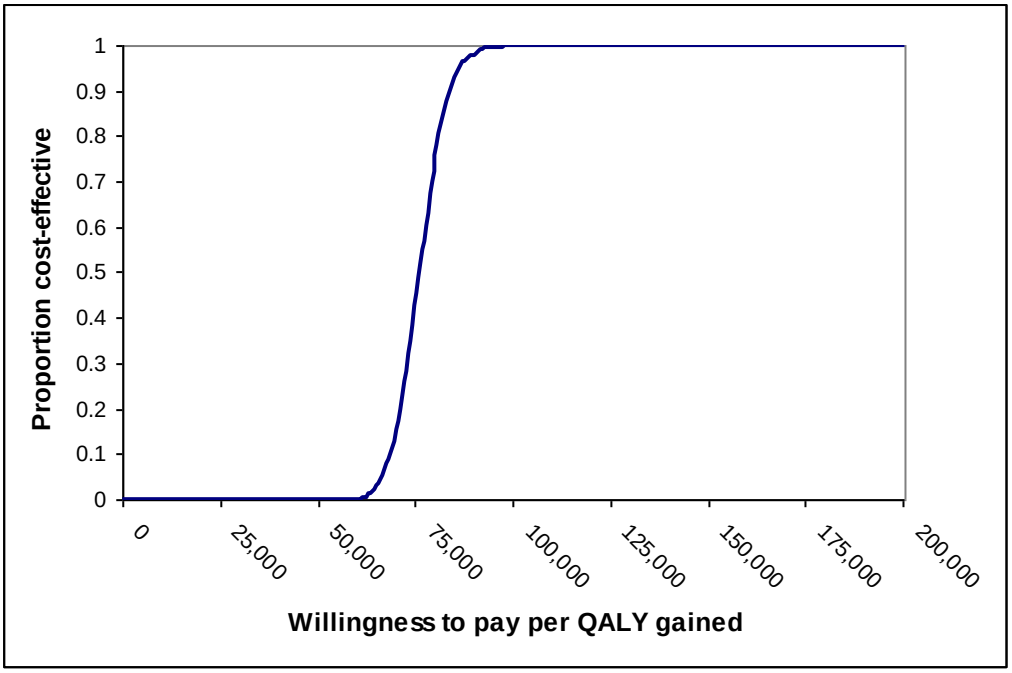
The cost-effectiveness scatter plot (based on 1,000 iterations), is shown below:

**Figure 6-6. PSA scatter plot cabazitaxel versus mitoxantrone (European patients with ECOG 0 -1 performance status and received ≥225 mg/m$^2$ docetaxel)**




This results in the following cost-effectiveness acceptability curve:

**Figure 6-7. Cost-effectiveness acceptability (European patients with ECOG 0 -1 performance status and received ≥225 mg/m$^2$ docetaxel)**



At a willingness-to-pay of £30,000 per QALY, the likelihood of cost-effectiveness is zero. At a willingness-to-pay of £100,000 per QALY, the probability of cabazitaxel being cost-effective is 99%.

### 6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

*Scenario: Use fitted curves throughout model*

As shown in Table 6-28 below, when the analysis was re-run with smoothed curves for OS and PFS throughout instead of the raw Kaplan–Meier data, the scenario analysis resulted in an ICER of £82,950.

**Table 6-28. Fitted curves used throughout (European patients with ECOG 0 -1 performance status and received ≥225 mg/m$^2$ docetaxel)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| Mitoxantrone | 13,047 | 1.172 | 0.849 | - | - | - | | |
| Cabazitaxel | 36,135 | 1.557 | 1.128 | 23,088 | 0.385 | 0.278 | 82,950 | 82,950 |
| Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year | | | | | | | | |

*Scenario: Mitoxantrone PFS data with Weibull distribution*

As shown in Table 6-29 below, when the analysis was re-run with the mitoxantrone PFS data using a Weibull distribution, rather than a Lognormal distribution, the scenario analysis resulted in an ICER of £74,786.

**Table 6-29. Mitoxantrone PFS data with Weibull distribution (European patients with ECOG 0 -1 performance status and received ≥225 mg/m$^2$ docetaxel)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| Mitoxantrone | 13,062 | 1.171 | 0.848 | - | - | - | | |
| Cabazitaxel | 35,372 | 1.584 | 1.147 | 22,310 | 0.413 | 0.298 | 74,786 | 74,786 |
| Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year | | | | | | | | |

*Scenario: UK-specific post-second-line treatment mix*

As shown in Table 6-30 below, when the analysis was re-run with post-second-line chemotherapy based on the UK audit rather than on TROPIC, the scenario analysis resulted in an ICER of £75,972.

**Table 6-30. UK post-second-line treatment (European patients with ECOG 0 -1 performance status and received ≥225 mg/m$^2$ docetaxel)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| Mitoxantrone | 11,840 | 1.171 | 0.849 | - | - | - | | |
| Cabazitaxel | 34,482 | 1.584 | 1.147 | 22,642 | 0.413 | 0.298 | 75,972 | 75,972 |
| Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year | | | | | | | | |

*Scenario: Second-line treatment costs based on mg used*

As shown in **Error! Not a valid bookmark self-reference.** below, when the analysis was re-run with the second-line drug costs allowing for vial sharing by using the cost per mg (that is, without including vial wastage) the scenario analysis resulted in an ICER of [redacted].

**Table 6-31. Second-line costs by cost per mg (European patients with ECOG 0 -1 performance status and received ≥225 mg/m$^2$ docetaxel)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| Mitoxantrone | [redacted] | 1.171 | 0.849 | - | - | - | | |
| Cabazitaxel | [redacted] | 1.584 | 1.147 | [redacted] | 0.413 | 0.298 | [redacted] | [redacted] |
| Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year | | | | | | | | |

*Scenario: UK estimated BSA used*

As shown in Table 6-32 below, when the analysis was re-run with a BSA of 1.9 m$^2$, as estimated by UK clinical experts, the scenario analysis resulted in an ICER of £75,003.

**Table 6-32. UK-specific BSA used (European patients with ECOG 0 -1 performance status and received ≥225 mg/m$^2$ docetaxel)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| Mitoxantrone | 12,941 | 1.171 | 0.849 | - | - | - | | |
| Cabazitaxel | 35,295 | 1.584 | 1.147 | 22,354 | 0.413 | 0.298 | 75,003 | 75,003 |
| Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year | | | | | | | | |

*Scenario: UK-specific G-CSF use*

As shown in Table 6-33 below, when the analysis was run with the frequency of G-CSF primary prophylaxis taken from the UK audit (0%), the scenario analysis resulted in an ICER of £74,387.

**Table 6-33. UK-specific G-CSF usage (European patients with ECOG 0 -1 performance status and received ≥225 mg/m$^2$ docetaxel)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| Mitoxantrone | 12,923 | 1.171 | 0.849 | - | - | - | | |
| Cabazitaxel | 35,069 | 1.584 | 1.146 | 22,146 | 0.413 | 0.298 | 74,387 | 74,387 |
| Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year | | | | | | | | |

*Scenario: Alternative utility decrement*

As shown in Table 6-34 below, when the analysis was re-run with the decrement for moving from stable to progressive disease taken from Sandblom 2004 instead of Sullivan 2007, the scenario analysis resulted in an ICER of £76,171.

**Table 6-34. Alternative utility analysis (European patients with ECOG 0 -1 performance status and received ≥225 mg/m$^2$ docetaxel)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| Mitoxantrone | 13,047 | 1.171 | 0.835 | - | - | - | | |
| Cabazitaxel | 35,372 | 1.584 | 1.128 | 22,325 | 0.413 | 0.293 | 76,171 | 76,171 |
| Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year | | | | | | | | |

*Scenario: Exclude AE-related disutilities*

As shown in Table 6-35 below, when the analysis was re-run without applying disutilities related to AEs, the scenario analysis resulted in an ICER of £74,536.

**Table 6-35. Exclude AE-related disutilities (European patients with ECOG 0 -1 performance status and received ≥225 mg/m$^2$ docetaxel)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| Mitoxantrone | 13,047 | 1.171 | 0.851 | - | - | - | | |
| Cabazitaxel | 35,372 | 1.584 | 1.150 | 22,325 | 0.413 | 0.300 | 74,536 | 74,536 |
| Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year | | | | | | | | |

*Scenario: Assume equivalent PD costs between arms*

As shown in Table 6-35 below, when the analysis was re-run assuming equivalent PD and end-of-lfie costs between treatment arms, the scenario analysis resulted in an ICER of £68,210.

**Table 6-36. Assume equivalent PD costs between arms (European patients with ECOG 0 -1 performance status and received ≥225 mg/m$^2$ docetaxel)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| Mitoxantrone | 15,043 | 1.171 | 0.849 | - | - | - | | |
| Cabazitaxel | 35,372 | 1.584 | 1.147 | 20,329 | 0.413 | 0.298 | 68,210 | 68,210 |
| Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year | | | | | | | | |

### 6.7.10 What were the main findings of each of the sensitivity analyses?

The sensitivity analysis demonstrated that the model's findings are relatively robust to changes in key parameters. There were few sensitivity analyses/scenario analyses which radically changed results. The direction of result changes was as expected. For example, cabazitaxel became more cost-effective in the following scenarios:

- As the price of cabazitaxel was reduced
- As the price of mitoxantrone increased
- As the QoL in the stable disease state increased
- As the QoL in the progressed disease state increased
- As the time horizon increased
- As costs were discounted at a greater rate than benefits

- As ‘background costs’ decreased in each disease state.

Deterministic sensitivity analyses indicated results were most sensitive to the time horizon – as the time horizon increased, cabazitaxel became more cost-effective, with a variation of ~£280,000 in the ICER. [redacted]

Scenario analyses conducted around structural assumptions also identified that results were relatively robust – using fitted curves throughout, or using an alternative distribution for mitoxantrone PFS had relatively little impact on the ICER.

The vial size of cabazitaxel allows for wastage; this is shown by the fact that varying the BSA had relatively little impact on results, but allowing vial sharing (therefore costing cabazitaxel per mg) reduced the ICER by ~£15,000 per QALY.

Probabilistic analysis indicated a low probability of cost-effectiveness at standard UK thresholds (p=0 at a WTP of £30,000 per QALY). This reflects the difficulty in achieving cost-effectiveness in late-stage oncology models.

### 6.7.11 What are the key drivers of the cost-effectiveness results?

The cost of active treatment was observed to be the key driver of the cost-effectiveness results. This is reflected in the sensitivity analyses around vial sharing and drug price.

As would be expected, utility in both stable and progressive disease states has an impact on results, with the progressive disease utility having a greater impact due to the longer time spent in the progressive disease state.

The costs of additional, supportive treatment also have an impact on the results. Patients with mHRPC require ongoing care, including hospitalisations, medical staff time and supportive medications. Because cabazitaxel results in longer survival than mitoxantrone, higher costs for ongoing care are incurred in the cabazitaxel arm. This is shown by the fact that if the progressive disease costs are set equal in both treatment arms, the ICER is reduced to £68,210.

## 6.8 Validation

### 6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

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.

## 6.9 Subgroup analysis

### 6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

The base-case considers patients with ECOG status 0–1 who had received ≥225 mg/m$^2$ docetaxel, based on European data from TROPIC. This group is considered most representative of the type of patients likely to receive cabazitaxel in UK clinical practice. In this section we present results from three broader patient groups, to explore the impact of the base-case restrictions on model results.

These groups are:

- Patients with ECOG status 0–1 who had received ≥225 mg/m$^2$ docetaxel (i.e. without restriction to European patients).
- European patients
- The entire TROPIC population

### 6.9.2 Please clearly define the characteristics of patients in the subgroup.

In the model, the subgroup input data that differs from the base-case whole TROPIC population data is the following:

- OS survival variables for cabazitaxel and mitoxantrone
- PFS survival variables for cabazitaxel and mitoxantrone
- Proportion of patients receiving the respective treatment options under the post-second-line chemotherapy mix from TROPIC
- Duration of each of the post-second-line chemotherapy mix options from TROPIC
- Adverse event rates for all AEs included in the model

- Relative dose intensity of cabazitaxel and mitoxantrone.

OS and PFS parameters for both subgroups are shown in Table 6-37.

The results of parametric curve fitting are shown in Appendix 15. Additional parameters (AE rates, post-second-line chemotherapy) are provided in Appendix 16.

**Table 6-37. Subgroup OS and PFS parameters**

| | MTX+PRED | | | CBZ+PRED | | | CBZ+PRED vs MTX+PRED | |
|---|---|---|---|---|---|---|---|---|
| **OS** | **Number dead / N (%)** | **median survival (95% C.I.)** | **Mean survival** | **Number dead / N (%)** | **median survival (95% C.I.)** | **mean survival** | **Hazard Ratio (HR)** | **Difference** |
| ECOG PS 0, 1 and ≥ 225 mg/m² of docetaxel | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| European patients | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Whole population | 279/377 (74.0%) | 12.7 (11.6–13.7) | 14.0 (13.1 – 14.9) | 234/378 (61.9%) | 15.1 (14.1–16.3) | 18.2 (17.0 – 19.4) | 0.70 (0.59–0.83) | 2.4 median<br>4.2 mean |
| **PFS** | **Number event / N (%)** | **median PFS (95% C.I.)** | **Mean PFS** | **Number event / N (%)** | **median PFS (95% C.I.)** | **mean PFS** | **Hazard Ratio (HR)** | **Median difference** |
| ECOG PS 0, 1 and ≥ 225 mg/m² of docetaxel | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| European patients | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Whole population | 367/377 (97.3%) | 1.4 (1.4–1.7) | 3.06 | 364/378 (96.3%) | 2.8 (2.4–3.0) | 4.14 | 0.74 (0.64–0.86) | 1.4 median<br>1.08 mean |

### 6.9.3 Please describe how the statistical analysis was undertaken.

Additional analysis was taken by applying the appropriate values (see section 6.9.2) into the model.

### 6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

Subgroup analyses are shown in Table 6-38 - Table 6-40. Cost-effectiveness acceptability curves for the three subgroups and the base-case population are shown in Figure 6-8.

**Table 6-38. Assessment of patients with ECOG 0 or 1 and received ≥225 mg/m$^2$ docetaxel**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| Mitoxantrone | 13,085 | 1.167 | 0.845 | - | - | - | | |
| Cabazitaxel | 34,493 | 1.527 | 1.105 | 21,408 | 0.359 | 0.259 | 82,530 | 82,530 |
| Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year | | | | | | | | |

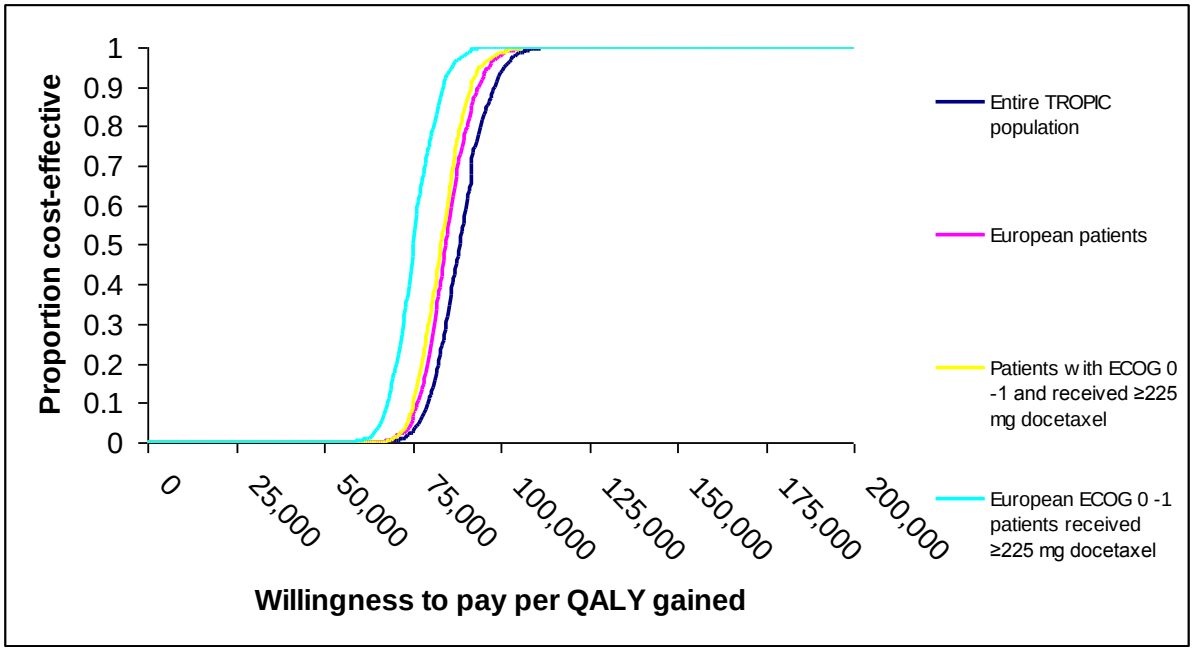
**Table 6-39. Assessment of European patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| Mitoxantrone | 12,736 | 1.145 | 0.831 | - | - | - | | |
| Cabazitaxel | 34,703 | 1.507 | 1.091 | 21,966 | 0.361 | 0.260 | 84,510 | 84,510 |
| Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year | | | | | | | | |

**Table 6-40. Assessment of Entire TROPIC population**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|---|---|
| Mitoxantrone | 12,724 | 1.133 | 0.821 | - | - | - | | |
| Cabazitaxel | 34,093 | 1.471 | 1.065 | 21,368 | 0.338 | 0.244 | 87,685 | 87,685 |
| Key: ICER = incremental cost-effectiveness ratio; LYG = life-years gained; QALY = quality-adjusted life-year | | | | | | | | |

**Figure 6-8. Cost-effectiveness curve for all patient groups**




### 6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

A number of preplanned subgroups were included in TROPIC but were not considered in the economic analysis. These included: disease measurability (measurable versus not), number of prior chemotherapy regimens (one versus more than one), age (<65 versus ≥65), pain at baseline (yes or no), PSA status (rising PSA at baseline recorded or not), time from last administration of docetaxel to randomisation, and time of progression from last administration of docetaxel.

The decision problem suggests subgroups by:

- Performance status
- Total docetaxel dose received
- Time since last administration of docetaxel.

The first two criteria are covered within the groups explored in this submission. The third is not, however the clinical analysis indicated broadly similar HRs between groups defined by different times since the last administration of docetaxel. In addition, if a patient has clearly progressed after docetaxel, it is unclear the time since last docetaxel treatment would influence whether or not they were considered for cabazitaxel.

## 6.10 Interpretation of economic evidence

### 6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No previous economic evaluations of cabazitaxel for this indication were identified in the literature search. As such, it is not possible to compare the findings of this study with those in other models.

### 6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

Cabazitaxel is indicated for the treatment of mHRPC patients previously treated with a docetaxel regimen. The model described in this submission is based on the TROPIC trial, the only head-to-head randomised controlled trial comparing cabazitaxel against alternative treatments for this indication. Data from the trial have not been modified or adjusted, other than for extrapolation for the small group of patients who had survived past the trial follow-up. We have presented in the base-case a patient population considered most representative of UK patients likely to receive cabazitaxel (European patients with ECOG performance status 0-1, who have received at least 225 mg/m$^2$ docetaxel). NICE guidance recommends docetaxel as first-line mHRPC treatment and it is unlikely that patients who had not received sufficient exposure to docetaxel would be considered for cabazitaxel in UK practice. Clinical opinion confirms that patients with poorer performance status (ECOG 2) are highly unlikely to receive cabazitaxel in UK clinical practice. So, by excluding patients who do not meet these criteria, we do not consider that we have excluded any relevant groups who could potentially receive cabazitaxel in the UK. Similarly, the use of European data in the base-case is intended to ensure the results are more closely reflective of expected benefits and harms in practice in the UK, as treatment practices in non-European countries differ from the UK and the rest of Europe and may have affected the treatment effects observed in TROPIC. The base-case ICER in this group is £74,908 and is relatively robust to various changes in parameters and model assumptions.

Costs and resource use have been updated in the model to reflect UK practice wherever possible. Utility data come from a prospective study of patients receiving cabazitaxel in the UK. As such, we consider that the evaluation included here is relevant to the key group of patients who could potentially benefit from its use.

### 6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The model is based directly on trial evidence, and uses very little extrapolation or prediction outside the trial's observed outcomes. Extensive data have been collected to populate the model's resource use and cost inputs, using UK audit data combined with observed trial outcomes to reflect UK clinical practice wherever possible. The model includes resource use and costs that are calculated in greater detail than have been previously collected for patients with this indication. The model uses utility data for the stable disease state from a prospective study of UK mHRPC patients treated with cabazitaxel.

As with all economic models, the analysis uses statistical techniques to present a simplified version of reality, while aiming to retain the key nuances of the disease progression and treatment pathways. To develop the model a number of simplifications were necessary. These included the assumption that all patients remain on treatment until their disease progresses (up to ten cycles). In reality, some patients may discontinue therapy for other reasons, such as patient preference or SAEs. Likewise, it was not possible to build in a treatment effect associated with post-second-line treatment, as there are no data on the efficacy of such treatments. However, since the PFS and OS curves were based on actual trial data (in which patients were treated with post-second-line therapy), the effect of such treatments would already be included.

Because the model includes *all* NHS costs, rather than simply the cost of treatment, the analysis accounts for any costs incurred as a result of increased survival. Because cabazitaxel results in increase PFS *and* OS (with the incremental OS being greater than the incremental PFS), there are substantial non-drug costs associated with its increased effectiveness. As discussed in section 5.10.2, there are limitations in the definition of PFS in prostate cancer, and the definition used here (and in other trials) results in a shorter PFS duration than that seen in other cancers. As the per-cycle costs for progressed disease are higher than for stable disease, the increase in survival in the progressed state results in increased non-drug costs for cabazitaxel. Because of this, an economic analysis of any effective treatment for mHRPC will penalise those therapies that result in increased survival of patients and, as such, the ICERs generated by such a model are not necessarily reflective of the cost of drug treatment alone. A scenario analysis in which end-of-life and progressive disease costs were set equal in both arms resulted in an ICER of £68,210.

### 6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Interim data from the EAP have been used to provide an estimate of QoL in the stable disease state in the model. Further analyses are planned for August 2011 (ad hoc) and December 2011 (final). As the EAP progresses, data will become available for the progressed disease state. This will increase the validity of the model by providing both key utility parameters in the model from a prospective, UK-based study of cabazitaxel in the relevant population.

There is currently very little evidence to predict the likely usage of G-CSF treatments for the primary prophylaxis of febrile neutropenia in patients treated with cabazitaxel. An audit of UK centres suggested that G-CSFs are used very rarely, although this may not be the case for patients receiving cabazitaxel. As such, the model used the rates observed in the clinical trial. Future studies should aim to capture this use, to improve the certainty around the estimates used in the model, even though this does not have a major impact on the cost-effectiveness results.

Patients with mHRPC have a poor prognosis, with a median life expectancy of around 12 months. In the base-case population, cabazitaxel increased the median life expectancy by [redacted] months, and increased the mean life expectancy by [redacted] months. For patients with such a poor prognosis, it may be that the *relative* improvement in survival may play a greater role than the *absolute* increase in survival. The relationship between life expectancy and the societal value placed on incremental survival improvements is still unclear, but there may be a greater weight placed by society on incremental improvements in survival when life expectancy is short. Currently, HTA decision-making is based primarily around the latter factor, so it is possible that this analysis is excluding some significant benefits to the patient.

# Section C – Implementation

# Section 7. Assessment of factors relevant to the NHS and other parties

To assess the overall cost impact of using cabazitaxel in mHRPC patients, we combined cost data generated by the economic model and epidemiology data.

As described in section 2.2, it is estimated that there are around 1,938 mHRPC patients eligible for second-line chemotherapy in England and Wales.[37]

The likely uptake of cabazitaxel, if approved for NHS use is not known. It has been assumed that the uptake in Years 1 to 5 would be: 20%, 50%, 75%, 85% and 85%. This results in the following numbers of patients being treated:

**Table 7-1. Number of patients treated**

| | | If approved for NHS use | | If not approved |
|---|---|---|---|---|
| **Year** | **Number eligible for cabazitaxel** | **Number receiving cabazitaxel** | **Number receiving mitoxantrone** | **Number receiving mitoxantrone** |
| 1 | 1,938 | 387.6 | 1,550 | 1,938 |
| 2 | 1,938 | 969 | 969 | 1,938 |
| 3 | 1,938 | 1,454 | 485 | 1,938 |
| 4 | 1,938 | 1,647 | 291 | 1,938 |
| 5 | 1,938 | 1,647 | 291 | 1,938 |

The economic analysis for cabazitaxel (see Section 6) estimates that the drug costs (including administration, premedication and concomitant medications) would be [redacted] and [redacted] per patient for cabazitaxel and mitoxantrone respectively. Therefore, we can estimate the overall budget impact of cabazitaxel as shown in Table 7-2.

**Table 7-2. Overall budget impact**

| | If approved for NHS use | | | If not approved | Incremental |
|---|---|---|---|---|---|
| Year | Cost of cabazitaxel | Cost of mitoxantrone | Total | Cost of mitoxantrone | |
| 1 | £8,614,798 | £3,964,351 | £12,579,149 | £4,955,439 | £7,623,710 |
| 2 | £21,536,995 | £2,477,719 | £24,014,714 | £4,955,439 | £19,059,276 |
| 3 | £32,305,492 | £1,238,860 | £33,544,352 | £4,955,439 | £28,588,913 |
| 4 | £36,612,891 | £743,316 | £37,356,207 | £4,955,439 | £32,400,768 |
| 5 | £36,612,891 | £743,316 | £37,356,207 | £4,955,439 | £32,400,768 |

# Section 8. References


1. *Cabazitaxel (Jevtana) Summary of Product Characteristics.* sanofi-aventis, 2010.
2. European Medicines Agency. *Assessment Report For Jevtana (cabazitaxel). Procedure No.: EMEA/H/C/002018.* www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002018/WC500104766.pdf (last accessed 19 April 2011)
3. Bissery MC, Bouchard H, Riou JF. Preclinical evaluation of TXD258, a new taxoid. *Proc Am Assoc Cancer Res* 2000; **41:** 214.
4. Vrignaud P, Lejeune D, Chaplin D. In Vivo Efficacy of TXD258, a new taxoid, against human tumor xenografts. *Proc Am Assoc Cancer Res* 2000; **41:** 214.
5. Lage MJ, Barber BL, Harrison DJ, Jun S. The cost of treating skeletal-related events in patients with prostate cancer. *Am J Manag Care* 2008; **14:** 317–322.
6. National Institute for Health and Clinical Excellence. *NICE Technology Appraisal Guidance 101: Docetaxel for the treatment of hormone-refractory metastatic prostate cancer.* www.nice.org.uk/Guidance/TA101 (last accessed 14 October 2010)
7. Osoba D, Tannock IF, Ernst DS, Neville AJ. Health-related quality of life in men with metastatic prostate cancer treated with prednisone alone or mitoxantrone and prednisone. *J Clin Oncol* 1999; **17:** 1654–1663.
8. Moore MJ, Osoba D, Murphy K, Tannock IF, Armitage A, Findlay B *et al*. Use of palliative end points to evaluate the effects of mitoxantrone and low-dose prednisone in patients with hormonally resistant prostate cancer. *J Clin Oncol* 1994; **12:** 689–694.
9. National Institute for Health and Clinical Excellence. *Cabazitaxel for the second line treatment of hormone refractory, metastatic prostate cancer: Final scope.* www.nice.org.uk/nicemedia/live/13237/54081/54081.pdf (last accessed 19 April 2011)
10. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I *et al*. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010; **376:** 1147–1154.
11. Oudard S, Joulain A, De Geer A, Sartor O. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Estimating mean overall survival (OS) for health economics analyses from a phase III trial (TROPIC). ASCO Genitourinary Cancers Symposium. Orlando, Fl, USA, 2011
12. Bissery MC. Preclinical evaluation of new taxoids. *Curr Pharm Des* 2001; **7:** 1251–1257.
13. US Food and Drug Administration. *Cabazitaxel.* www.fda.gov/AboutFDA/CentersOffices/CDER/ucm216214.htm (last accessed 14 October 2010)
14. Cancer Research UK. *CancerStats. Key Facts. Metastatic Hormone-Refractory Prostate Cancer.* http://publications.cancerresearchuk.org/WebRoot/crukstoredb/CRUK_PDFs/CSPROSTATEKEYFACT08.pdf (last accessed 4 January 2011)
15. Cancer Research UK. *Prostate cancer - UK mortality statistics.* http://info.cancerresearchuk.org/cancerstats/types/prostate/mortality/ (last accessed 5 April 2011)
16. Shaneyfelt T, Husein R, Bubley G, Mantzoros CS. Hormonal predictors of prostate cancer: a meta-analysis. *J Clin Oncol* 2000; **18:** 847–853.
17. Cancer Research UK. *CancerStats. Mortality UK.* http://publications.cancerresearchuk.org/WebRoot/crukstoredb/CRUK_PDFs/CSMORT06.pdf (last accessed 4 January 2011)
18. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. *AJCC Cancer Staging Manual,* New York: Springer, 2009.
19. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. *J Urol* 1974; **111:** 58–64.

20. Ellison LF, Stokes J, Gibbons L, Lindsay J, Levy I, Morrison H. Monograph series on aging-related diseases: X. Prostate cancer. *Chronic Dis Can* 1998; **19:** 1–18.
21. Theodorescu D, Krupski T. *Prostate cancer: biology, diagnosis, pathology, staging, and natural history.* http://emedicine.medscape.com/article/458011-media (last accessed 4 January 2011)
22. Bubendorf L, Schopfer A, Wagner U, Sauter G, Moch H, Willi N *et al*. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Hum Pathol* 2000; **31:** 578–583.
23. Carlin BI, Andriole GL. The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. *Cancer* 2000; **88:** 2989–2994.
24. Khan MA, Partin AW. Prostate cancer and chemotherapy. *Rev Urol* 2004; **6:** 167–169.
25. National Collaborating Centre for Cancer. *Clinical guideline 58: Prostate cancer. Diagnosis and treatment.* www.nice.org.uk/nicemedia/pdf/CG58NICEGuideline.pdf (last accessed 21 October 2010)
26. Gommersall LM, Hayne D, Shergill IS, Arya M, Wallace DM. Luteinising hormone releasing hormone analogues in the treatment of prostate cancer. *Expert Opin Pharmacother* 2002; **3:** 1685–1692.
27. Petrylak DP, Tangen CM, Hussain MH, Lara PN, Jr., Jones JA, Taplin ME *et al*. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; **351:** 1513–1520.
28. European Association of Urology. *EAU Guidelines on Prostate Cancer.* www.uroweb.org/gls/pdf/08_Prostate_Cancer.pdf (last accessed 1 June 2011)
29. Small EJ, Vogelzang NJ. Second-line hormonal therapy for advanced prostate cancer: a shifting paradigm. *J Clin Oncol* 1997; **15:** 382–328.
30. Mottet N, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V *et al*. EAU Guidelines on Prostate Cancer. Part II: Treatment of Advanced, Relapsing, and Castration-Resistant Prostate Cancer. *Eur Urol* 2011; **59:** 572–583.
31. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN *et al*. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; **351:** 1502–1512.
32. Cancer Research UK. *Age-standardised (European) incidence and mortality rates for prostate cancer, EU-27, 2008 estimates.* http://info.cancerresearchuk.org/cancerstats/types/prostate/incidence/ (last accessed 3 November 2010)
33. British Association of Urological Surgeons. *BAUS Cancer Registry Analyses of Minimum data set for Urological cancers: January 1st – 31st December 2009.* www.baus.org.uk/OneStopCMS/Core/CrawlerResourceServer.aspx?resource=8D488DF0-55DA-41AB-9A55-2EEA30E55932&mode=link&guid=9a08726924b448ab8c674f40634fc7c6 (last accessed 19 April 2011)
34. Stephenson AJ, Eastham JA. Role of salvage radical prostatectomy for recurrent prostate cancer after radiation therapy. *J Clin Oncol* 2005; **23:** 8198–8203.
35. Cooperberg MR, Cowan J, Broering JM, Carroll PR. High-risk prostate cancer in the United States, 1990-2007. *World J Urol* 2008; **26:** 211–218.
36. American College of Surgeons. *National Cancer Database: Survival reports*. 2008.
[redacted]
38. Firek P, Pfister DA, Thüer D, Brehmer B, Epplen R, Heidenreich A. Docetaxel rechallenge at PSA relapse after docetaxel chemotherapy at hormone-refractory prostate cancer. ASCO Genitourinary Cancers Symposium. San Francisco, CA, USA, 2010.
39. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L *et al*. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011; **364:** 1995–2005.
40. Hoyle M, Dreyfus B, Muhsin M. Decision Resources Inc. *Prostate cancer*. 2008.
41. National Institute for Health and Clinical Excellence. *Guidance on Cancer Services: Improving Outcomes in Urological Cancers, The Manual.* www.nice.org.uk/nicemedia/pdf/Urological_Manual.pdf (last accessed 14 October 2010)
[redacted]

43. National Comprehensive Cancer Network. *NCCN clinical practice guidelines in oncology - prostate cancer.* www.nccn.org (last accessed 1 June 2011)
44. Horwich A, Parker C, Kataja V. Prostate cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009; **20 Suppl 4:** 76–78.
45. Pagliuca A, Carrington PA, Pettengell R, Tule S, Keidan J. Guidelines on the use of colony-stimulating factors in haematological malignancies. *Br J Haematol* 2003; **123:** 22–33.
46. Aapro MS, Cameron DA, Pettengell R, Bohlius J, Crawford J, Ellis M *et al*. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer* 2006; **42:** 2433–2453.
47. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L *et al*. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; **24:** 3187–3205.
48. All Wales Medicines Strategy Group. *Final Appraisal Report: Pegfilgrastim (Neulasta®) for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (Amgen Ltd )* Cardiff: AWMSG, 2008.
49. Scottish Medicines Consortium. *Pegfilgrastim (Neulasta®) No. 67/03 (Amgen Ltd): Summary of Recommendations*. Glasgow: SMC, 2003.
50. National Health Service. *NHS reference costs 2009–2010.* www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459 (last accessed 15 April 2011)
51. National Insitute for Health and Clinical Excellence. *Specification for manufacturer/sponsor submission for Single Technology Appraisal (STA).* www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/singletechnologyappraisalsprocess/specification_for_manufacturer_sponsor_submission_for_single_technology_appraisal_sta.jsp (last accessed 3 February 2011)
52. Sartor AO, Oudard S, Oxguroglu M, Hansen S, Machiels JPH, Shen L *et al*. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results of a multinational phase III trial (TROPIC). American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium San Francisco, USA, 2010
53. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Shen L *et al*. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results of a multinational phase III trial (TROPIC). ASCO Annual Meeting. Chicago, USA, 2010
[redacted]
55. Sternberg CN, Petrylak DP, Sartor O, Witjes JA, Demkow T, Ferrero JM *et al*. Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. *J Clin Oncol* 2009; **27:** 5431–5438.
56. Witjes JA, Petrylak D, Sartor AO, Wirth M, Billiet I, Petrone ME *et al*. Radiologic progression predicts overall survival in patients (pts) with androgen independent prostate cancer (AIPC) who received first line docetaxel; An analysis from the SPARC trial. *Eur Urol* 2009; **8 (Suppl):** 133.
57. Sartor AO, Petrylak DP, Witjes JA, Berry WR, Chatta GS, Vaughn DJ *et al*. Satraplatin in patients with advanced hormone-refractory prostate cancer (HRPC): Overall survival (OS) results from the phase III satraplatin and prednisone against refractory cancer (SPARC) trial. ASCO Annual Meeting. Chicago, IL, USA, 2008
58. Sartor AO, Petrylak DP, Sternberg C, Witjes F, Halabi S, Berry W *et al*. Use of pain at baseline and pain progression to predict overall survival (OS) in patients (pts) with docetaxel pretreated metastatic castration-refractory prostate cancer (CRPC): Results from the SPARC trial. ASCO Annual Meeting. Chicago, FL., 2009

59. Saad F, Hotte SJ, North S, Eigl BJ, Chi KN, Czaykowski P *et al*. A phase II randomized study of custirsen (OGX-011) combination therapy in patients with poor-risk hormone refractory prostate cancer (HRPC) who relapsed on or within six months of 1st-line docetaxel therapy. ASCO Annual Meeting. Chicago, IL, 2008
60. de Bono JS, Fizazi K, Flechon A, Heidenreich A, Voog E, Davis NB *et al*. Randomized phase II study of CNTO 328 (C), an anti-IL-6 monoclonal antibody, in combination with mitoxantrone (M) versus M alone in metastatic castration-resistant prostate cancer (CRPC). Genitourinary Cancers Symposium. San Francisco, CA, 2010
61. Fleming MT, Kolodziej MA, Awasthi S, Hutson TE, Martincic D, Sonpavde G *et al*. Results of a randomized phase II study of mitoxantrone versus mitoxantrone with cetuximab in metastatic castrate-resistant prostate cancer (CRPC) previously treated with docetaxel-based chemotherapy. ASCO General Meeting. Chicago, IL, USA, 2010
62. Rosenberg JE, Weinberg VK, Kelly WK, Michaelson D, Hussain MH, Wilding G *et al*. Activity of second-line chemotherapy in docetaxel-refractory hormone-refractory prostate cancer patients : randomized phase 2 study of ixabepilone or mitoxantrone and prednisone. *Cancer* 2007; **110:** 556–563.
63. Fleming MT, Morris MJ, Heller G, Scher HI. Post-therapy changes in PSA as an outcome measure in prostate cancer clinical trials. *Nat Clin Pract Oncol* 2006; **3:** 658–667.
64. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA *et al*. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008; **26:** 1148–1159.
65. National Cancer Institute, Cancer Therapy Evaluation Program. *Common Terminology Criteria for Adverse Events v3.0 (CTCAE)*. 2006.
66. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol* 2008; **26:** 242–245.
67. Nelson JB, Isaacson JD, Eliopoulos HB, Allen AR. Relationship between time to PSA progression and time to disease progression in patients with hormone-refractory prostate cancer (HRPC). ASCO General Meeting. Chicago, IL, USA, 2003 (Abstract 1642).
68. Halabi S, Vogelzang NJ, Ou SS, Owzar K, Archer L, Small EJ. Progression-free survival as a predictor of overall survival in men with castrate-resistant prostate cancer. *J Clin Oncol* 2009; **27:** 2766-2771.
69. US Food and Drug Administration. *Mitoxantrone.* www.accessdata.fda.gov/drugsatfda_docs/label/2009/019297s030s031lbl.pdf (last accessed 21 April 2011)
70. Berthold DR, Pond G, de Wit R, Eisenberger MA, Tannock IF. Association of pain and quality of life (QOL) response with PSA response and survival of patients (pts) with metastatic hormone refractory prostate cancer (mHRPC) treated with docetaxel or mitoxantrone in the TAX-327 study. ASCO Prostate Cancer Symposium. San Francisco, CA, 2006
71. European Medicines Agency. *Committee for medicinal products for human use (CHMP). Summary of opinion. Jevtana (cabazitaxel)*. London: EMEA, 2010.
72. *British National Formulary,* 2011; **61.**
73. Curtis L. *Personal Social Services Research Unit: Kent. Unit Costs of Health and Social Care 2010.* www.pssru.ac.uk/pdf/uc/uc2010/uc2010.pdf (last accessed 15 April 2011)
[redacted]
76. Sandblom G, Carlsson P, Sennfalt K, Varenhorst E. A population-based study of pain and quality of life during the year before death in men with prostate cancer. *Br J Cancer* 2004; **90:** 1163-1168.
77. Sullivan PW, Mulani PM, Fishman M, Sleep D. Quality of life findings from a multicenter, multinational, observational study of patients with metastatic hormone-refractory prostate cancer. *Qual Life Res* 2007; **16:** 571-575.
78. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes* 2008; **6:** 84.

79. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *Br J Cancer* 2006; **95:** 683-690.
80. Lloyd A, van Hanswijck de Jonge P, Doyle S, Cornes P. Health state utility scores for cancer-related anemia through societal and patient valuations. *Value Health* 2008; **11:** 1178-1185.
81. Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. *Lung Cancer* 2008; **62:** 374-380.
82. Gould MK, Dembitzer AD, Sanders GD, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A cost-effectiveness analysis. *Ann Intern Med* 1999; **130:** 789-799.
83. Treasure T, Hill J. National Clinical Guidelines Centre for Acute and Chronic Conditions. *Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital.* http://guidance.nice.org.uk/CG/Wave14/26 (last accessed 3 March 2011)
84. Lewis G, Peake M, Aultman R, Gyldmark M, Morlotti L, Creeden J *et al*. Cost-effectiveness of erlotinib versus docetaxel for second-line treatment of advanced non-small-cell lung cancer in the United Kingdom. *J Int Med Res* 2010; **38:** 9-21.
85. Kelly S, Wheatley D. Prevention of febrile neutropenia: use of granulocyte colony-stimulating factors. *Br J Cancer* 2009; **101 Suppl 1:** S6-10.
86. Scottish Medicines Consortium. *filgrastim, 30 million units (300 microgram)/0.5mL and 48 million units (480 microgram)/0.8mL, prefilled syringe containing solution for injection or infusion (Ratiograstim).* 2009.
87. Surrey, West Sussex and Hampshire Cancer Network *Guidelines for the Use of G-CSF Following Chemotherapy.* www.swshcn.nhs.uk/healthcare-professionals/clinical-policies-and-protocols/supportive-care/g-csf_network_policy_v1_7.07.pdf (last accessed 3 March 2011)
88. Evans M. London Cancer New Drugs Group. *Guidance on the use of prophylactic Granulocyte Colony Stimulating Factor (GCSF) to support chemotherapy administration.* www.nelm-web.lbi.co.uk/en/Communities/NeLM/LCNDG/Resources/Guidance-on-the-use-of-prophylactic-Granulocyte-Colony-Stimulating-Factor-GCSF-to-support-chemotherapy-administration (last accessed 3 March 2011)
89. Vogel CL, Wojtukiewicz MZ, Carroll RR, Tjulandin SA, Barajas-Figueroa LJ, Wiens BL *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.

28 June 2011

NHS
National Institute for Health and Clinical Excellence

NICE
Midcity Place
71 High Holborn
London
WC1V 6NA

Tel: 020 7045 2236
Fax: 020 7061 9830

Email: jennifer.heaton@nice.org.uk

www.nice.org.uk

Dear [redacted] and [redacted],

**Re: Single Technology Appraisal – cabazitaxel for the second line treatment of hormone refractory, metastatic prostate cancer**

The Evidence Review Group SCHARR and the technical team at NICE have now had an opportunity to take a look at submission received on the 10th June 2011 by Sanofi Aventis. 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 **17:00, 12 July 2011**. 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 emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Anwar Jilani – Technical Lead (anwar.jilani@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

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

## Section A: Clarification on effectiveness data

A1. **Priority question:** p63 – Please clarify why the hazard ratio (HR) used in the submission is that published in the Lancet (0.70) and not the HR of 0.72 calculated in the updated analysis based on 585 rather than 513 deaths. Clarify the effect such as change would have on the ICER.

A2. **Priority question:** p66-67 - Were there a priori reasons why it was believed that the relative effect of treatment would be different between geographical regions? Please provide the results from a test for a treatment by subgroup interaction to determine if these differences are statistically significant.

A3. **Priority question:** p77 and Appendix 16 – Please clarify the apparent disparity between the values reported in Appendix 16 (and used within the model) and those given in Table 5-10, page 77 of the main submission.

A4. p40 – Please confirm that studies of mitoxantrone have been included as an active intervention in the systematic review of all RCTs in second-line metastatic hormone refractory prostate cancer (mHRPC). If not, clarify the rationale for the exclusion.

A5. p40 – Please clarify why the systematic reviews of all RCTs in second-line therapy of mHRPC and of all non-randomised studies in mHRPC were limited to studies published in the English language, while no language restrictions were applied to the systematic review of studies of cabazitaxel versus mitoxantrone.

A6. p44 – Please provide the rates of adverse events from the phase II trial and detail whether adverse events associated with cabazitaxel for breast cancer patients are believed to be different to those for prostate cancer patients.

A7. p50 – Please provide the rationale for why it was considered necessary to avoid extreme imbalance of treatment assignment within a centre, and therefore to use minimisation, which the FDA does not consider to be a truly random allocation method.

A8. p64 – Please confirm that the numbers censored in the cabazitaxel arm and the mitoxantrone arm have been transposed.

## Section B: Clarification on cost-effectiveness data

A9. **Priority question:** Conceptual - The methodology of using the proportions of events between time-cycles for a fitted Weibull curve in addition to the Kaplan-Meier data has been denoted the base case, whereas using the Weibull curve for the entire time period is undertaken as a scenario analysis. This implies a belief that the former method is more appropriate. Please clarify whether this is the case and provide a discussion of the relative advantages and disadvantages of both methodologies. It is noted that the ICER is sensitive to this decision, primarily due to differential numbers in each health state between the Kaplan-Meier data and the Weibull fit.

A10. **Priority question**: Conceptual – Please detail whether any formal statistical tests were used and at which time to decide when the Kaplan–Meier data were considered unreliable. Please clarify the effect on the ICER if these time points were assumed to take different values.

A11. **Priority question:** Conceptual - Parametric distributions were fitted to each curve ignoring the greater number of early deaths, but prolonged survival in the cabazitaxel arm. Please provide a rationale for why this approach was considered more appropriate than estimating proportion of deaths within 30 days and then fitting curves to the remaining (and more coherent) data. Clarify the potential limitations of the method used.

A12. **Priority question:** Best supportive care (BSC) & Post-2nd line mix Sheet (d28:d37 and d44:d53) - The proportion of patients receiving each treatment type for cabazitaxel and mitoxantrone have been transposed compared with the submission (p123). Data for cabizataxel in submission are entered for mitoxanteron in the model and vice versa. Please clarify whether the model or the submission is correct.

A13. **Priority question:** Calculations sheet – Please clarify why the Probabilistic Sensitivity Analyses (PSA) for the base case does not use a distribution the Kaplan-Meier data thus assuming no uncertainty in the survival estimates for the initial cycles.

A14. **Priority question:** Appendix p85-86 - What is the clinical rationale for choosing the Weibull distribution over the Log-logistic distribution for overall survival in the cabazitaxel arm? Please clarify the sensitivity of the results to the choice of distribution.

A15. **Priority question:** Resource Input (d188) – Please clarify why the utility from the 2nd cycle of the early access program (EAP) was used to provide the value for utility in the stable disease state in preference to the baseline value, the cycle 4 value or the all country / UK values from Sullivan et al. Please clarify how sensitive the ICER is to the choice of value of utility in the stable disease state (whilst maintaining the decrement to the progressive disease state).

A16. **Priority question:** KM data and KM subgroups Sheets in the model - Please provide all observations including those censored.

A17. Resource Input Sheet cell (E49) – Please provide a reference for the average weight of 80kg.

A18. Resource Input Sheet cell (J78) – Please provide a fuller reference for the treatment duration of docetaxel, mitoxantrone and carboplatin.

A19. Resource Input Sheet cell (d103) – Please clarify whether the value (2.97) used in the model for total inpatient days per neuropathy episode or the value provided in the submission (2.77 – p129) is correct.

A20. Resource Input Sheet cell (i89:j103) – Please provide references for the drug doses following adverse events and the proportion of patients taking each drug.

A21. Resource Input Sheet cell (d160 and elsewhere) – Please clarify whether these data come from expert opinion (as commented in the model) or whether these are from the UK audit as reported on p119 of the submission.

A22. Resource Input Sheet cell (d202) – Please clarify whether the value (0.245) used in the model for the disutility associated with pulmonary embolism or the value provided in the submission (0.145 – p111) is correct.

A23. Resource Input Sheet cell (d202) – Please clarify whether the value (£107) used in the model for the cost of external beam radiation or the value provided in the submission (£112 – p127) is correct.

A24. AE Care - Patients receiving treatment for adverse effects are assumed to have zero outpatient visits or GP appointments implying that the drugs are prescribed without additional resource implications. Please clarify the rationale for this assumption.

A25. Risk AEs Sheet cell (j10:j38) – Please reference the values for the duration of adverse effects.

A26. Risk AEs Sheet cell ("RRneutropeniaProph") - The value for this variable has been set blank (i.e. zero) in the deterministic models, and the distribution that should be assigned in the lognormal PSA values has been left blank. Please rectify as appropriate.

A27. Risk AEs ("M10:M42") - For consistency, please divide these cells by 365.25 not 365.

A28. Calculations (throughout) - It is unclear why the periodically discounted values have not been calculated using the standard approach of …* 1/ (t)1.035. Using the standard approach provides different values to those within the model. Please clarify the appropriateness of the methodology.

A29. Calculations Sheet cell (columns u and w) – Please clarify why these columns are multiplied by the survival rate within the relevant time period.

A30. PSA calculations Sheet cell (columns e44:e55 and e57:e58) – Please clarify why the standard errors for these cells have been assumed to be estimated from the ratio of base value to SE of bone pain.

A31. PSA Calculations Sheet cell (e43) – Please clarify why the standard error for the utility in progressive state is assumed to be half of the base value.

A32. PSA Calculations Sheet cell (e59) – Please clarify how the standard error for body surface area was estimated.

A33. PSA Calculations Sheet cell (row 59) – Please clarify why the distribution for body surface area used in the probabilistic sensitivity has a mean of 1.93 whilst the deterministic value is 2.01.

A34. PSA Calculations Sheet cell (e110:e124) - The standard errors used in the model have been estimated using the Beta-Pert method, however the report (p134) indicates this would be calculated from quartile data from NHS costs. Please explain this discrepancy.

A35. p133 – Please provide a reference for the Beta-Pert methodology.

## Section C: Textual clarifications and additional points

**A36. If any corrections are made to the economic model as a result of clarification please provide an updated model with an explanation of all corrections.**

## Section A: Clarification on effectiveness data

A1. **Priority question:** p63 – Please clarify why the hazard ratio (HR) used in the submission is that published in the Lancet (0.70) and not the HR of 0.72 calculated in the updated analysis based on 585 rather than 513 deaths. Clarify the effect such as change would have on the ICER.

This data referred to within the submission was used to be consistent with the data in the regulatory submissions to the EMA and FDA, the peer-reviewed Lancet publication and the clinical study report. Using the original OS data-set also provides consistency between endpoints – the cut-off time-point for all secondary endpoints was the same as that for the original OS data-set.

The difference between the incremental mean OS calculated from the earlier data-set compared to the updated analysis is 0.06 months (~1.8 days) for the European population with ECOG PS 0,1 and with ≥225 mg/m$^2$ of previous docetaxel (base case - Table 1) or 0.2 months (~6 days) for the whole TROPIC population. Using the updated data-set in the model gives an ICER of £82,963 per QALY (using the fitted curves throughout) which is very similar to the ICER of £82,950 obtained with the original OS data.

A comparison of the updated data-set with the original data-set for the *whole* TROPIC population, as reported in the Lancet publication and regulatory submissions, is shown in Table 2.

**Table 1: Comparison of original and updated OS data for European patients with ECOG PS 0, 1 and with ≥ 225 mg/m² of previous docetaxel (N=340)**

| | MTX+PRED | | | CBZ+PRED | | | CBZ+PRED vs MTX+PRED | | |
|---|---|---|---|---|---|---|---|---|---|
| | Number dead / N (%) | median survival (95% C.I.) | mean survival | Number dead / N (%) | median survival (95% C.I.) | mean survival | Hazard Ratio (HR) | Median difference | Mean difference |
| Updated data-set | [redacted] | | | | | | | | |
| Original data-set used in submission | | | | | | | | | |

**Table 2: Comparison of original and updated OS data for whole TROPIC population (N=755)**

| OS | MTX+PRED | | | CBZ+PRED | | | CBZ+PRED vs MTX+PRED | | |
|---|---|---|---|---|---|---|---|---|---|
| | Number dead / N (%) | median survival (95% C.I.) | mean survival | Number dead / N (%) | median survival (95% C.I.) | mean survival | Hazard Ratio (HR) | Median difference | Mean difference |
| Updated OS | 308/377 (81.7%) | 12.7 (11.5–13.7) | 14.5 | 277/378 (73.3%) | 15.1 (14.0–16.5) | 18.5 | 0.72 (0.61–0.84) | 2.4 | 4.0 |
| Original OS | 279/377 (74.0%) | 12.7 (11.6–13.7) | 14.0 | 234/378 (61.9%) | 15.1 (14.1–16.3) | 18.2 | 0.70 (0.59–0.83) | 2.4 | 4.2 |

A2. **Priority question:** p66-67 - Were there a priori reasons why it was believed that the relative effect of treatment would be different between geographical regions? Please provide the results from a test for a treatment by subgroup interaction to determine if these differences are statistically significant.

As is common with international clinical trials, analyses of regional sub-groups were pre-planned. There was no a priori clinical hypothesis for a difference in treatment effect by region. However, treatment practices vary between different countries, and these different practices can affect treatment outcomes.

The interaction of treatment by region is not statistically significant. This is true of the whole population (p value =0.1535), or in the base-case, ECOG 0-1 patients who received ≥225 mg/m$^2$ docetaxel (p = 0.4098).

A3. **Priority question:** p77 and Appendix 16 – Please clarify the apparent disparity between the values reported in Appendix 16 (and used within the model) and those given in Table 5-10, page 77 of the main submission.

In the clinical section, AE rates are presented as the percentage of patients experiencing each specified adverse event, as is standard for presenting clinical safety data, and reflects the information presented in the SmPC. The model however, accounts for the fact that some patients in the TROPIC trial experienced the same AE more than once. This was done to provide a more accurate estimate of the AE costs likely to be experienced with cabazitaxel in practice. Furthermore, in the clinical section, rates of neutropenia, thrombocytopenia and leukopenia were based on laboratory data, whereas in the model, these were retrieved from clinical AE report forms.

A4. p40 – Please confirm that studies of mitoxantrone have been included as an active intervention in the systematic review of all RCTs in second-line metastatic hormone refractory prostate cancer (mHRPC). If not, clarify the rationale for the exclusion.

Yes, studies of mitoxantrone were included in this review. Searches and inclusion of studies were not limited by drug.

p40 – Please clarify why the systematic reviews of all RCTs in second-line therapy of mHRPC and of all non-randomised studies in mHRPC were limited to studies published in the English language, while no language restrictions were applied to the systematic review of studies of cabazitaxel versus mitoxantrone.

These reviews were conducted at different times and with slightly different objectives, which is the reason for this slight difference in the inclusion criteria.

For the systematic review of all RCTs in second-line chemotherapy, we have reviewed the list of 29 studies that were excluded on the basis of being non-English language; they would all have been excluded for the following reasons (one of which was published after the original search date). A full list of studies is provided in Appendix 1.

- Review articles or expert opinion - 11
- Non-RCTs or non-comparative studies - 11
- Not mHRPC - 5
- Duplicates - 1
- No abstract - 1

A5. p44 – Please provide the rates of adverse events from the phase II trial and detail whether adverse events associated with cabazitaxel for breast cancer patients are believed to be different to those for prostate cancer patients.

Differences would be expected between the safety profile of cabazitaxel in breast cancer versus prostate cancer. In addition to the difference in gender, patients in the breast cancer trial were younger (median age 53 versus 67-68 in TROPIC). There were also differences in prior therapy received – for example in the breast cancer population, 35% patients had received paclitaxel as the previous taxane, and 65% had received docetaxel. Almost 10% had received more than one prior taxane. It is also likely many breast cancer patients would have received combination therapy with a taxane and anthracycline, as is common in breast cancer, whereas prostate cancer patients would typically receive single agent docetaxel. Fifty-four (76%) of patients in the breast cancer trial had prior exposure to an anthracycline. In addition, radiotherapy is more frequently used in prostate cancer compared to breast cancer. Differences in prior therapy are likely to have had an effect on bone marrow depletion and thus on rates of neutropenia and other haematological AEs. An additional difference is that in the breast cancer trial, the intended cabazitaxel dose was 20 $mg/m^2$, as compared to 25 $mg/m^2$ in prostate cancer, although in the breast cancer trial 28% of patients received the increased dose of 25 $mg/m^2$. Baseline characteristics are provided in Appendix 2 to allow comparison.

Rates of AEs from the Phase II breast cancer trial are shown in Table 3.

**Table 3: Grade 3 – 5 AEs possibly or probably related to study treatment in Phase II breast cancer study (Pivot 2008[1])**

| AE | All – N (%) | Grade 3 – 4– N (%) |
|---|---|---|
| Neutropenia | 67 (94) | 52 (73) |
| Leukopenia | 69 (97) | 39 (55) |
| Anaemia | 64 (90) | 2 (3) |
| Thrombocytopenia | 7 (10) | 3 (4) |
| All grade 4 neutropenia | | 35 (49) |
| Lasting >5 days | | 19 (27) |
| Febrile neutropenia | | 2 (3) |
| Neutropenic infection | | 3 (4) |
| Hypersensitivity reaction | 4 (6) | 3 (4) |
| Fatigue | 25 (35) | 2 (3) |
| Haemorrhagic cystitis | 2 (3) | 2 (3) |
| Diarrhoea | 21 (30) | 1 (1) |
| Headache | 7 (10) | 1 (1) |
| Peripheral oedema | 6 (8) | 1 (1) |
| Infection without neutropenia | 3 (4) | 1 (1) |
| Arrhythmia supraventricular | 1 (1) | 1 (1) |
| Cyanosis | 1 (1) | 1 (1) – death |
| Dyspnoea | 1 (1) | 1 (1) – death |
| Incontinence | 1 (1) | 1 (1) |
| Injection site reaction | 1 (1) | 1 (1) |
| Irregular menses | 1 (1) | 1 (1) |
| Pleural effusion | 1 (1) | 1 (1) |
| Thromboembolism | 1 (1) | 1 (1) |

A6. p50 – Please provide the rationale for why it was considered necessary to avoid extreme imbalance of treatment assignment within a centre, and therefore to use minimisation, which the FDA does not consider to be a truly random allocation method.

A stratified randomisation was used with two stratifications - measurable disease and ECOG performance status. Centre was considered as a factor only when extreme imbalance of treatment occurred within a centre. These cases were rare. Even in such a situation, dynamic allocation was not a deterministic assignment. Investigators were not informed of the algorithm of the assignment. We agree that minimisation within a centre should be avoided in clinical trials. For this trial, the main reason of using this method was to minimise the impact of centre effects on the factors such as the management of pain, adverse events (e.g. G-CSF use for neutropenia) and quality of tumour assessments.

A7. p64 – Please confirm that the numbers censored in the cabazitaxel arm and the mitoxantrone arm have been transposed.

Numbers were incorrectly transposed in the text. The text should read “Patients were censored in both arms (144 in the cabazitaxel group, 98 in the mitoxantrone group).”

## Section B: Clarification on cost-effectiveness data

A8. **Priority question:** Conceptual - The methodology of using the proportions of events between time-cycles for a fitted Weibull curve in addition to the Kaplan-Meier data has been denoted the base case, whereas using the Weibull curve for the entire time period is undertaken as a scenario analysis. This implies a belief that the former method is more appropriate. Please clarify whether this is the case and provide a discussion of the relative advantages and disadvantages of both methodologies. It is noted that the ICER is sensitive to this decision, primarily due to differential numbers in each health state between the Kaplan-Meier data and the Weibull fit.

There are two key reasons why parametric functions are required in survival analysis. Firstly, to extrapolate for events occurring beyond the trial cut-off point and secondly, to account for the small patient numbers and instability in the tail of the Kaplan-Meier curves. A parametric function addresses this instability to generate transition probabilities which show a more consistent pattern.

In the base-case we use the Kaplan-Meier data, over the period for which these were considered reliable by the modelling team, followed by fitted curves.

The approach used in the base-case allows for calculations to be based on the actual empirical trial data, rather than a 'best-fit' mathematical function, for the timeframe over which such data are available and reliable. With this method, the calculations in the model therefore reflect more accurately the actual proportions of patients progressing and dying in the TROPIC trial.. Whilst we have taken every effort to ensure the parametric functions, wherever applied, represent the best possible fit to the trial data, these are still fitted functions and we considered that using the actual empirical data offered greater validity to the assessment.

The main disadvantage of using Kaplan-Meier data is as mentioned above, the unreliability towards the tail of the curve due to low patient numbers. However, this is avoided in our model by switching to the parametric functions when the Kaplan-Meier data are judged unreliable (see answer to question A10). A further disadvantage is that probabilities are derived from 'standard' stepped-survival curve overtime time, rather than a smoothed function providing precise estimates at each time interval.

A9. **Priority question**: Conceptual – Please detail whether any formal statistical tests were used and at which time to decide when the Kaplan–Meier data were considered unreliable. Please clarify the effect on the ICER if these time points were assumed to take different values.

No formal statistical tests were used to decide when the Kaplan-Meier data were considered unreliable. This assessment was based on judgement. For modelling overall survival in the UK base case the switch is performed when four consecutive cycles reported zero events. This occured at week 114 (cycle 38) for OS.
If the switch is performed to avoid any cycles with zero events, the switch occurs at cycle 9 and gives an ICER of £82,173 per QALY.
If the switch is performed to have a maximum of one zero, the switch occurs at cycle 35 and gives an ICER of £80,311.
If the switch is performed to have a maximum of two zeros, the switch occurs at cycle 36 and gives an ICER of £77,581.

If the switch is performed to have a maximum of three zeros, the switch occurs at cycle 37 and gives an ICER of £76,220.

When assuming different timepoints for the switch, the ICER varies between 72 184 and 90 786 £/QALY, as shown in Table 4.

**Table 4: Impact of switching from Kaplan-Meier data to parametric function at different timepoints**

| Cycle | Week | ICER (£/QALY) for UK base case |
|---|---|---|
| 39 | 118 | 72 348 |
| **38** | **114** | **74 908 base case** |
| 37 | 111 | 76 220 |
| 36 | 108 | 77 581 |
| 35 | 105 | 80 311 |
| 34 | 102 | 82 997 |
| 33 | 99 | 82 875 |
| 32 | 96 | 85 422 |
| 31 | 93 | 86 231 |
| 30 | 90 | 82 400 |
| 29 | 87 | 86 140 |
| 28 | 84 | 90 786 |
| 27 | 81 | 87 757 |
| 26 | 78 | 89 004 |
| 25 | 75 | 87 480 |
| 24 | 72 | 90 593 |
| 23 | 69 | 87 820 |
| 22 | 66 | 88 626 |
| 21 | 63 | 78 534 |
| 20 | 60 | 73 957 |
| 19 | 57 | 75 355 |
| 18 | 54 | 77 636 |
| 17 | 51 | 72 184 |
| 16 | 48 | 73 698 |
| 15 | 45 | 75 009 |
| 14 | 42 | 80 864 |
| 13 | 39 | 80 329 |
| 12 | 36 | 80 921 |
| 11 | 33 | 80 542 |
| 10 | 30 | 80 118 |
| 9 | 27 | 82 173 |
| 8 | 24 | 76 528 |
| 7 | 21 | 76 433 |
| 6 | 18 | 72 748 |
| 5 | 15 | 73 579 |
| 4 | 12 | 76 451 |
| 3 | 9 | 79 955 |
| 2 | 6 | 82 428 |
| 1 | 3 | 79 523 |

For PFS the model switches from KM to Weibull or lognormal at week 60 (cycle 20). The curve for PFS would be expected to be less sensitive to the issue of the timepoint at which to switch to the fitted curves because the entire PFS curve is much shorter than for OS and therefore there is a shorter period over which the choice to switch could be made.

A10. **Priority question:** Conceptual - Parametric distributions were fitted to each curve ignoring the greater number of early deaths, but prolonged survival in the cabazitaxel arm. Please provide a rationale for why this approach was considered more appropriate than estimating proportion of deaths within 30 days and then fitting curves to the remaining (and more coherent) data. Clarify the potential limitations of the method used.

In the base-case we use the actual Kaplan-Meier data over the initial part of the curves (which includes the early deaths) and therefore these early deaths are fully accounted for within the analysis. Furthermore, as the entire shape of the K-M curve is used when fitting the parametric functions, the early deaths are not ignored

In addition, the clinical relevance of early deaths in the TROPIC trial, as indicated on the Kaplan-Meier curve, should be considered when hypothesising the likely real-life impact of cabazitaxel on overall survival. In the ITT population, there were 8 deaths in the cabazitaxel arm and 3 in the mitoxantrone arm which occurred within 30 days of randomisation (in the safety population, there were 7 deaths on cabazitaxel and 2 deaths on mitoxantrone within this time period as 2 patients never received study drug). These deaths prompted an ad hoc meeting of the IDMC, which concluded that these deaths were mainly due to neutropenic events, particularly in the cabazitaxel arm, and that the events leading to death should have been manageable. Based on IDMC recommendations the investigators were advised to follow strictly the protocol regarding dose delay and modifications and to treat neutropenia per ASCO guidelines. These recommendations were instituted and no new neutropenic deaths were reported. As a result of this experience in TROPIC, the need to actively manage side-effects is emphasised in cabazitaxel prescribing materials. UK physicians have experience in managing neutropenia and its complications through experience with docetaxel.

[Please note that unfortunately there is an error in the main submission document in relation to this topic. In the submission (pg 64) we report 18 deaths due to cabazitaxel, and 7 due to mitoxantrone occurred within 30 days. However, these numbers do not just include deaths occurring within 30 days of randomisation. There were 18 treatment-emergent adverse events leading to death with cabazitaxel, all of which occurred within 30 days of the last infusion. There were 7 treatment-emergent adverse events leading to death with mitoxantrone, 5 of which occurred within 30 days of the last infusion.]

**Additional analyses**

To fully explore the impact of the early deaths, we performed an analysis removing the patients who died within 30 days. Mean OS was extrapolated using a Weibull distribution as in the primary analyses. This was performed for both the base-case population (European, ECOG 0 -1, and received ≥225 mg/m$^2$ docetaxel) and the whole TROPIC population. Further details of statistical analyses undertaken are provided in Appendix 3.

***Base-case population*:**

1 patient in the mitoxantrone arm (0.6%) and 2 patients in the cabazitaxel arm (1.1%) died within the first month after randomisation. Parameters removing these patients are shown in Table 5.

**Table 5: Parameters for base-case population excluding patients who died within the first 30 days**

| | MTX+PRED | | | CBZ+PRED | | | CBZ+PRED vs MTX+PRED | |
|---|---|---|---|---|---|---|---|---|
| OS | Number dead / N (%) | median survival (95% C.I.) | mean survival | Number dead / N (%) | median survival (95% C.I.) | Mean survival | Hazard Ratio (HR) | Median difference |
| European patients with ECOG PS 0, 1 and received ≥ 225 mg/m² of docetaxel - Removing patients who died within 30d | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

The ICER using this Weibull parameterisation from cycle 38 onwards is £78,319 per QALY.

It should be noted that the loglogistic and lognormal distributions provide slightly lower AIC, BIC criteria compared to the Weibull distribution for the cabazitaxel arm when removing the patients that died within 30 days. However, these both tend to overestimate survival at the tail of the curve. Mean OS using the loglogistic distribution is 24.6 months in cabazitaxel arm, and 23.4 using the lognormal distribution (vs 19.3 with Weibull). Using the loglogistic or lognormal distributions in preference to the Weibull would therefore be expected to decrease the ICER.

*The whole TROPIC population:*

Three patients in the mitoxantrone arm (0.8%) and eight patients in the cabazitaxel arm (2.1%) died within the first month after randomization. Parameters removing these patients are shown in Table 6.

**Table 6: OS parameters for whole population excluding patients who died within the first 30 days**

| | **MTX+PRED** | | | **CBZ+PRED** | | | **CBZ+PRED vs MTX+PRED** | |
|---|---|---|---|---|---|---|---|---|
| OS | Number dead / N (%) | median survival (95% C.I.) | mean survival | Number dead / N (%) | median survival (95% C.I.) | Mean survival | Hazard Ratio (HR) | Median difference |
| Whole TROPIC population - Removing patients who died within 30d | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

The ICER using this Weibull parameterisation from cycle 38 onwards is £95 691/QALY.

A11. **Priority question:** Best supportive care (BSC) & Post-2nd line mix Sheet (d28:d37 and d44:d53) - The proportion of patients receiving each treatment type for cabazitaxel and mitoxantrone have been transposed compared with the submission (p123). Data for cabizataxel in submission are entered for mitoxanteron in the model and vice versa. Please clarify whether the model or the submission is correct.

The model is correct. The numbers were incorrectly reported in the submission; this error therefore does not affect the cost-effectiveness results.

A12. **Priority question:** Calculations sheet – Please clarify why the Probabilistic Sensitivity Analyses (PSA) for the base case does not use a distribution the Kaplan-Meier data thus assuming no uncertainty in the survival estimates for the initial cycles.

The original submitted model did not assign distributions to the Kaplan-Meier data, and thus underestimates the uncertainty in the survival estimates. We recognise that this is a considerable limitation in the submitted model and have developed an approach that does assign uncertainty to the Kaplan-Meier data. It is quite challenging to incorporate this within the model structure, and thus we have provided a separate "probabilistic" model, which can only be run for the PSA, while the deterministic model remains the same (other than some minor corrections addressed in response to these clarification questions).

**Methods:**
In order to assign uncertainty to each parameter in the K-M trial outputs, beta distributions were used to generate different curves, each time the model is run. The alpha and beta parameters were calculated by:

*α = [Probability survive] x [sample size]*

*β = [(1 – probability survive)] x [sample size]*

However, in order to generate a logical curve (i.e. avoiding 'unlikely' steps or 'impossible' increases in the curve), a single random seed was generated, which would populate the whole curve. That is, for any cycle, n, in the model, the probabilistic parameter was calculated by:

*PSA value = BETAINV(FIXED RANDOM SEED,alpha,beta)*

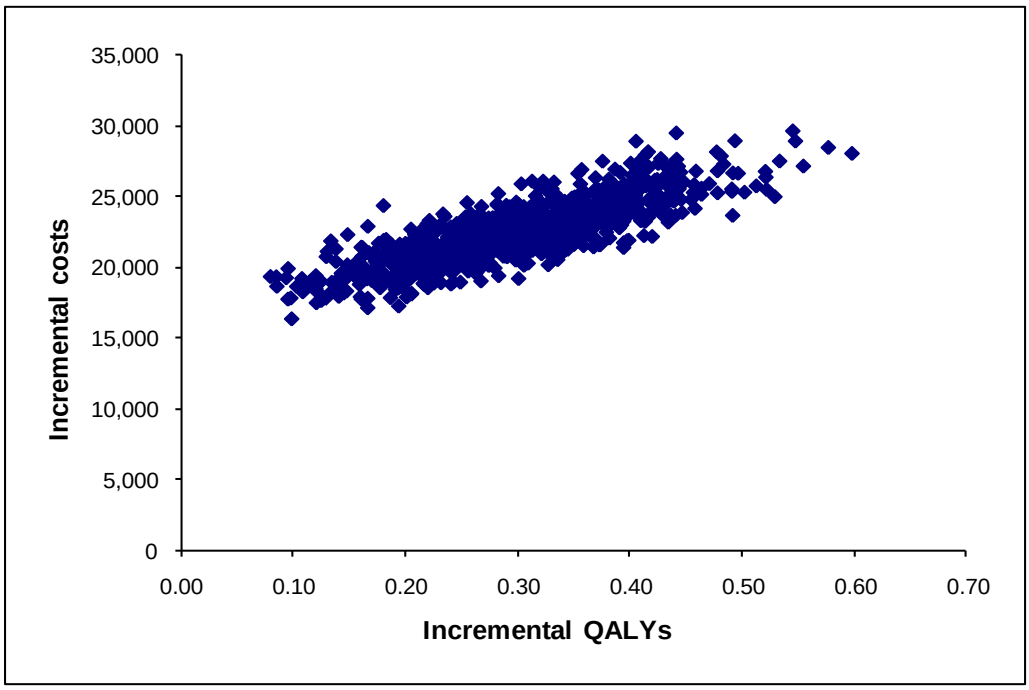
A separate seed was used for the cabazitaxel and mitoxantrone arms, since there would be no dependence between the two, and this approach allows the curves to overlap. However, the same seed was used *within* each arm for the OS and PFS parameters. This was to ensure that the PFS curve could not be higher than the OS curve.

The full PSA inputs can be seen in the following sheets:

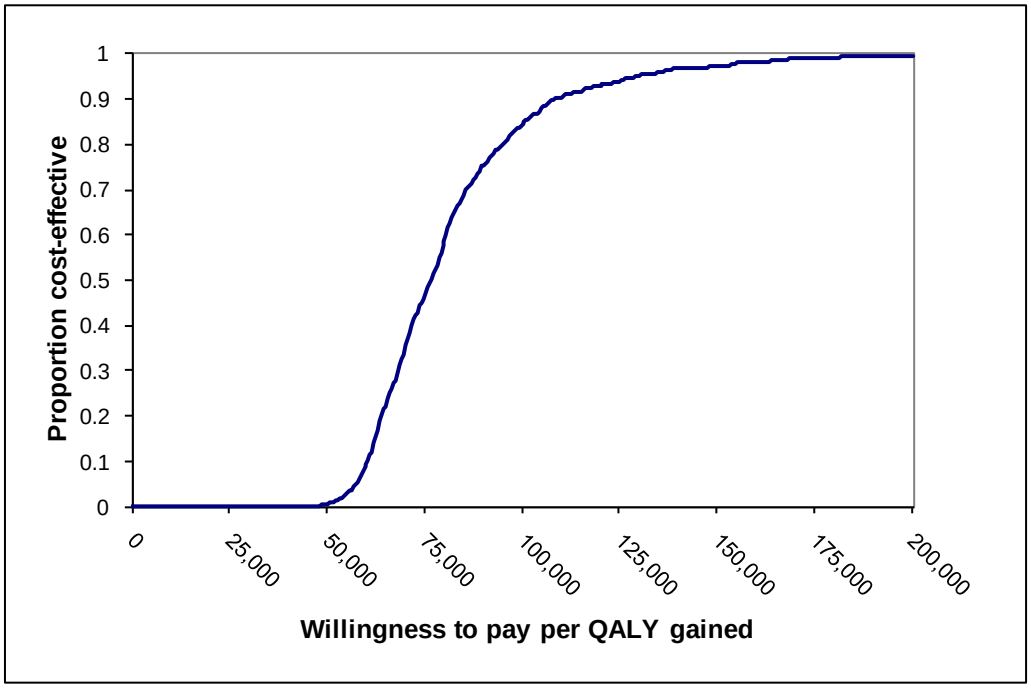
'KM data' sheet:
Random seeds: cells E1 and K1.
Probabilistic inputs: cells E4:E40, K4:K40, AM4:AM21, AS4:AS21 (and subsequent cells for two additional subgroups)
Mean probabilities and sample size: cells DH1:DO40.

'KM subgroups' sheet:
Random seeds: cells E2 and K2.
Probabilistic inputs: cells E5:E41, K5:K41, AM5:AM23, AS5:AS23 (and subsequent cells for two additional subgroups)
Mean probabilities and sample size: cells BU2:CB41 (and subsequent cells for two additional subgroups).

The probabilistic sensitivity analysis was subsequently re-run with the above inputs, and this produced the following cost-effectiveness scatter-plot:



This generated the following cost-effectiveness acceptability curve:




At a willingness-to-pay per QALY of £60,000, there is a 9.4% chance of cabazitaxel being cost-effective. At a willingness-to-pay of £70,000, the probability is 35.5%. At £80,000, the probability is 58.7%, whilst at £90,000 it is 75.4%.

A13. **Priority question:** Appendix p85-86 - What is the clinical rationale for choosing the Weibull distribution over the Log-logistic distribution for overall survival in the cabazitaxel arm? Please clarify the sensitivity of the results to the choice of distribution.

There is no clinical rationale for this choice. According to AIC and BIC criteria, both the Weibull and log-logistic distributions provide a good fit to the data in the cabazitaxel arm. The choice of the Weibull was based on two further considerations. Firstly, the Weibull is the best fit for the cabazitaxel OS in all the other patient subgroups and the whole TROPIC population, and also in the mitoxantrone arm. Given that both are a good fit, it seems reasonable to maintain consistency between analyses by using the same distribution for different patient subgroups. Secondly, graphically, the log-logistic distribution appears to overestimate OS at the end of the curve. It was on this basis that the Weibull was chosen for the cabazitaxel arm.

With the log-logistic, the mean OS for cabazitaxel is 26.4 months, in comparison with 19.4 months with the Weibull distribution. This is much higher than that seen with the other subgroups and would be somewhat inconsistent with them. Thus the choice of Weibull distribution can be viewed as best reflecting the overall dataset.

A14. **Priority question:** Resource Input (d188) – Please clarify why the utility from the 2nd cycle of the early access program (EAP) was used to provide the value for utility in the stable disease state in preference to the baseline value, the cycle 4 value or the all country / UK values from Sullivan et al. Please clarify how sensitive the ICER is to the choice of value of utility in the stable disease state (whilst maintaining the decrement to the progressive disease state).

The utility from the 2nd cycle of the EAP dataset was considered the most appropriate value for the stable disease state in the model. Stable disease is disease which is not progressing and is controlled by treatment.

The baseline value in the EAP comes from patients who have been selected for cabazitaxel treatment on the basis of disease progression after first-line docetaxel treatment (but they have not yet begun second-line treatment). Therefore, the baseline value represents the utility for "first-line disease progression patients". It does not represent stable disease. Further, patients are not receiving cabazitaxel at this timepoint. Therefore, it is less appropriate than the Cycle 2 value. Cycle 4 data were not used due to the small number of patients (7) for whom data were available. As the EAP matures, we plan to update both SD and PD values and could potentially calculate a value for SD based on an average across all cycles for which robust data are available.

The Sullivan 2007[2] paper is not considered as robust a data source for SD as the Cycle 2 EAP data. This study included patients with mHRPC, however, in terms of treatment, patients were managed "according to standard clinical practice". There was no requirement for patients to have their disease managed through active chemotherapy. In addition, the study is not restricted to the second-line setting. Therefore, not all patients necessarily have stable disease on second-line treatment. The study is also not restricted to patients suitable for active chemotherapy. The EAP data are therefore more representative of patients in the base-case model as they were all receiving active therapy with cabazitaxel.

A summary of the impact on the ICER of using alternative sources for the SD utility is shown in Table 7.

**Table 7: Impact of alternative SD utility values on the ICER**

| Scenario | ICER |
|---|---|
| Base-case | 74,908 |
| EAP baseline utility value | 83,584 |
| Cycle 4 utility value | 81,345 |
| Average of cycle 2 and cycle 4 utility | 77,994 |
| Sullivan 2001 baseline value | 82,449 |

A15. **Priority question:** KM data and KM subgroups Sheets in the model - Please provide all observations including those censored.

Four Excel files attached to email – all considered academic in confidence

A16. Resource Input Sheet cell (E49) – Please provide a reference for the average weight of 80kg.

This value came from expert opinion. An average weight of 75 kg is often used for the general population, but the slightly higher weight of 80 kg was judged more realistic for an all-male population, particularly given the relatively high BSA (2.01, as from TROPIC). It should be noted that this value has very little impact as only G-CSF is dosed on a per kg basis; varying either way by 10 kg varies the ICER by £127.

A17. Resource Input Sheet cell (J78) – Please provide a fuller reference for the treatment duration of docetaxel, mitoxantrone and carboplatin.

The UK treatment audit provided the mean duration of treatment for patients receiving docetaxel, mitoxantrone, and two carboplatin-based regimens (Table 8). The average was taken of the two carboplatin-based regimens. Data were provided in months, and are presented in weeks in the model.

**Table 8: Duration of post-second-line treatment from UK treatment audit**

| Duration (months) of 3rd line treatment | Docetaxel | Mitoxantrone | ECarboF | Carboplatin + etoposide |
|---|---|---|---|---|
| n | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean | | | | |

A18. Resource Input Sheet cell (d103) – Please clarify whether the value (2.97) used in the model for total inpatient days per neuropathy episode or the value provided in the submission (2.77 – p129) is correct.

The correct figure is 2.77 days per stay, based on the data for non-elective inpatient visits (see below).

**Table 9: Neuropathy management costs**

| Currency Code | Currency Description | Activity | National Average Unit Cost | Lower Quartile Unit Cost | Upper Quartile Unit Cost | No. of Bed Days | Average Length of Stay - Days | No. Data Submissions |
|---|---|---|---|---|---|---|---|---|
| PA01B[3] | Nervous System Disorders without CC | 1,230 | £1,537 | £781 | £1,641 | 3,411 | 2.77 | 338 |

This has been corrected in the model, and the change in results is shown below:

**Table 10: Impact of correcting neuropathy length of stay on model results**

| | Incremental cost | Incremental QALYs | ICER |
|---|---|---|---|
| Original submitted model | £22,325 | 0.298 | £74,908 |
| Corrected model | £22,325 | 0.298 | £74,908 |

It be seen that the change in input has a negligible effect on the results (so negligible that the change does not impact upon the results when rounded to integers).

A19. Resource Input Sheet cell (i89:j103) – Please provide references for the drug doses following adverse events and the proportion of patients taking each drug.

Both these parameters were based on clinical expert opinion. This was because it is difficult to accurately assign drugs filed in the TROPIC database to management of specific AEs. A summary of responses received from the four experts consulted is provided in

Table 11.

**Table 11: Expert opinion on AE management**

| AE (grade >3) | Treatment | Mean (%) Proportion | Dosing | Treatment duration |
|---|---|---|---|---|
| **Neutropenia** | filgastrim | 50% | 300 micrograms per day | 7-14 days |
| | not treated | 50% | | |
| **Febrile neutropenia** | filgastrim | 20% | 300 micrgrams | 3 days |
| | teicoplanin | 20% | 100 mg od | 3 days |
| | gentamicin | 60% | 200 mg od | 3 days |
| **Leukopenia** | filgastrim | 25% | 300 micrograms per day | 7-14 days |
| | not treated | 75% | | |
| **Thrombocytopenia** | platelet transfusion | 5% | 1 pool per day | 2 days |
| | not treated | 95% | | |
| **Fatigue** | dexamethasone | 20% | 4-8mg | 2-4 weeks |
| | not treated | 80% | | |
| **Nausea** | domperidone | 30% | 20mg qds | 8 |
| | metoclopramide | 30% | 10mg tds | 8 |
| | cyclizine | 20% | 10 mg qds | 8 |
| | ondansetron | 20% | 8 mg bd | 8 |
| **Diarrhea** | imodium | 100% | 1mg | 1-2 weeks |
| **Bone Pain** | co-codamol | 50% | 1000/60 qds | 7 |
| | diclofenac | 50% | 50mg tds | 7 |
| **Peripheral Sensory Neuropathy** | amitryptilline | 10% | 25mg | 3-6 months |
| | not treated | 90% | | |
| **Deep Vein Thrombosis** | warfarin | 100% | 3mg od | 6months |
| **Pulmonary Embolism** | warfarin | 100% | 3mg od | 6months |
| **Anemi** | blood transfusion | 60% | 2 u | once |
| | not treated | 40% | | |
| **Asthenia** | dexamethasone | 20% | 4-8mg | 2-4 weeks |
| | not treated | 80% | | |
| **Back pain** | co-codamol | 50% | 1000/60 qds | 7 |
| | diclofenac | 50% | 50mg tds | 7 |
| **Dehydration** | Intravenous drip | | | |

A20. Resource Input Sheet cell (d160 and elsewhere) – Please clarify whether these data come from expert opinion (as commented in the model) or whether these are from the UK audit as reported on p119 of the submission.

These come from expert opinion as commented in the model (and also in line with the methods section of the submission – 6.5.4). This was incorrectly listed as coming from the audit in the submission.

A21. Resource Input Sheet cell (d202) – Please clarify whether the value (0.245) used in the model for the disutility associated with pulmonary embolism or the value provided in the submission (0.145 – p111) is correct.

The value in the submission is correct. This was incorrectly entered in the model. As reported in the submission, the value of 0.145 represents an average of two studies reporting the disutility due to pulmonary embolism (Haentjens 2004[4], referencing Gould 1999[5], and Treasure 1999[6]). This has been updated in the model and the impact on results is shown below.

**Table 12: Impact of correcting disutility due to pulmonary embolism**

| | Incremental cost | Incremental QALYs | ICER |
|---|---|---|---|
| Original submitted model | £22,325 | 0.298 | £74,908 |
| Corrected model | £22,325 | 0.298 | £74,938 |

A22. Resource Input Sheet cell (d202) – Please clarify whether the value (£107) used in the model for the cost of external beam radiation or the value provided in the submission (£112 – p127) is correct.

The cost of £107 is correct in the model. The source is NHS Reference Costs 2009-2010, 'SC22Z: Deliver a fraction of treatment on a megavoltage machine' in 'NHS Trusts Radiotherapy Treatment: Outpatient'[3].

A23. AE Care - Patients receiving treatment for adverse effects are assumed to have zero outpatient visits or GP appointments implying that the drugs are prescribed without additional resource implications. Please clarify the rationale for this assumption.

It is assumed that chemotherapy, and the management of AEs associated with chemotherapy, will occur largely within the specialist uro-oncology setting, rather than within the community (general practice) setting. We assume that patients experiencing severe AEs will be hospitalised, using rates that were observed in the TROPIC trial. Because not all hospitalisations may be recorded as being due to specific AEs in the TROPIC database, rates were validated with external experts to ensure they were clinically reasonable.

We assume that AEs in patients who do not require hospitalisation will be managed through the outpatient visits that occur regularly throughout the treatment period – including both visits associated with chemotherapy administration and the regular visits not directly related to chemotherapy administration. This assumption was validated by clinical expert opinion. The model was built with the flexibility to allow GP visits/ outpatient visits to be incorporated should these be identified through research, but as clinical expert opinion indicated AEs could be managed through the regular chemotherapy visits, these cells are not actually used in the model.

A24. Risk AEs Sheet cell (j10:j38) – Please reference the values for the duration of adverse effects.

These values were derived from the TROPIC database and were based on the clinical report forms which recorded the start and stop dates of AEs. The output from the TROPIC database is provided in Appendix 4.

A25. Risk AEs Sheet cell ("RRneutropeniaProph") - The value for this variable has been set blank (i.e. zero) in the deterministic models, and the distribution that should be assigned in the lognormal PSA values has been left blank. Please rectify as appropriate.

This value was deleted unintentionally. The value in that cell should read 0.077256077, and has now been corrected within the model. This correction does not affect the base case analysis; it is used only for sensitivity analyses.
Updated one-way sensitivity analyses are shown below incorporating this input.

**Table 13: Updated one-way sensitivity analysis for G-CSF usage**

| Proportion with G-CSF as primary prophylaxis | Incremental cost | Incremental QALYs | Incremental LYs | ICER per QALY | ICER per LY |
|---|---|---|---|---|---|
| Caba & Mitox: 0% | £22,133 | 0.30 | 0.41 | £74,337 | £53,586 |
| Caba & Mitox: 20% | £22,125 | 0.30 | 0.41 | £74,254 | £53,565 |
| Caba & Mitox: 40% | £22,116 | 0.30 | 0.41 | £74,171 | £53,545 |
| Caba & Mitox: 60% | £22,108 | 0.30 | 0.41 | £74,088 | £53,525 |
| Caba & Mitox: 80% | £22,100 | 0.30 | 0.41 | £74,006 | £53,505 |
| Caba & Mitox: 100% | £22,091 | 0.30 | 0.41 | £73,923 | £53,484 |

A26. Risk AEs ("M10:M42") - For consistency, please divide these cells by 365.25 not 365.

The model has been updated to reflect this. The results are shown below:

| | Incremental cost | Incremental QALYs | ICER |
|---|---|---|---|
| **Original submitted model** | £22,325 | 0.298 | £74,908 |
| **Corrected model** | £22,325 | 0.298 | £74,908 |

A27. Calculations (throughout) - It is unclear why the periodically discounted values have not been calculated using the standard approach of …* 1/ (t)1.035. Using the standard approach provides different values to those within the model. Please clarify the appropriateness of the methodology.

Continuous discounting is applied within the model in order to avoid 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). For further information, please see:

Brealey R.A. & Myers S.C. Principles of Corporate Finance. 5th ed. New York: McGraw-Hill. pp. 41-45;[7]
Lipscomb J., Weinstein M.C., Torrance G.W., Chapter 7, Time preference, in Gold M.E. et al. Cost-effectiveness in Health and Medicine. New York: OUP, 1996[8].

Table 14 below shows the expected difference over various periods of time.

**Table 14: Continuous versus discrete discounting**

| Years | Discrete | Continuous | Difference |
|---|---|---|---|
| | $1/(1+r)^t$ | exp(-r*t) | |
| 1 | 0.9662 | 0.9656 | -0.06% |
| 2 | 0.9335 | 0.9324 | -0.12% |
| 3 | 0.9019 | 0.9003 | -0.18% |
| 4 | 0.8714 | 0.8694 | -0.24% |
| 5 | 0.842 | 0.8395 | -0.30% |
| 6 | 0.8135 | 0.8106 | -0.36% |
| 7 | 0.786 | 0.7827 | -0.42% |
| 8 | 0.7594 | 0.7558 | -0.48% |
| 9 | 0.7337 | 0.7298 | -0.54% |
| 10 | 0.7089 | 0.7047 | -0.60% |

A28. Calculations Sheet cell (columns u and w) – Please clarify why these columns are multiplied by the survival rate within the relevant time period.

The reason for this is that we apply a separate cost for the cost of the last month of life. This is applied as a transition cost on death. However, this cost actually occurs in the month prior to death. It is therefore necessary to remove this cost from the costs of progressive disease, for the patients in the progressive disease state who die within that cycle. This avoids double-counting the cost of the last month of life.

A29. PSA calculations Sheet cell (columns e44:e55 and e57:e58) – Please clarify why the standard errors for these cells have been assumed to be estimated from the ratio of base value to SE of bone pain.

Bone pain was the only utility for which a SE was available. Given the lack of alternative data, it was assumed that the SE for other disutilities would follow a similar pattern to that observed for bone pain, and therefore were calculated by multiplying the SE of bone pain by the ratio of the base values (i.e. the ratio of the base value for bone pain versus that for the particular AE disutility under consideration).

A30. PSA Calculations Sheet cell (e43) – Please clarify why the standard error for the utility in progressive state is assumed to be half of the base value.

The utility estimate for progressive disease was inferred from two other values – the SD value from the EAP and the decrement reported in the literature (Sullivan 2007) and, hence, a standard error for that value was not reported. As such, an assumption was made that the standard deviation was equal to 50% that of the base value. The standard error was then calculated based on the standard deviation and the N reported in Sullivan 2007.

An alternative approach would be to use the same standard error as that found in the EAP for SD.

We expect that, with further analyses from the EAP, we will be able to provide a value from this for the utility for progressive disease and an associated standard error from this based on the EAP sample.

A31. PSA Calculations Sheet cell (e59) – Please clarify how the standard error for body surface area was estimated.

The standard error was calculated based on data directly from the TROPIC trial. The interval implied by the standard error used in the probabilistic analysis is 1.89 – 2.13.

A32. PSA Calculations Sheet cell (row 59) – Please clarify why the distribution for body surface area used in the probabilistic sensitivity has a mean of 1.93 whilst the deterministic value is 2.01.

It would be helpful to understand further where the mean of 1.93 was found. The PSA inputs for body surface area are set up to generate a mean value of 2.01. The mean value can be calculated by multiplying the ‘base’ value for the beta distribution (i.e. 0.44) by the difference between the minimum and maximum (i.e. 1.50), and adding that value (0.67) to the minimum value (1.34) to give 2.01.

A33. PSA Calculations Sheet cell (e110:e124) - The standard errors used in the model have been estimated using the Beta-Pert method, however the report (p134) indicates this would be calculated from quartile data from NHS costs. Please explain this discrepancy.

Originally it was planned to use quartile data from NHS costs and this was written in the report. However, as quartile data are not provided for length of stay values in the NHS reference costs, the Beta-Pert methodology was used instead. The original wording was included within the submission as an oversight.

A34. p133 – Please provide a reference for the Beta-Pert methodology.

This is described in:
Eppen, G.D., F.J. Gould, and C.P. Schmidt, Introductory Management Science. 4th ed. 1993, London: Prentice-Hall International[9].

**Section C: Textual clarifications and additional points**

A35. **If any corrections are made to the economic model as a result of clarification please provide an updated model with an explanation of all corrections.**

An updated deterministic model is supplied. The corrections made are:

- A value of 2.97 days for total inpatient days per neuropathy episode replaces the previous figure of 2.77. See response to A19.
- The value for the risk ratio for neutropenia prophylaxis, previously left blank, has been updated to 0.077256077. This correction does not affect the base case analysis; it is used only for sensitivity analyses. See response to A26.
- The risk of AEs is now divided by 365.25 instead of 365. See response to A27.
- The disutility for pulmonary embolism is corrected to 0.145 instead of 0.2445. See response to A22.

In addition, we have supplied a model which allows a probabilistic sensitivity analysis incorporating uncertainty in the Kaplan-Meier inputs. This can only be used for probabilistic analysis; the methodology is described in the response to A13. This model incorporates the additional four corrections above.

## References


1: Pivot X, Koralewski P, Hidalgo L, Chan A, Goncxalves A, Schwartsmann G. A multicenter phase II study of XRP6258 administered
as a 1-h i.v. infusion every 3 weeks in taxane-resistant
metastatic breast cancer patients. Annals Oncology 2008; **19**: 1547 – 1552.
2: Sullivan PW, Mulani PM, Fishman M, Sleep D. Quality of life findings from a multicenter, multinational, observational study of patients with metastatic hormone-refractory prostate cancer. *Qual Life Res* 2007; **16:** 571-575.
3: National Health Service. *NHS reference costs 2009–2010.* www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459 (last accessed 15 April 2011)
4: Haentjens P, De Groote K, Annemans L**.** Enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. A cost-utility analysis. Arch Orthop Trauma Surg 2004; **124 :** 507–517
5: Gould MK, Dembitzer AD, Sanders GD, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A cost-effectiveness analysis. *Ann Intern Med* 1999; **130:** 789-799.
6: Treasure T, Hill J. National Clinical Guidelines Centre for Acute and Chronic Conditions. *Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital.* http://guidance.nice.org.uk/CG/Wave14/26 (last accessed 3 March 2011)
7: Brealey R.A. & Myers S.C. Principles of Corporate Finance. 5th ed. New York: McGraw-Hill. pp. 41-45;
8: Lipscomb J., Weinstein M.C., Torrance G.W., Chapter 7, Time preference, in Gold M.E. et al. Cost-effectiveness in Health and Medicine. New York: OUP, 1996[8].
9: Eppen, G.D., F.J. Gould, and C.P. Schmidt, Introductory Management Science. 4th ed. 1993, London: Prentice-Hall International[9].

## Appendix 1 – Non-English language studies excluded from systematic review of all RCTs in second-line mHRPC

| No. | Query | Results | Date |
|---|---|---|---|
| #51 | #49 NOT #50 | 29 | 4 Jul 2011 |
| #50 | #29 AND #36 AND #47 AND [english]/lim AND [2000-2011]/py | 430 | 4 Jul 2011 |
| #49 | #29 AND #36 AND #47 AND [2000-2011]/py | 459 | 4 Jul 2011 |
| #48 | #29 AND #36 AND #47 | 556 | 4 Jul 2011 |
| #47 | #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 | 71525 | 4 Jul 2011 |
| #46 | 'pre-treated' OR 'pretreated' OR 'prior therapy' | 59449 | 4 Jul 2011 |
| #45 | '2nd line' OR 'second line' | 12381 | 4 Jul 2011 |
| #44 | taxane NEAR/3 prior | 98 | 4 Jul 2011 |
| #43 | taxane NEAR/4 previous* | 85 | 4 Jul 2011 |
| #42 | taxane NEAR/4 pretreat* | 128 | 4 Jul 2011 |
| #41 | taxane NEAR/4 initial* | 18 | 4 Jul 2011 |
| #40 | (docetaxel OR taxotere) NEAR/3 prior | 84 | 4 Jul 2011 |
| #39 | (docetaxel OR taxotere) NEAR/4 previous* | 186 | 4 Jul 2011 |
| #38 | (docetaxel OR taxotere) NEAR/4 pretreat* | 93 | 4 Jul 2011 |
| #37 | (docetaxel OR taxotere) NEAR/4 initial* | 68 | 4 Jul 2011 |
| #36 | #30 OR #31 OR #32 OR #33 OR #34 OR #35 | 129152 | 4 Jul 2011 |
| #35 | cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR adeno* AND castrat* NEAR/3 resistant | 1149 | 4 Jul 2011 |
| #34 | cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR adeno* AND hormone NEAR/3 (resistant OR refractory) | 3655 | 4 Jul 2011 |
| #33 | hrpc OR crpc | 1293 | 4 Jul 2011 |
| #32 | prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial) | 128701 | 4 Jul 2011 |
| #31 | 'prostate tumor'/exp | 114529 | 4 Jul 2011 |
| #30 | 'prostate cancer'/exp | 93399 | 4 Jul 2011 |
| #29 | #23 NOT #28 | 4255567 | 4 Jul 2011 |
| #28 | #24 OR #25 OR #26 OR #27 | 2579584 | 4 Jul 2011 |
| #27 | 'letter'/exp OR 'letter' | 796098 | 4 Jul 2011 |
| #26 | 'abstract report'/exp OR 'abstract report' | 89485 | 4 Jul 2011 |
| #25 | 'case report'/exp OR 'case report' | 1805151 | 4 Jul 2011 |
| #24 | 'case study'/exp OR 'case study' | 61997 | 4 Jul 2011 |
| #23 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 | 4375180 | 4 Jul 2011 |
| #22 | 'prospective study'/exp OR 'prospective study' | 220172 | 4 Jul 2011 |
| #21 | (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) | 176843 | 4 Jul 2011 |
| #20 | 'triple blind procedure'/exp OR 'triple blind procedure' | 40 | 4 Jul 2011 |
| #19 | 'crossover procedure'/exp OR 'crossover procedure' | 31008 | 4 Jul 2011 |

| No. | Query | Results | Date |
|---|---|---|---|
| #18 | 'double blind procedure'/exp OR 'double blind procedure' | 104109 | 4 Jul 2011 |
| #17 | 'single blind procedure'/exp OR 'single blind procedure' | 13741 | 4 Jul 2011 |
| #16 | 'placebo'/exp OR 'placebo' OR placebo* | 268370 | 4 Jul 2011 |
| #15 | allocated NEAR/2 random | 839 | 4 Jul 2011 |
| #14 | rct | 8899 | 4 Jul 2011 |
| #13 | 'allocated randomly' | 1728 | 4 Jul 2011 |
| #12 | 'randomly allocated' | 15494 | 4 Jul 2011 |
| #11 | 'random allocation'/exp OR 'random allocation' | 54352 | 4 Jul 2011 |
| #10 | 'randomization'/exp OR 'randomization' | 64445 | 4 Jul 2011 |
| #9 | 'randomisation'/exp OR 'randomisation' | 56348 | 4 Jul 2011 |
| #8 | 'randomised controlled trials' | 9612 | 4 Jul 2011 |
| #7 | 'randomized controlled trials'/exp OR 'randomized controlled trials' | 26459 | 4 Jul 2011 |
| #6 | 'randomised controlled trial'/exp OR 'randomised controlled trial' | 288874 | 4 Jul 2011 |
| #5 | 'randomized controlled trial'/exp OR 'randomized controlled trial' | 301922 | 4 Jul 2011 |
| #4 | 'controlled clinical trial'/exp OR 'controlled clinical trial' | 401405 | 4 Jul 2011 |
| #3 | 'clinical trials'/exp OR 'clinical trials' | 164067 | 4 Jul 2011 |
| #2 | 'clinical trial'/exp OR 'clinical trial' | 927204 | 4 Jul 2011 |
| #1 | 'controlled study'/exp OR 'controlled study' | 3637289 | 4 Jul 2011 |

HERON report indicated that Embase and Medline (Embase.com), were acceded on 16 Novemeber 2010

## RECORD 1 not available at the time of the running of the search strategy

Actualities in prostate cancer in ASCO annual meeting 2010 Pouessel D. Culine S.

Bulletin du Cancer (2010) 97:12 (1563-1572). Date of Publication: December

2010

In urologic oncology, prostate cancer represented, even this year, a wide part during the ASCO 2010 meeting. In the non metastatic diseases, two phase III trials confirmed the benefit of radiotherapy combined with hormonotherapy in locally advanced stage. For patients with metastatic hormonoresistant cancer, two randomized trials will probably change the daily practice in the next months. On the one hand, denosumab versus zoledronate decreased significantly the risk of skeletal-related events in bone metastases. On the other hand, compared with mitoxantrone, cabazitaxel in docetaxel pretreated patients improved overall survival. On the contrary, docetaxel in monotherapy remains the standard of care in first line chemotherapy in castration refractory metastatic prostate cancer. Indeed, in two trials, combination of bevacizumab or calcitriol with docetaxel showed no benefit for patients with more toxicities. Finally, docetaxel-based chemotherapy was again evaluated in two other situations: biological recurrence, and hormono-sensitive metastatic stage. Preliminary results of tolerance were presented this year. No doubt that communications during future ASCO

meetings would reported definitive results of efficiency of these phase III studies. (copyright) John Libbey Eurotext.

## RECORD 2

Satraplatin as a second-line therapy for castrate-refractory prostate cancer Heidenreich A.

Onkologe (2010) 16:3 (314-315). Date of Publication: March 2010 (No abstract)

## RECORD 3

Toxicity and efficacy of intermittent docetaxel chemotherapy for hormone refractory prostate cancer Olbert P.J. Weil C. Hegele A. Hofmann R. Schrader A.J.

Tumor Diagnostik und Therapie (2009) 30:5 (257-261). Date of Publication:

2009

Background: Until today, docetaxel is the only EMEA and FDA approved active agent in hormone refractory prostate cancer (HRPC). In the absence of other effective and approved drugs we evaluated the toxicity and efficacy of intermittent docetaxel-chemotherapy in patients whose cancers progressed after successful first-line docetaxel therapy. Methods:46, 18, and 5 patients with HRPC received 1, 2, or 3 cycles of docetaxel based chemotherapy. Toxicity, PSA response and general condition were evaluated systematically. SPSS 15.0 was applied for statistic analysis. Results:26 (56 %) patients achieved a PSA response of > 50 %, another 10 (22 %) patients of up to 50 %; 10 (22 %) patients were progressive under docetaxel. The median overall survival of the whole cohort calculated from the first docetaxel application was 16 (3 60 +) months. Tolerance, toxicity and general condition were crucial for the administration of a second cycle (n = 18); in contrast, age or the degree of the PSA decline incycle 1 did not seem to be of importance. The median overall survival of all patients who received at least two blocks was 35 months; moreover, 13 / 18 patients achieved a biochemical response in cycle 2. Toxicity did not rise significantly. Five patients were given a third docetaxel cycle, three of whom responded. Higher frequencies of grade 3 / 4 stomatitis, skin toxicity and leukocytopaenia were observed. Conclusion:Intermittent docetaxel therapy is well tolerated and shows high response rates in the second and third sequences of treatment in selected HRPC patients who presented with low docetaxel toxicity, good clinical condition and responded to prior docetaxel-based treatment. (copyright) Georg Thieme Verlag KG Stuttgart.

## RECORD 4

Toxicity and efficacy of intermittent docetaxel chemotherapy for hormone refractory prostate cancer Olbert P.J. Weil C. Hegele A. Hofmann R. Schrader A.J.

Aktuelle Urologie (2009) 40:3 (164-168). Date of Publication: 200905

Background: Until today, docetaxel is the only EMEA and FDA approved active agent in hormone refractory prostate cancer (HRPC). In the absence of other effective and approved drugs we evaluated the toxicity and efficacy of intermittent docetaxel-chemotherapy in patients whose cancers progressed after successful first-line docetaxel therapy. Methods : 46,18, and 5 patients with HRPC received 1,2, or 3 cycles of docetaxel based chemotherapy.

Toxicity, PSA response and general condition were evaluated systematically. SPSS 15.0 was applied for statistic analysis. Results :

26(56%) patients achieved a PSA response of >50%, another 10(22%) patients of up to 50%; 10(22%) patients were progressive under docetaxel. The median overall survival of the whole cohort calculated from the first docetaxel application was 16 (3-60+) months. Tolerance, toxicity and general condition were crucial for the administration of a second cycle (n = 18); in contrast, age or the degree of the PSA decline in cycle 1 did not seem to be of importance. The median overall survival of all patients who received at least two blocks was 35 months; moreover, 13/18 patients achieved a biochemical response in cycle 2. Toxicity did not rise significantly. Five patients were given a third docetaxel cycle, three of whom responded. Higher frequencies of grade3/4 stomatitis, skin toxicity and leukocytopaenia were observed. Conclusion: Intermittent docetaxel therapy is well tolerated and shows high response rates in the second and third sequences of treatment in selected HRPC patients who presented with low docetaxel toxicity, good clinical condition and responded to prior docetaxel-based treatment. (copyright) Georg Thieme Verlag KG Stuttgart. New York. ISSN 001-7868.

# RECORD 5

Patients with metastatic hormone-refractory prostate cancer: Second-line chemotherapy with mitoxantrone plus prednisone Thomas C. Hadaschik B.A. Thuroff J.W. Wiesner C.

Urologe - Ausgabe A (2009) 48:9 (1070-1074). Date of Publication: September

2009

Background: To date there has been no accepted standard for second-line chemotherapy in docetaxel-refractory patients with metastatic hormone-refractory prostate cancer (mHRPC). Therefore, we evaluated our experience with mitoxantrone plus prednisone (MP) in this setting. Material and methods: Ten patients with docetaxel-refractory mHRPC were treated with MP. The parameters under investigation were prostate-specific antigen (PSA) remission, biochemical progression-free survival, and pain reduction under chemotherapy. Results: Partial PSA remission was seen in two patients, « stable disease » in three patients, and progression in five patients receiving MP. Progression-free survival was 8 months (mean) for patients with partial PSA remission and 2 months (median) for patients with « stable disease. » Four of seven patients experienced pain reduction with MP. Grade 4 neutropenia was noted in only 10%. Patients with a decline of PSA under docetaxel and MP had a progression-free survival of 11.5 months (median). Conclusions: Presently, we see the indication for MP as being second-line chemotherapy in docetaxel-refractory patients with mHRPC who cannot be included in phase II/III studies. Even with only a moderate rate of partial PSA remission, every second patient had an improvement in tumor-related pain. Progression-free survival was prolonged, and the side effects of MP were comparatively low. (copyright) 2009 Springer Medizin Verlag.

# RECORD 6

Effects of doxazosin in combination with low concentration of doxorubicin on apoptosis induction in prostate cancer cells Kang J. Sun Y.-W. Zhang L. Chen F. Qi J.

Journal of Shanghai Jiaotong University (Medical Science) (2009) 29:5

(548-550). Date of Publication: May 2009

Objective: To observe the effects of doxazosin in combination with low concentration of doxorubicin on apoptosis induction in hormone-sensitive prostate cancer cell line LNCaP and hormone-insensitive prostate cancer cell line PC-3. Methods In experiment group, LNCaP and PC-3 cells were pretreated with low concentration of doxorubicin (0.86 (mu)mol;/L), and then incubated with doxazosin of different concentrations (25, 50, 100 (mu)mol/L) for 48 h. In control group, LNCaP and PC-3 cells were incubated with doxazosin of different concentrations (25, 50, 100 (mu)mol/L) without pretreatment with doxorubicin. Cell apoptosis was assessed by flow cytometry after treatment with different concentrations of doxazosin. Results: For LNCaP cells, the apoptosis rates in control group were (21.7 (plus or minus) 11.9)%, (22.4 (plus or minus) 16.5)% and (33.9 (plus or minus) 12.5)%, respectively after treatment with 25, 50 and 100 (mu)mol/L doxazosin for 48 h, and those in experiment were (36.5 (plus or minus) 11.2)%, (42.3 (plus or minus) 17.6)% and (48.7 (plus or minus) 17.2)%, respectively. There were significant differences in the apoptosis rates of LNCaP cells between these two groups($P < 0.05$). For PC-3 cells, the apoptosis rates in control group were (33.5 (plus or minus) 16.1)%, (38.6 (plus or minus) 12.6) % and (43.8 (plus or minus) 17.9) %, respectively after treatment with 25, 50 and 100 (mu)mol/L doxazosin for 48 h, and those in experiment group were (48.4 (plus or minus) 19.2)%, (56.6 (plus or minus) 18.7)% and (64.3 (plus or minus) 19.6)%, respectively. There were significant differences in the apoptosis rates of PC-3 cells between these two groups($P < 0.05$). The apoptosis rates of LNCaP cells were significantly lower than those of PC-3 ($P <0.05$). Conclusion: Lower concentration of doxorubicin can enhance the apoptosis effect of doxazosin with different concentrations on both LNCaP and PC-3 cells. The apoptosis effect of doxazosin is concentration-dependent. The apoptosis rates of PC-3 cells are significantly higher than those of LNCaP cells after treatment with doxazosin in combination with doxorubicin.

# RECORD 7

Morphine and hydromorphone in palliative care patients with renal impairment Clemens K.E. Klaschik E.

Anasthesiologie und Intensivmedizin (2009) 50:2 (70-76). Date of

Publication: February 2009

Aim: Morphine (M) is the reference opioid against which the effectiveness and side effects of other opioids are evaluated. Its metabolites morphine-3-glucuronide and morphine-6-glucuronide are known to accumulate in the presence of renal impairment, which can enhance the spectrum of side effects. The aim of the present study was to determine whether the use of hydromorphone (HM) resulted in fewer side effects and improved pain relief in palliative care patients. Methods: In this retrospective study the data of 546 patients admitted to our palliative care unit between 2004 and 2006 were analysed. Included were patients (n=140) with renal failure (serum creatinine concentration (greater-than or equal to)2.0 mg/dl) and cancer pain who were opioid-naive or previously treated with M. During their stay in our unit treatment was changed to HM. Demographic and epidemiological/disease-related data were documented. Statistics: mean (plus or minus) SD, median (range); Wilcoxon's test, significance $p <0.05$. Results: Renal impairment was documented in 140 (25.6 %) patients, (age 66.3(plus or minus)12.5 years, 60 (42.9 %) male). One of the reasons for admission was pain, and all patients had advanced-stage cancer (mainly carcinoma of the prostate, lung, and breast). Mean Karnofsky Index was 49.0(plus or minus)14.1, mean serum creatinine concentration 4.8(plus or minus)3.0 mg/dl, and mean blood urea nitrogen 64.0(plus or minus)53.3 mg/dl. On admission, 9 of the 140 patients were opioid-naive, and 131 pretreated

with M (mean daily dose 165.5(plus or minus)135.0 mg). On discharge, the mean daily dose of HM was 37.0(plus or minus)34.1 mg (277.8(plus or minus)255.0 mg M equivalent dose; (conversion ratio M:HM = 7.5:1). Under treatment with HM, pain intensity was significantly reduced, as were such adverse effects as nausea and vomiting, myoclonus and sedation. Conclusions: HM is an effective and safe opioid for the treatment of pain in cancer patients also suffering from renal impairment. (copyright) Anasth Intensivmed.

# RECORD 8

## *Metastatic prostate cancer: What's new since docetaxel?*

Gross-Goupil M. Fizazi K.

Oncologie (2008) 10:11 (648-652). Date of Publication: November 2008

Docetaxel is the standard first line treatment in metastatic castration-resistant prostate cancer. The time to begin docetaxel remains questionable. Regarding conventional therapy, the old cytotoxic agent estramustine is still controversial, but data suggest a survival advantage when combined with docetaxel. This therapeutic improvement has resulted in the clinical development of several new agents, some as monotherapy, others in combination with docetaxel, as first or second line treatment. Numerous clinical trials have improved the comprehension of the disease continuum, generating new recommendations, especially concerning outcome measures. Two new drugs are being tested: the satraplatin and the ixabepilone. The principle of targeting bone metastasis has induced new options of treatment, such as targeting RANK-ligand, systemic radioisotopes, or the inhibition of the endothelin 1 receptor A. Antiangiogenic agents are also tested in clinical trials, especially bevacizumab, VEGF-trap and vandetanib. Furthermore, hormone manipulations appear promising, especially abiraterone acetate and the antagonists of the androgen receptor. (copyright) 2008 Springer Verlag.

# RECORD 9

Somatostatin analogs for the treatment of advanced, hormone-refractory prostate cancer: A possibility for secondary hormonal ablation? Schilling D. Kufer R. Kruck S. Stenzl A. Kuczyk M.A. Merseburger A.S.

Urologe - Ausgabe A (2008) 47:10 (1334-1338). Date of Publication: October

2008

Almost all patients with hormone-refractory prostate cancer under primary androgen deprivation therapy will develop progression, frequently initially marked by an asymptomatic increase of prostate-specific antigen (PSA). Recent data showed that taxane-based chemotherapy offers significant survival benefit to patients with advanced prostate cancer; however, the toxic side effects frequently exert a significant negative impact on the quality of life. At the androgen-independent stage of the cancer, before becoming hormone refractory, progression might still be delayed by secondary manipulation of either androgen or

confounding receptors and their signaling pathways. Secondary hormonal manipulations traditionally included antiandrogen withdrawal, second-line antiandrogens, direct adrenal androgen inhibitors, estrogens, and progestins. We discuss the mode of action and application of somatostatin analogs as an emerging secondary hormonal treatment concept in patients with advanced prostate cancer on the basis of the current literature. 

# RECORD 10

Effects of 5(alpha)-dihydrostestosterone on calcium mobilization and growth of prostate cancer cell line LNCaP Tang Y.-J. Sun Y.-H. Gao X. Xu C.-L. Wang L.-H.

Academic Journal of Second Military Medical University (2008) 29:10

(1166-1170). Date of Publication: October 2008

Objective: To investigate the effects of 5(alpha) - dihydrostestosterone (DHT) on calcium mobilization and growth of prostate cancer cell line LNCaP. Methods: Intracellular calcium concentration ([Ca(2+)](i)) was assayed by MiraCal Image System using Fura-2/AM as Ca(2+) fluorescence probe. Cell viability was observed by MTT assay and apoptosis by flow cytometry. Results: The calcium levels rapidly increased following addition of DHT, with the latency of response only in seconds. DHT at the concentrations of 1, 10, 100 and 1 000 nmol/L increased [Ca(2+)](i) from (28(plus or minus)5), (29(plus or minus)5), (28(plus or minus)4) and (28(plus or minus)9) nmol/L to (31(plus or minus)3) (P>0.05,65(plus or minus)9) (P<0.01), (193(plus or minus)33) (P<0.001) and (208(plus or minus)42) nmol/L (P<0.001), respectively. The response induced by 1 000 nmol/L DHT was similar to that induced by 100 nmol/L DTH. DHT 1 000 nmol/L did not increase [Ca(2+)](i) under extracellular Ca(2+) -free condition. Blockers of L-type voltage-gated calcium channels, including verapamil (50 (mu)mol/L), diltiazem (100 (mu)mol/ L) or nifedipine (5 mmol/L) at 37(degrees)C for 5 min prior to stimulation with 1 000 nmol/L DHT, completely inhibited DHT-induced [Ca(2+)](i) rise. Pre-treatment with inhibitor of phospholipase C such as neomycin sulfate (1 mmol/L) at 37(degrees)C for 3 min or inhibitor of ryanodine receptor such as procaine (50 mmol/L) at 37(degrees)C for 3 min had no influence on [Ca(2+)](i) rise induced by 1 000 nmol/L DHT. The optical density (D) values and early apoptosis rates of the cells stimulated with 1 000 nmol/L DHT for 48 h were significantly different from those of cells pre-treated with verapamil prior to stimulation with 1 000 nmol/L DHT ([0.67(plus or minus)0.10]% vs [2.13(plus or minus)0.16] % and [14.31(plus or minus)2.29]% vs [1.07(plus or minus)0.19]%,P<0.01). Conclusion: DHT can induce rapid [Ca(2+)](i), rise in LNCaP cells in a concentration-dependent manner. The increase of [Ca(2+)](i), induced by DHT involves L-type voltage-gated calcium channels, but does not involve release of intracellular Ca(2+) stores. The increase of [Ca(2+)](i) induced by DHT increases apoptosis and inhibits growth of LNCaP cells.

# RECORD 11

## *Chemotherapy for prostate cancer*

Rauchenwald M. De Santis M. Fink E. Holtl W. Kramer G. Marei I.-C. Neumann H.-J. Reissigl A. Schmeller N. Stackl W. Hobisch A. Krainer M.

Wiener Klinische Wochenschrift (2008) 120:13-14 (440-449). Date of

Publication: July 2008

For many years the benefit of chemotherapy in patients with prostate cancer was thought to be limited to palliation of late-stage disease, and thus this treatment option only became involved in patient care towards the end of the disease process, if at all. However, two landmark phase-III trials with docetaxel-based therapy (TAX 327 and Southwest Oncology Group, SWOG,

9916) have shown a survival benefit for patients with hormone refractory prostate cancer (HRPC) thus prompting a change in patterns of care. With raising interest for chemotherapeutic options and clinical trials for new drugs and new indications (neoadjuvant therapy, adjuvant therapy, increasing PSA levels after local treatment, and hormone sensitive cancer) under way our goal was to review within the context of a multidisciplinary team the available evidence and explore the standard for the medical treatment of prostate cancer outside of clinical trials. We are carefully evaluating the current treatment recommendations based on the available evidence and highlight potential future treatment options but also discuss important clinical topics (treatment until progression versus the advantage of chemo holidays, definition of particular patient subgroups and potential second line options) for which there are no clear cut answers to date. The role and importance of radiotherapy, biphosphonate treatment and the medical management of pain and side effects is also discussed. The multitude of treatment options for patients with advanced prostate cancer clearly asks for a close collaboration between urologists, medical oncologists and radiation therapists. (copyright) 2008 Springer-Verlag.

# RECORD 12

Intraurethrally applicated alprostadil for the treatment of organic erectile dysfunction in practice / A multicenter clinical monitoring study (non-interventional investigation)

Potempa A.-J. Potempa D.M. Gorlich H.D. Stolpmann R.M.
Arzneimittel-Forschung/Drug Research (2007) 57:6 (299-308). Date of
Publication: 2007
In a multicenter clinical monitoring study (observation of use investigation according to (section) 67.6 of the German Drug Law), which was conducted between 2003 and 2005 in 105 urological practices in 314 patients with organic erectile dysfunction (ED), efficacy, safety, convenience and acceptance of intraurethral administered alprostadil (CAS 745-65-3; MUSE - Medicated Urethral System for Section) was studied. 306 patients could statistically be evaluated. The patients were 61.3 (plus or minus) 9.2 years old (median(plus or minus) SD) (181 patients between 60 and 80 y). The time of ED was from 2 to 120 months with a mean duration of 21.5 (plus or minus) 22 months (median(plus or minus) SD. Genesis of the ED was in 55% of the patients a local damage, which followed in 42.8% a prostate cancer surgery. 46% of the patients had vascular, 28% metabolic diseases including diabetes and 11% neural damages. In 51.3% of the patients drugs, which were known to induce ED, were suspected to have caused or partially caused the impairment. The degree of the disturbance was in 93% of the cases moderate to severe. Alprostadil (MUSE(registered trademark)) was applicated three times in doses of 250,500 or 1000 (mu)g. The dosage of 1000 (mu)g was used for the third application by 65% of the patients. Very good and good efficacy increased from 45.8% of the patients after the first through 63.7% after the second to 69.3% after the third application. In patients after surgery because of prostate cancer very good and good efficacy improved in comparison to the first application about 20% and concerned 53.9% of the patients after the third application. Sexual intercourse was possible by 67% of the patients after the first, 83% after the second and 87% after the third use. Tolerability of alprostadil (MUSE) was very good and good in 90% of the patients. 81.1% intended to continue the treatment. The handling of alprostadil (MUSE) was assessed very good and good by 75%, the acceptance was very good and good in 96% of the patients. In a retrospective comparison with other drugs for the treatment of ED intracavernosal alprostadil (« SKAT ») was slightly more effective than intraurethral alprostadil (MUSE) (32.1% vs 25%), but alprostadil (MUSE) was assessed more useful by 82.1% and preferred by 78.6% of the patients. In comparison to

phosphodiesterase-5- (PDE-5)-inhibitors alprostadil (MUSE) was more effective in 77.7%, and 79.6% of the patients preferred it. In comparison to apomorphin 94.1% preferred alprostadil (MUSE). 98% of the patients reported better efficacy of alprostadil (MUSE), and 94.1% preferred it. Five adverse events were reported (slight urethral pain). No patient dropped out. In this non-interventional investigation the good efficacy and tolerability of intraurethral applicated alprostadil (MUSE) as a second-line therapy after failure or minor efficacy of PDE-5 inhibitors and other oral drugs was comparable with the results of the clinical trials. The patients in the urological practices assessed handling and acceptance of the system high. (copyright) ECV Editio Cantor Verlag.

# RECORD 13

Metastasizing hormone-refractory prostate cancer. Chemotherapy and new treatment approaches Wierecky J. Bokemeyer C.

Onkologe (2007) 13:8 (726-731). Date of Publication: August 2007

In patients with hormone-refractory prostate cancer, chemotherapy has been considered relatively ineffective until recently. Based on the results of two randomized phase-III trials that demonstrated extended survival and a significantly higher prostate-specific antigen (PSA) response for docetaxel-based chemotherapy, treatment with docetaxel every 3 weeks should now be considered standard chemotherapy for hormone-refractory prostate cancer. Nevertheless, most patients will eventually experience progression of their illness after docetaxel-based chemotherapy, and the optimal second-line treatment is still unclear. Other cytotoxic agents such as mitoxantrone and vinorelbine have a moderate effect in this situation. New drugs such as satraplatin and ixabepilone have shown promising results and are the subject of ongoing clinical testing. Trials with targeted therapeutic strategies including monoclonal antibodies and anti-angiogenic drugs have been conducted alone and in combination with chemotherapy and have demonstrated increased PSA response and improvement in quality of life. However, their role in the standards of treatment must still be defined. (copyright) 2007 Springer Medizin Verlag.

# RECORD 14

Novel promising treatment options for metastatic androgen independent prostate cancer Tan W.

Actas Urologicas Espanolas (2007) 31:6 (680-685). Date of Publication: June

2007

Objective: Review the recent advances in the treatment of androgen independent prostate cancer (AIPC). Methods: Review recent abstracts and literature utilizing Medline/PubMed using key words: androgen independent/hormone refractory prostate cancer, novel treatment options, Phase II, III trials and meeting abstracts/presentations. Conclusion: Two pivotal trials SWOG (Southwest Oncology Group) study 9916 and Taxotere 327 have shown that survival can be improved in this population by administration of chemotherapy with docetaxel every three weeks intravenously. An overall survival of 19 months could be achieved with docetaxel/prednisone compared to16 months with mitoxantrone/ prednisone. Despite this, there is a need to improve on this survival benefit because the relapse free survival among responders is often short (6 months) and patients often would have progression of their cancer leading to death. Satraplatin, a novel platinum analogue had been found to provide an

additional 1.5 week progression free survival benefit in this population in the second line setting. There is however, a need to develop less toxic drugs that would improve survival significantly.

## RECORD 15

Clinical study of bladder tamponade resulting from clots of blood Miyamae K. Otsuka T. Otsuka Y. Nagayoshi M. Hamada Y.

Japanese Journal of Urology (2006) 97:5 (743-747). Date of Publication:

July 2006

(Purpose) There were many case reports about bladder tamponade resulting from clots of blood. However, there were few reports about the clinical study that result from collecting cases of bladder tamponade. Thus, we performed a retrospective study about bladder tamponade resulting from clots of blood that we had managed. (Material and Methods) We investigated 20 patients who had bladder tamponade and were consulted at our facility between October 2002 and September 2005. We researched causes of the bleeding, characteristics of the patients, the laboratory data of coagulation system and treatments of our experience in managing patients. There were 17 males and 3 females. The average age of the patients was 74.0 years old. (Results) 8 cases took anticoagulant drugs, 6 cases had medical history of cerebral infarction or cardiac infarction, 4 cases took anticholinergic drugs and 9 cases had benign prostate hypertrophy or urethral stricture. Bleeding was due to bladder tumor in 9, prostate cancer in 1, radiation cystitis in 3, chronic cystitis in 1, malignant lymphoma in 1, idiopathic causes in 3 and unknown causes in 2 cases. Except 1 case, in all cases, evacuation of the clots was the first procedure followed by saline irrigation. This initial line of treatment was able to control the hemorrhage in 40% of the patients. For the remaining cases, transurethral coagulation and resection of bladder tumor were used as the second line treatment, and furthermore, radical cystectomy was performed in 1 case. Surgical treatments were required in 12 cases. Blood transfusion was required in 4 cases. (Conclusion) According to progress aging society, the amounts of taken anticoagulant drugs and the patients who had lower urinary tract dysfunction may increase. It may be suggested that the cases of bladder tamponade resulting from clots of blood without bladder tumor or radiation cystitis tend to increase.

## RECORD 16

Regressive changes after short-term neoadjuvant antihormonal therapy in prostatic carcinoma: The value of Gleason grading Grobholz R. Riester A. Sauer C.G. Siegsmund M.

Pathologe (2006) 27:1 (33-39). Date of Publication: February 2006

Although neodjuvant, antihormonal therapy does not lead to an improvement in the outcome of prostatic carcinoma it is still used in the short-term in a subset of patients. Here we report the regressive changes due to this short-term treatment and analyse the impact on Gleason grading. The most frequent regressive changes in 82 tumors treated short-term were determined and quantified.The results were compared to a matched control group and also to the preoperative needle biopsies. A steep increase in regressive changes was observed within the first 4 weeks. After this point, changes increased only mildly. Within the first 2 weeks of treatment no significant changes compared to control tissue were present. Compared to the preoperative needle biopsies, pretreated tumors showed a significant upgrading. After 2 weeks

of neoadjuvant antihormonal therapy, regressive changes are so great, that Gleason grading can no longer be recommended. 

# RECORD 17

Prognostic factors for PSA relapse of prostate cancer after endocrine therapy Nakata S. Nakano K. Takahashi H. Shimizu K. Kawashima K.

Japanese Journal of Urology (2005) 96:7 (685-690). Date of Publication:

November 2005

(Purpose) Advanced prostate cancer responds well to endocrine therapy initially, but soon becomes refractory and has a poor prognosis. We analyzed the prognostic factors of prostate cancer responding well initially to endocrine therapy with lowering of serum prostate specific antigen (PSA) level but later showing PSA relapse. (Materials and Methods) In prostate cancer patients newly diagnosed from January 1992 to December 2004 at our institution, there were 93 patients in that the PSA level of 10 ng/ml or more before therapy initially dropped below 10 ng/ml by endocrine therapy, but showed PSA relapse thereafter. We investigated the relationship between clinical stage, pathological differentiation, initial PSA, duration between initiation of therapy and PSA nadir, the value of PSA nadir, duration between initiation of therapy and PSA relapse, PSA doubling time (PSA-DT) at relapse, PSA response three months after initiation of second line therapy and prognosis after PSA relapse. (Results) In Kaplan-Meier method, between all or some categories investigated showed significant difference in prognosis after PSA relapse. In multivariate analysis, the factors that significantly affected prognosis after PSA relapse were clinical stage, pathological differentiation, PSA nadir value, duration between initiation of therapy and PSA relapse and PSA response three months after initiation of second line therapy. (Conclusion) We investigated the prognostic factors refractory to endocrine therapy. These results are useful in planning the therapy, and in explaining the status or future prospective of the disease to patients and families.

# RECORD 18

ERK1/2 and p38 kinases are important regulators in P2Y receptor-mediated prostate cancer invasion Chen L. He H.-Y. Li H.-M. You J.-F. Heng W.-J. Li Y. Fang W.-G.

National Medical Journal of China (2005) 85:2 (111-114). Date of

Publication: 12 Jan 2005

Objective: To explore whether ERK1/2 and p38 pathways mediate P2Y receptor-induced prostate cancer invasion. Methods: The two subclones from the PC-3 human prostate carcinoma cell line. $1^{E}8$ (highly metastatic) and 2B4 (non-metastatic), were cultured and transfected with the plasmid pcDNA3-KA-MEK1 containing the dominant negative mutant of MEK1 (KA-MEK1) and wild type MKP-5 (a dual-specificity phosphatase of p38). P2Y receptor-activated ERK1/2 and p38 kinases were detected using phospho-specific antibodies directed against the dually phosphorylated active forms of these kinases by Western blotting. P2Y receptor agonists ATP and P2Y receptor antagonist suramin were used respectively to observe their effects on the activity of ERK1/2. The roles ERK1/2 and p38 pathways play in P2Y receptor-induced in vitro invasion were detected by in vitro invasion assay. The cells were pre-treated with ATP, SB203580, a p38 inhibitor, and PD98059, a blocker of ERK1/2 pathway, respectively. Results:

ATP activated ERK1/2 and p38 kinase time-dependently. Suramin significantly inhibited the activation of ERK1/2 and p38 kinase by ATP. ATP stimulated prostate cancer cell invasion. The stimulated cancer cell invasion was significantly inhibited by pretreatment of the cells with PD98059 or SB203580. Transfected of $1^{E}8$ cells with KA-MEK1 or up-regulation of MKP-5 both, while inhibiting phosphorylation of ERK1/2 or p38, significantly reduced the invasion of prostate cancer cells in vitro. Conclusion. P2Y receptor-induced prostate cancer cell invasion is mainly regulated through ERK1/2 and p38 pathways.

## RECORD 19

Docetaxel enables initial survival time lengthening

Der Urologe. Ausg. A (2004) 43:9 (1183-1184). Date of Publication: Sep 2004

## RECORD 20

Current strategies in the management of hormone refractory prostate cancer Martel C.-L. Gumerlock P.-H. Meyers F.-J. Lara Jr. P.-N.

Annales d'Urologie (2004) 38:3 (85-102). Date of Publication: Jun 2004

Prostate cancer is the most common cancer diagnosed in American males, and is the second leading cause of cancer-related deaths. Most patients who develop metastatic disease will initially respond to androgen deprivation, but response is invariably temporary. Most patients will develop androgen-independent (« hormone-refractory ») disease that results in progressive clinical deterioration and ultimately death. This progression to androgen independence is accompanied by increasingly evident DNA instability and alterations in genes and gene expression, including mutations in p53, over-expression of Bcl2, and mutations in the androgen receptor gene, among others. Treatment options for hormone-refractory disease include intensive supportive care, radiotherapy, bisphosphonates, second-line hormonal manipulations, cytotoxic chemotherapy and investigational agents. A post-treatment reduction in the level of prostate specific antigen (PSA) by 50% has been shown to correlate with survival and has been accepted by consensus as a valid endpoint in clinical trials. Chemotherapeutic agents such as mitoxantrone, estramustine, and the taxanes have yielded improved response rates and palliative benefit, but not improved survival. Therefore, current efforts must be focused on enrolling patients onto clinical trials of investigational agents with novel mechanisms of action, and on using survival, time to progression, and quality of life as end points in routine clinical practice. 

## RECORD 21

Diagnosis and management of advanced hormone-refractory prostate cancer:

Results of a practice survey on 301 French urologists Colombel M. Davin J.-L. Filleul A. Rousseau C.

Progres en Urologie (2004) 14:2 (182-188). Date of Publication: April 2004

As no treatment has been demonstrated to prolong survival in hormone-refractory prostate cancer, it was interesting to define the current management of these patients. This survey was

designed to identify the criteria used to define hormonal escape, to more clearly define the treatment modalities at this stage of the disease and to evaluate the various therapeutic approaches used. A self-administered questionnaire accompanied by 3 clinical cases was sent by mail to all French urologists registered with the AFU. Three hundred and one (31%) questionnaires were returned. The diagnosis of hormone-refractory cancer was based on the presence of clinical signs or elevated PSA levels in 61% of cases. 65% of urologists reported that they changed treatment as soon as symptoms appeared. The objectives of treatment were improvement of quality of life in 95% of cases and relief of symptoms in 90% of cases. The first-line treatment after hormonal escape is very predominantly (at least 90% of cases) multiple hormonal manipulations. Chemotherapy or referral of patients to an oncologist is performed by more than one third of doctors as second-line treatment (35% of cases) and in almost all cases as third-line treatment (87% of cases). Mitoxantrone-prednisone is the combination chemotherapy most frequently reported in this survey (2 out of 3 doctors). These data illustrate the application by French urologists of the current CCAFU guidelines (Oncology Committee of the French Urology Association) for hormone-refractory prostate cancer.

## RECORD 22

Therapeutic effects of bicalutamide for hormone-refractory prostate cancer Fujimoto N. Harada S. Takahashi K. Matsumoto T.

Nishinihon Journal of Urology (2002) 64:4 (188-192). Date of Publication:

2002

Prostate cancer is an androgen-dependent tumor. Even when the patient shows progression to a hormone-refractoy androgen-independent state, prostate cancer cells can still be hormonally dependent. We assessed the efficacy of bicalutamide in hormone-refractory prostate cancer. Fourteen patients received bicalutamide, 80 mg once daily, after showing progression following treatment with castration or maximum androgen blockade with or without chemotherapy. Of these 14 patients, 6 (42.9%) had a PSA decrease of 50% or more. Of 4 patients who had shown progression after gonadal androgen ablation and 3 who had shown progression after maximum androgen blockade, 3 (75.0%) and 2 (66.7%), respectively, demonstrated a PSA decline of more than 50%. Of 7 patients treated by endocrine therapy and chemotherapy, only 1 patients showed a PSA response. Regarding pathological findings, 6 of 9 (66.7%) patients with moderately differentiated adenocarcinoma had a PSA decrease of more than 50%. However, none of the patients with poorly differentiated carcinoma showed any PSA response. Bicalutamide was well tolerated and appears to offer some benefit as a second-line therapy in patients with hormone-refractory prostate cancer.

## RECORD 23

Oral estramustine phosphate and oral etoposide for the treatment of hormone-refractory prostate cancer Hashine K. Koizumi T. Sumiyoshi Y.

Nishinihon Journal of Urology (2002) 64:4 (217-221). Date of Publication:

2002

We evaluated the efficacy and toxicity of oral estramustine phosphate (EMP) and oral etoposide in patients with hormone-refractory prostate cancer. Thirty-three patients were

enrolled into this trial. Oral EMP was administered twice daily, for a total daily dose of 560 mg, and oral etoposide (50mg/day) was given on days 1~21 but not on days 22~35. Treatment was continued until evidence of disease progression. Eighteen of 33 patients showed a decrease of 50% or more in their PSA values from an initially elevated PSA level after therapy (responders). The median survival time was 21 months and the 2-year overall survival rate was 34.8% in all patients. The median survival time of responders was 29.8 months and this was significantly longer than that of non-responders. There were no significant differences in age, pretreatment PSA value, duration from initial treatment to relapse, or prior therapy between responders and non-responders. The main toxicities (grade ¾) were gastrointestinal disorder, leukocytopenia, thrombocytopenia and hepatic disorder, which occurred in 12, 6, 3 and 3 % of the patients, respectively. The combination of oral EMP and etoposide is considered to be a well-tolerated outpatient treatment regimen for patients with hormone-refractory prostate cancer, and a decrease of 50% or more in PSA value after this therapy was associated with prolonged median overall survival.

# RECORD 24

Chemoendocrine and radiation therapy for hormone-refractory prostate cancer Nishiyama K. Enokida H. Kubo H. Hayami H. Imazono Y. Kitagawa T. Eta S.-I. Yagi S. Kawahara M. Nakagawa M.

Nishinihon Journal of Urology (2002) 64:4 (242-249). Date of Publication:

2002

We reviewed 29 patients with hormone-refractory prostate cancer between January, 1996 and December, 2000. The mean interval from the start of initial therapy until cancer relapse was 21.2 months. Twenty-five of the 29 patients had enrolled in second-line therapy with several treatment arms, including chemoendocrine and external beam radiation therapy (EBRT). The overall 1-, 3- and 5-year survival rates after the start of second-line therapy were 83.8%, 48.9% and 12.2% respectively. The patients with a PSA decline of 50% or more showed significantly better prognosis than the other patients. In the chemoendocrine arm using estramustine phosphate, UFT (uracil/tegaful) and cyclophosphamide, 7 (53.8%) of 13 patients showed a PSA decline of 50% or more. The median response duration was 6 months. Although it was not statistically significant, the patients with a PSA decline of 50% or more showed better prognosis than the other patients. About 30% of patients had gastrointestinal symptoms, and those resulted in a dose reduction or discontinuation of the agents. Supportive care is essential in order to improve the clinical effect. In the EBRT arm, 5 (55.6%) of 9 patients showed a PSA decline of 50% or more, although local responses were observed in 7 (77.8%) patients. The median response duration was 12 months. The patients with a PSA decline of 50% or more showed significantly better prognosis than the other patients. Although no survival advantage was proven in this study, these data suggest that the development of therapy providing a high response rate may improve the prognosis of patients with hormone-refractory prostate cancer.

# RECORD 25

Endocrine therapy and chemo-endocrine therapy in hormone-refractory prostate cancer Matsubara A. Inoue S. Mutaguchi K. Yasumoto H. Usui T. Mochizuki H. Moriyama H. Nakahara M.

Nishinihon Journal of Urology (2002) 64:4 (193-198). Date of Publication:

2002

Background: To assess the effects of endocrine and chemo-endocrine therapy in patients with hormone-refractory prostate cancer. Patients and Methods:

The group receiving deferred antiandrogens comprised eight patients aged 74 years old on average who received antiandrogens which included 125 mg of flutamide administered 3 times daily in 5 patients, 80 mg of bicalutamide administered once daily in 2 patients, and 100 mg of chlormadinone acetate administered twice daily in one patient as a second-line therapy after progression following treatment with luteinizing hormone-releasing hormone (LHRH) analogue. The group receiving high-dose intravenous diethylstilbestrol diphosphate (DES-DP) therapy comprised twenty-three patients aged 68 years on average who were treated with an i.v. dose of DES-DP 500 mg daily for 20 days followed by a daily dose of 300 mg per os every day. Of the 23 patients, 9 were treated as a second-line therapy, 9 were treated as a third-line therapy and 5 were treated as a fourth-line therapy. Preceding treatment in 5 out of 23 patients comprised LHRH or combined androgen blockade (CAB), while the other 18 patients had received estramustine phosphate (EMP) alone or in combination with VP-16 or vinblastin in addition to the endocrine therapy. The group receiving EMP monotherapy comprised twenty patients aged 71 years on average who received EMP 560 mg daily. Of the 20 patients, 15 were treated as a second-line therapy. Treatment for the other 5 patients was divided into third-line for 3 patients, fourth-line for 1 patient and fifth-line for 1 patient. Eighteen out of the 20 patients had received endocrine therapy as their preceding treatment, while in 2 patients, EMP or UFT had been used as an additive to the endocrine therapy. Results: Four of 8 patients had a decline in PSA greater than 50% for 6 to 43 (median, 23) months with deferred antiandrogen therapy. Ten of 23 patients had a 50% or higher decrease in PSA levels for 5 to 16 (median, 11) months with high-dose intravenous DES-DP therapy. Eight of 20 patients had a decline in PSA greater than 50% for 3 to 7 (median, 6) months with EMP monotherapy. Conclusion: Deferred antiandrogens are recommended after LHRH monotherapy. High-dose intravenous DES-DP therapy was found to be the most useful therapy for hormone-refractory prostate cancer in the present study. EMP monotherapy demonstrated a relatively good result as a second-line therapy, however the duration of response was rather short.

# RECORD 26

The efficiency of second-line hormone therapy and hormone chemotherapy in treatment of hormone-refractory prostate cancer Okumura K. Hirofumi K. Naito S. Yamaguchi A.

Nishinihon Journal of Urology (2002) 64:4 (206-212). Date of Publication:

2002

The efficacy of second-line hormone therapy (oral low-dose DES-DP) and combination of estramustine phosphate (EMP) plus vinblastine (VBL) or taxotere (TXT) was estimated in patients with hormone-refractory prostate cancer. PSA response was obtained in 63.6% of patients treated with low-dose DES-DP with median duration of 6.5 months. There was no significant adverse effect in this therapy. Combination of EMP plus VBL and TXT induced PSA response in 60% and 55.6%, respectively. Subjective response in terms of gross hematuria, bone pain and dysuria was obtained in 30-70% and 70-100% of patients treated with EMP plus VBL and EMP plus TXT, respectively. Grade 3 anemia and deep vein thrombus were observed in 11.8% and 5.9% of patients treated with EMP plus VBL,

respectively, whereas grade 3 or grade 4 leukopenia and anemia were observed in 72.7% and 9.1% of patients treated with EMP plus TXT, respectively. These data suggest that these second-line hormone therapy and chemoendocrine therapies can be one of the useful options for the treatment of hormone-refractory prostate cancer.

## RECORD 27

Anthology of the first clinical studies with hypothalamic hormones: The story of a successful international collaboration Schally A.V. Gual C.

Gaceta Medica de Mexico (2002) 138:1 (89-100). Date of Publication: 2002

Our early pioneering clinical trials in Mexico with natural and synthetic thyrotropin-releasing hormone (TRH) and luteinizing hormone releasing hormone (LH-RH) also known as gonadotropin releasing hormone (Gn-RH), were reviewed. Highly purified TRH of porcine origin was shown to stimulate Thyrotropin (TSH) release in hypothyroid cretins. Subsequent tests with synthetic TRH also demonstrated significant increases in plasma TSH in normal men and women as well as in patients with primary hypothyroidism and other endocrine disorders. Even more extensive clinical studies were carried out with highly purified natural porcine LH-RH. Subjects with normal basal serum levels of gonadotropins, low levels (men and women pretreated with steroids) and high levels (e.g. post menopausal women) all reponded to LH-RH with a release of LH and FSH. The results of these early studies with the natural LH-RH were confirmed by the use of synthetic LH-RH. These investigations made in Mexico with TRH and LH-RH preceded all other clinical studies by a wide margin. Subsequently various clinical investigations with LH-RH agonists and antagonists were also carried out. All these studies played a major role in introducing hypothalamic-releasing hormones into clinical medicine.

## RECORD 28

Selective inhibition of tyrosine kinases - A new therapeutic principle in oncology Hochhaus A. Lahaye T. Kreil S. Berger U. Metzgeroth G. Hehlmann R.

Onkologie (2001) 24:SUPPL. 5 (65-71). Date of Publication: 2001

Tyrosine kinases are enzymes that regulate mitosis, differentiation, migration, neovascularization, and apoptosis. Their spectrum and association with specific malignancies offer multiple targets for therapeutic intervention. Chronic myelogenous leukemia (CML) represents an ideal target for a therapy using a selective inhibitor of the BCR-ABL tyrosine kinase. The 2-phenylpyrimidine derivative STI571 was rationally designed to inhibit ABL and BCR-ABL tyrosine kinase activities through competitive ATP-binding pocket interactions. Phase II data demonstrate hematologic and cytogenetic responses in interferon refractory chronic-phase, accelerated-phase and blast crisis patients. However, long-term observation is needed to confirm that response data result in prolongation of survival. STI571 is being studied in other malignancies, including leukemias characterized by expression of alternate molecular forms of BCR-ABL and those expressing protein tyrosine kinases with ATP-binding pockets structurally similar to ABL, e.g. c-kit and PDGF-R. Gastrointestinal stromal tumor (GIST) cells overexpress the stem cell factor receptor CD117, the product of the proto-oncogene c-kit. Inhibition of c-kit in vivo results in an immediate metabolic change of the tumor cells, detectable by positron emission tomography. Since c-kit overexpression is inhibited in small-cell lung cancer cell lines, a study with STI571 as second-line therapy of c-

kit-positive small-cell lung cancer is in progress. Clinical studies are ongoing in malignancies associated with an enhanced activity of the PDGF-R, such as high-grade glioma, prostate cancer and leukemias with rearrangements of PDGF-R. The development of selective tyrosine kinase inhibitors is considered a promising approach for the design of new drugs. Clinical responses to STI571 in various malignancies may stimulate greater interest in the clinical use of tyrosine kinase inhibitors.

## RECORD 29

What are the treatment options of metastatic breast cancer?
Salvini P. Ripa C. Ginanni V.
Tumori (2000) 86:5 SUPPL. 1 (S22-S28). Date of Publication: 2000
The medical approach to the treatment of metastatic breast cancer has changed in the last decade since the introduction of new drugs that demonstrate high activity and better tolerability profiles. The hormonal treatment, usually considered the first choice therapy for ER-positive metastatic breast cancer patients, has seen several improvements with the discovery of new selective aromatase-inhibitor agents and pure antiestrogens. New aromatase-inhibitors have shown higher activity and fewer side effects compared to megestrol acetate in second line treatment. The first line treatment has unchanged so far, but in the next future is possible that different agents, with lower toxicity, will replace tamoxifen since studies comparing this agent with pure antiestrogens or selective aromatase-inhibitors are ongoing. These new drugs would provide a better palliation of metastatic breast cancer in terms of higher clinical benefit, tolerability and quality of life. Chemotherapy is often used in ER-negative patients or in aggresive hormone refractory disease. Randomized trials have demonstrated that anthracycline-containing regimens were more effective than combinations without anthracyclines. New cytotoxic drugs with high activity, such as taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine and capecitabine, have been introduced. Compared with older therapies, improved objective response rates and/or improved duration of response have been reported with these newer agents alone or in combination with other drugs. However, no clear improvement of overall survival has been shown so far. Taxanes alone or in combination are today considered the second line treatment of choice and studies are assessing the value of a taxane-anthracycline containing regimen in first line treatment. Some new agents (vinorelbine) showed, alone or in combination, an interesting cost-effectiveness ratio with similar or higher « quality adjusted progression free survival » if compared to taxanes. Promising are also the results of agents that own low toxicity with comparable efficacy such as liposomal anthracycline. Attempts to improve overall survival with increased dose intensity or with high dose chemotherapy are disappointing. Conclusions: Since the goal of treatment of metastatic breast cancer is disease control rather than disease kill i.e palliation of patients with complications of progressive cancer, the new agents have brought significant improvements (higher response rates, median time to progression, cost benefit and better tolerability). Future progresses for this disease, hopefully even in overall survival, will depend on the introduction of new therapies such as immunotherapy, inhibition of intracellular signaling, interference with tumor angiogenesis, gene-therapy and the development of vaccines.

## Appendix 2 – Baseline characteristics of TROPIC trial and Phase II Breast cancer trial

### Baseline characteristics in TROPIC

| TROPIC trial<br>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 treatment | | |
| During | 104 (28% | 115 (30%) |
| <3 months from last dose | 181 (48%) | 158 (42%) |
| ≥3 months from last dose | 90 (24%) | 102 (27%) |
| Unknown | 2 (1%) | 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
Source: de Bono *et al*

### Breast cancer trial - Patient demography and primary tumor characteristics

| | All (N=71) |
|---|---|
| Age (years)<br>Median (range) | 53 (35-77) |

| | | |
|---|---|---|
| ECOG performance status at baseline, N (%) | 0 | 30 (42%) |
| | 1 | 33 (46%) |
| | 2 | 7 (10%) |
| | Missing | 1 (1%) |
| Hormonal status ER and/or PgR, N (%) | Positive | 37 (52%) |
| | Unknown | 6 (8%) |
| Her-2 status, N (%) | Positive | 19 (27%) |
| | Not done | 15 (21%) |
| Disease-free interval (DFI), months – median (min – max) (for 64 pts with nonmetastatic disease at presentation) | | 33.3 (1.58 – 214.01) |
| Number of organs involved, N (%) | 1 | 15 (21%) |
| | 2 | 26 (37%) |
| | 3 | 14 (20%) |
| | 4 | 16 (23%) |
| Main organs involved, N (%) | Any visceral | 53 (75%) |
| | Liver | 42 (59%) |
| | Lymph nodes | 33 (46%) |
| | Bone | 31 (44%) |
| | Lung | 22 (31%) |
| | Breast | 16 (23%) |
| | Connective soft tissue | 11 (15%) |
| | Skin | 8 (11%) |
| | Brain | 7 (10%) |
| Prior chemotherapy exposure, N (%) | Adjuvant | 1 (1%) |
| | Advanced | 70 (99%) |
| | One line (including patients with adjuvant chemotherapy with a DFI <12 months) | 49 (69%) |
| | Two lines | 19 (27%) |
| | Three lines | 2 (3%) |
| Prior anthracycline exposure, N (%) | | 54 (76%) |
| Last taxane exposure, N (%) | | 71 (100%) |
| | Docetaxel | 46 (65%) |
| | Paclitaxel | 25 (35%) |
| | More than one line of taxane | 7 (10%) |

Source: Pivot 2008

## Appendix 3 : Further details on analysis removing patients dying before 30 days

1- Subgroup **ITT population - Removing patients who died within 30 days – original OS data**

[redacted]

The tables below display the AIC and BIC criteria obtained using different distributions.

For Mitoxantrone arm:

| Distribution | Log Likelihood LL | N | df | AIC | BIC |
|---|---|---|---|---|---|
| Exponential (λ) | -185,62 | 158 | 1 | 373,24 | 376,30 |
| **Weibull (λ, σ)** | -165,50 | 158 | 2 | **335,00** | **341,13** |
| Lognormal (λ, σ) | -170,18 | 158 | 2 | 344,36 | 350,49 |
| Loglogistic (λ, σ) | -168,21 | 158 | 2 | 340,42 | 346,55 |
| Gompertz (λ, σ) | -169,96 | 158 | 2 | 343,92 | 350,05 |

Df: degree of freedom, AIC=2*df-2*LL, BIC=-2*LL+df*ln(N)

Using AIC, BIC criteria and graphical comparisons, the Weibull distribution provides a better fit than the other distributions for mitoxantrone.

For Cabazitaxel arm:

| Distribution | Log Likelihood LL | N | df | AIC | BIC |
|---|---|---|---|---|---|
| Exponential (λ) | -201,86 | 179 | 1 | 405,72 | 408,91 |
| Weibull (λ, σ) | -185,40 | 179 | 2 | 374,80 | 381,17 |
| Lognormal (λ, σ) | -183,43 | 179 | 2 | **370,86** | **377,23** |
| Loglogistic (λ, σ) | -183,29 | 179 | 2 | **370,58** | **376,95** |
| Gompertz (λ, σ) | -192,15 | 179 | 2 | 388,30 | 394,67 |

Df: degree of freedom, AIC=2*df-2*LL, BIC=-2*LL+df*ln(N)

Lognormal and Loglogistic distribution provides a slightly lower AIC, BIC criteria compared to the Weibull distribution for cabazitaxel arm when removing the patients that died within 30 days, meaning a slightly better fit to the data.

## Appendix 4: Output from TROPIC database – duration for AEs

Dictionary-Derived Term=ANAEMIA

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 19 | [redacted] | [redacted] |

Dictionary-Derived Term=ASTHENIA

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 28 | [redacted] | [redacted] |

Dictionary-Derived Term=BACK PAIN

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 26 | [redacted] | [redacted] |

Dictionary-Derived Term=BONE PAIN

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 11 | [redacted] | [redacted] |

Dictionary-Derived Term=DEEP VEIN THROMBOSIS

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 10 | [redacted] | [redacted] |

Dictionary-Derived Term=DEHYDRATION

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 11 | [redacted] | [redacted] |

Dictionary-Derived Term=DIARRHOEA

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 25 | [redacted] | [redacted] |

Dictionary-Derived Term=FATIGUE

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 29 | [redacted] | [redacted] |

Dictionary-Derived Term=FEBRILE NEUTROPENIA

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 32 | [redacted] | [redacted] |

Dictionary-Derived Term=LEUKOPENIA

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 24 | [redacted] | [redacted] |

Dictionary-Derived Term=NAUSEA

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 9 | [redacted] | [redacted] |

Dictionary-Derived Term=NEUROPATHY PERIPHERAL

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 3 | [redacted] | [redacted] |

Dictionary-Derived Term=NEUTROPENIA

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 146 | [redacted] | [redacted] |

Dictionary-Derived Term=PULMONARY EMBOLISM

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 16 | [redacted] | [redacted] |

Dictionary-Derived Term=THROMBOCYTOPENIA

| Analysis Variable : duration | | |
|---|---|---|
| N | Mean | Std Dev |
| 9 | [redacted] | [redacted] |

# 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] [redacted]

**Name of your organisation : British Uro-Oncology Group**

**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.)? ***Committee member of British Uro-Oncology Group***
- other? (please specify)

## NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## 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 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?

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.

***Cabazitaxel is the first drug to show improvement in survival in a Phase III trial in patients with metastatic CRPC who have progressed despite docetaxel chemotherapy.***
***Currently for this group of patients there is no NICE approved treatment which offers a survival benefit.***
***Cabazitaxel is licensed in US and has been used in this setting clinically. It has also got its European license.***
***It would be used by oncologists who specialise in treating prostate cancer and will be an option of treatment for patients with metastatic prostate cancer whose disease shows progression despite docetaxel chemotherapy.***

## NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

**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 patient's should be managed as per guidelines of managing patient's on cytotoxic therapy which will incorporate guidance for managing neutropaenia.***

## NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

**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.***

**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 can be provided in these already established units.***

**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?

# 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:**
University of Southampton/Southampton University Hospitals NHS Trust

**Are you (tick all that apply):**

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

Yes. I am a Senior Lecturer and Honorary Consultant in Medical Oncology with clinical and research specialist interests in genitourinary cancers including prostate cancer.

- 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.)?

No

- other? (please specify)

Member of the Royal College of Physicians, the Association of Cancer Physicians and the Castration-Resistant Prostate Cancer Subgroup of the NCRI Prostate Cancer Clinical Studies Group.

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## 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 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?**

Initial treatment for metastatic prostate cancer is by testosterone suppression. This can be achieved surgically through castration, but it is usually done chemically using either luteinising hormone releasing hormone (LHRH) analogues (e.g. goserelin, leuprorelin, triptorelin) or LHRH antagonists (e.g. degarelix).(1,2) 80% of patients respond to this approach. However, eventual disease progression in the face of castrate levels of testosterone occurs in almost all patients. This was previously referred to as hormone refractory but is more correctly termed castration resistant prostate cancer (CRPC). Median time to treatment failure ranges from 6 to 26 months with 24 to 55% free of treatment failure at 2 years.(3) Additional hormonal interventions may then be clinically effective. Options used in the UK include androgen receptor antagonists (e.g. bicalutamide, flutamide), oestrogens (e.g. diethylstilboestrol) of adrenal androgen depletion (e.g. ketoconazole, steroids).(1,2)

Once hormonal interventions fail to maintain disease control, CRPC is commonly treated with docetaxel chemotherapy. NICE Technology Appraisal No. 101 (Docetaxel for the treatment of hormone-refractory metastatic prostate cancer) recommends docetaxel as a treatment option for men with hormone-refractory metastatic prostate cancer, with a Karnofsky performance-status score ≥60% for up to 10 cycles. This is based on randomised phase III trial evidence demonstrating a survival advantage over mitoxantrone chemotherapy (median survival 19 versus 16.5 months respectively).(4) To date no alternative or addition to docetaxel has been found to be superior in the first line chemotherapy setting. Docetaxel is used to the exclusion of other options in the UK therefore.

Until 2010, evidence for clinical benefit from ‘second line’ chemotherapy after progression on or during docetaxel was limited. No randomised trial had shown a survival advantage in this setting and there was no defined standard of care. Satraplatin combined with prednisone had been shown to produce a progression free survival advantage compared to placebo/prednisone in a phase III clinical trial but failed to show an overall survival advantage.(5) Satraplatin is not available in the UK.

Second line chemotherapy is widely used in the UK by oncologists specialising in CRPC. Choice of chemotherapy varies between individual oncologists reflecting the low level evidence available on which to base treatment decisions. Informally accrued data from the UK used to facilitate discussions and clinical trial design within the NCRI Prostate Cancer Clinical Studies Group indicate that commonly utilised treatment options in the UK are as follows. Docetaxel retreatment or mitoxantrone

are the most common. None of these have been tested in randomised trials of patients previously treated with docetaxel.

- Mitoxantrone: Mitoxantrone produced palliative benefit in combination with steroids versus steroids alone in randomised trials of chemotherapy naive CRPC patients but did not improve overall survival.(6,7) It has therefore been used in the UK as a pragmatic option for patients in the second line setting following the use of docetaxel and as the control arm in the TROPIC trial (see below). Published series suggest lesser activity and increased toxicity in the second line setting. Although not licensed for use in prostate cancer in the UK its use has been widespread.
- Retreatment with docetaxel: In a retrospective analysis of 148 patients who had responded to first line docetaxel chemotherapy, 34% were retreated at disease progression and in these prostate specific antigen (PSA) responses occurred in 48%.(8) Current NICE guidance (NICE Technology Appraisal No. 101) in fact recommends that docetaxel retreatment should not be used. As a result its availability varies by treatment centre in the UK but is used by some.
- Epirubicin/carboplatin/5-flourouracil (ECarboF). This combination regimen has been used in some UK centers with evidence of clinical activity in retrospective analysis following prior use of docetaxel.(9)
- Non randomised data are also available indicating efficacy for the use of various combinations of platinum agents (e.g. carboplatin, cisplatin), taxanes (e.g. docetaxel, paclitaxel) and estramustine.(10) Estramustine is not used in the UK.

In the absence of randomised comparisons, treatment choice has been based on clinician preference based on perceived efficacy and toxicity, as well as availability in different UK centers. It is probably true to say that docetaxel would be perceived as potentially more efficacious but also more toxic than mitoxantrone although the evidence base for this statement is highly limited in the second line setting.

In addition to chemotherapy, other options used in many UK centers for bony metastatic disease are the radioisotope strontium-89 and bisphosphonates (e.g. pamidronate, zoledronate, clodronate). External beam radiotherapy is commonly used for metastases, particularly to bone. Access to palliative care services is important in this patient group who are commonly frail and elderly.(11) Most centers will also offer entry into clinical trials.

Two recently reported randomised phase III trials in CRPC patients who received prior treatment with docetaxel have now shown a survival advantage in the second line setting. The TROPIC trial treated patients with prednisone and randomised to cabazitaxel or mitoxantrone. Median survival was 15.1 and 12.7 months respectively ($p<0.0001$). Cabazitaxel also improved median progression free survival, time to tumour progression and rates of tumour and PSA response.(12) A separate trial of treatment with prednisone and randomisation to the CYP17 inhibitor abiraterone acetate or placebo found a median survival of 14.8 versus 10.9 months respectively ($p<0.001$).(13) UK centres took part in these trials and have also used both drugs in named patient access schemes. There is therefore considerable experience in the UK for both agents. As of June 2011, cabazitaxel is commercially available in the UK. Abiraterone is expected to receive a licence within a few months.

## NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

On the basis of the survival advantages demonstrated for both cabazitaxel and abiraterone, UK oncologists would choose to utilise both at relapse following or during docetaxel, if available, in preference to previously available chemotherapy options for CRPC. It is important to recognise that cabazitaxel and abiraterone hold fundamentally different mechanisms of action. Furthermore significantly different selection criteria were used to determine the trial populations in the registration studies and very different criteria for determining disease progression. Therefore it is particularly important not to make cross trial comparisons of the data from the two studies. Furthermore, based on currently available data, many patients will be suitable for both drugs at different times in their disease process. The view of UK specialists is that both are part of current gold standard therapy for this disease and not alternatives to each other. An optimum scheduling strategy is currently unknown.

**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?**

Prognosis in this patient group is affected by performance status, presence of pain, number of metastatic sites, presence of liver metastases, haemoglobin level, alkaline phosphatase level, PSA level, time since diagnosis and duration of and progression during first line docetaxel.(14) Factors that may predict response to first line docetaxel include pain, visceral metastases, anaemia and bone scan progression and for second line chemotherapy (generally rather than for cabazitaxel specifically) include response to and time since prior docetaxel.(14,15)

Data from the TROPIC trial assessed outcome (for overall survival by treatment group) in a variety of clinically relevant subgroups based on baseline characteristics (performance status, presence of measurable disease, number of prior chemotherapy regimens received, age, presence of pain, presence of a rising PSA, cumulative prior docetaxel dose received, disease progression during or following docetaxel). No interactions between these subgroups and treatment outcome were seen allowing for small numbers in some subgroups. As such no differences in capacity to benefit are currently known for this agent that would allow subgroup selection for treatment. We currently lack predictive biomarkers for cabazitaxel.

The most severe and frequent toxicities seen with cabazitaxel in the TROPIC study were myelosuppression, diarrhoea and infection. Rates of neutropenia and diarrhoea increased with age (≥65), prior radiotherapy and by geographical region. Careful patient selection by oncologists with expertise in this setting is required. However these are selection judgements which oncologists undertake routinely for docetaxel and other second line chemotherapy options. 18 (5%) patients treated with cabazitaxel died within 30 days of treatment versus 9 (2%) for mitoxantrone. The most frequent cause of these deaths in the cabazitaxel group was neutropenic sepsis. However these appear to have resulted from poor sepsis management in some Eastern European and Indian centres. In the UK established chemotherapy support teams and clear algorithms for management of neutropenic sepsis exist

making this risk manageable. Pharmacogenomics studies to aid prediction of inter-individual variation in cabazitaxel metabolism and thus toxicity are awaited.

**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)?**

In the UK chemotherapy for CRPC is administered exclusively in Cancer Centres and Cancer Units by Medical and Clinical Oncologists as members of a wider multidisciplinary team for the disease. Specific expertise in the treatment of CRPC and of the use of cytotoxic agents similar to cabazitaxel exists in such centres with facilities and personnel to manage expected complications such as severe infection. 24 hour specialist emergency care for patients will already exist based on national guidelines for chemotherapy. Infrastructure is therefore already established to deliver this treatment approach safely. No additional professional input would be required.

**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?**

Cabazitaxel is licensed and became commercially available in the UK in May 2011. Prior to this 6 UK centres had participated in the TROPIC trial and treated 37 patients and 12 centres treated 86 patients in the expanded access scheme. It is inevitable that CRPC specialists will now seek to access it for use in the second line setting for prostate cancer (for example via the Cancer Drugs Fund) pending NICE appraisal. Outside of clinical trials its use for unlicensed indications is highly unlikely.

**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.**

Current European Association of Urology Guidelines on Prostate Cancer (updated January 2011) recommend that ‘cabazitaxel should be considered in the management of progressive CRPC following docetaxel therapy’. This is on the basis of level I evidence from the TROPIC trial.(1,12)

NICE clinical guidelines (Prostate Cancer: Diagnosis and Treatment) state that ‘it is not clear whether there is a significant benefit from second line treatment with mitoxantrone or newer chemotherapy drugs for men who have failed docetaxel’. However this guidance was published in 2008 prior to the availability of data for cabazitaxel.

**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?**

Patients with CRPC who progress on or during docetaxel in the UK generally do so under the care of a clinician and in a centre currently using an alternative chemotherapy approach for second line treatment (e.g. mitoxantrone, docetaxel retreatment, ECarboF). Cabazitaxel is given intravenously for up to 10 cycles as are mitoxantrone and docetaxel retreatment. Cabazitaxel has a well documented toxicity profile. In the absence of direct comparisons in clinical trials its toxicity is broadly similar in severity to docetaxel retreatment. It was modestly more toxic than mitoxantrone in the TROPIC trial. Assessment of treatment response by clinical assessment, PSA and imaging tests will not differ from other second line chemotherapy agents in this setting. Ease/difficulty of use will therefore be broadly comparable to current options for second line chemotherapy but with a proven survival benefit which other currently available options lack. There are no particular practical implications for adoption of cabazitaxel over current options in the UK.

**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 with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 were entered into the TROPIC trial on the basis of radiological progression of measurable disease and/or demonstration of new bony metastases and/or PSA progression by standardised criteria. These and other eligibility criteria were consistent with a UK population of CRPC patients suitable to commence second line chemotherapy. These criteria are therefore entirely compatible with those that UK oncologists would deem appropriate to select patients for use of cabazitaxel. Criteria to designate disease progression were used in TRPOIC for cessation of treatment prior to a maximum of 10 cycles of treatment. Again these were consistent with normal UK practice in this setting. Subgroups assessed in the TROPIC trial did not show any variation in efficacy outcomes as described above and so we do not have any further means for subgroup selection for treatment or 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?**

The conditions used in the TROPIC trial directly reflect that seen in UK practice and a number of UK centres participated in it. There are no particular issues in its assessment for use specifically in the UK therefore. The key outcome measure in this clinical setting is overall survival which was the primary endpoint used in TROPIC.

Other important secondary endpoints were also presented. Progression free survival, tumour response rate and PSA response rate were all favourable in the cabazitaxel versus the mitoxantrone arm. Pain response rate and time to pain progression were not improved by cabazitaxel. Safety (described above) was modestly worse with cabazitaxel but to an acceptable level in view of the overall survival benefit.

**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 produces toxicity that is not markedly different in magnitude and severity to other taxane chemotherapy agents used in this setting in the UK (e.g. docetaxel). They are modestly greater than mitoxantrone based on data from the TROPIC trial. Predominant toxicities are myelosuppression, diarrhoea and infection including febrile neutropenia. These are important side effects but this may be balanced against extended survival and control of symptoms as a result of treatment. There is no quality of life data yet presented for cabazitaxel although this was collected in the expanded access program. The toxicity profile of cabazitaxel would be viewed by most oncologists treating this condition as acceptable in the face of the demonstrated survival advantage with this approach and the limitations of other currently available options. Informal discussions with UK experts with significant experience of this agent from both the TROPIC trial and expanded access program have been positive. They have described it as well tolerated and concerns about excessive toxicity have proven unfounded with demonstrable quality of life improvements.

**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.**

No other sources of such data are known to me.

**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)?**

Implementation of cabazitaxel should not impact on delivery of care for CRPC given that most UK centres are already providing chemotherapy in the post-docetaxel setting as described above. Indeed many are likely to be accessing cabazitaxel for use in this setting for example through the Cancer Drugs Fund. No additional resources are expected to be required based on current infrastructure and practice making immediate implementation possible.

**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?**

There are no such concerns in this setting.

1. Guidelines on Prostate Cancer. European Association of Urology. January 2011. http://www.uroweb.org/?id=217&tyid=1.
2. MDT (Multi-disciplinary Team) Guidance for Managing Prostate Cancer, 2nd Edition. British Uro-oncology Group. November 2009. http://www.bug.uk.com/index.php
3. Seidenfeld J, Samson DJ, Hasselblad V, Aronson N, Albertsen PC, Bennett CL, et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. Ann Intern Med. 2000;132:566-77.
4. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. N Engl J Med. 2004;351:1502-12.
5. Sternberg CN, Petrylak DP, Sartor O, Witjes JA, Demkow T, Ferrero JM, et al. Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. J Clin Oncol. 2009;27:5431-8.
6. Kantoff PW, Halabi S, Conaway M, Picus J, Kirshner J, Hars V, et al. Hydrocortisone With or Without Mitoxantrone in Men With Hormone-Refractory Prostate Cancer: Results of the Cancer and Leukemia Group B 9182 Study. J Clin Oncol. 1999;17:2506-13.
7. Tannock I, Osoba D, Stockler M, Ernst D, Neville A, Moore M, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol. 1996;14:1756-64.
8. Eymard JC, Oudard S, Gravis G, Ferrero JM, Theodore C, Joly F, et al. Docetaxel reintroduction in patients with metastatic castration-resistant docetaxel-sensitive prostate cancer: a retrospective multicentre study. BJU Int. 2010;106:974-8.
9. McGovern UB, Harland SJ. Use of epirubicin, carboplatin, and 5-fluorouracil (ECarboF) as a second-line treatment in metastatic castration-resistant prostate cancer. J Clin Oncol. 2011;29:173
10. Regan MM, O'Donnell EK, Kelly WK, Halabi S, Berry W, Urakami S, et al. Efficacy of carboplatin-taxane combinations in the management of castration-resistant prostate cancer: a pooled analysis of seven prospective clinical trials. Ann Oncol. 2010;21:312-8.
11. Clarke NW. Management of the spectrum of hormone refractory prostate cancer. Eur Urol. 2006;50:428-38.
12. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376:1147-54.
13. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364:1995-2005.
14. Armstrong AJ, Garrett-Mayer E, de Wit R, Tannock I, Eisenberger M. Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. Clin Cancer Res. 2010;16:203-11.
15. Loriot Y, Massard C, Gross-Goupil M, Di Palma M, Escudier B, Bossi A, et al. The interval from the last cycle of docetaxel-based chemotherapy to progression is associated with the efficacy of subsequent docetaxel in patients with prostate cancer. Eur J Cancer. 2010;46:1770-2.

# Patient/carer organisation statement template

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

**About you**

**Your name:** [redacted]

**Name of your organisation: Trustee and Member Representing-**
**PCaSO Prostate Cancer Network**
**And**
**Prostate Cancer Support Federation**

**Are you (tick all that apply):**

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)
- other? (please specify)

**What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?**

1. **Advantages**
(a) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make.

CRPC -Longer survival time of patient

Increase in time to when the disease progresses

Greater number of patients responding to treatment

(b) Please list any short-term and/or long-term benefits that patients expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example family, friends, employers)
- other issues not listed above.

Reduced pain giving greater mental and physical health

Longer time with family

Ability to take greater part in family activities

Possibility to return to work reducing impoverishness that the disease might bring about

**What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition? (continued)**

2. **Disadvantages**
Please list any problems with or concerns you have about the technology.
Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

Patients will need to regularly visit a hospital for IV causing unbudgeted expense

Patients would have to tolerate possible side effects of diarrhoea, sickness etc

Certain men could not take the drug if allergic to Taxane or have a low blood white cell count or liver problemsLess resistant to infections

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

The majority of patients will tolerate many side effects to prolong their life once Docetaxel or a second line treatment has failed

There are however a small proportion who would rather have palliative care.

No study has been carried to ascertain the exact numbers

4. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

Only those where a second line treatment such as docetaxel has failed. This is not for all HRPC patients where the above failure has not taken place

**Comparing the technology with alternative available treatments or technologies**

NICE is interested in your views on how the technology compares with with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.
Mitoxantrone, 5- fluorouracil, cyclophosphamide and carboplatin/etoposide.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

Greater numbers respond to Cabazitaxel

Prolonged survival
There are problems with side effects but there also additives that can combat these issues

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)

- side effects (for example nature or number of problems, how often, for how long, how severe).

None

**Research evidence on patient or carer views of the technology**

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine NHS care reflects that observed under clinical trial conditions.

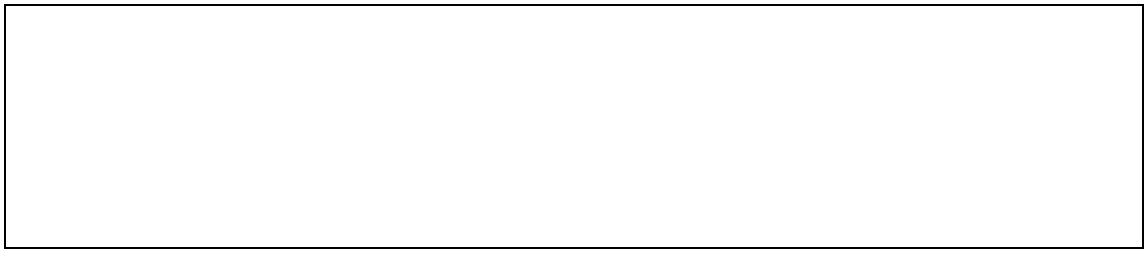
Not sufficient detailed knowledge of individuals experience to be able to comment but understand that a rigorous study was undertaken under the name TROPIC involving 755 men who had been previously treated with Docetaxel

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?

None known

Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.

None known



**Availability of this technology to patients in the NHS**

What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

A longer life for the patient is the key difference

What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

Dissatisfaction with a health service that failed to provide a significant life lengthening treatment

Are there groups of patients that have difficulties using the technology?

Those with Allergies to Taxane, low white cell count and liver disease

**Other Issues**

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.

The expense for this technology is high but an extra 15 months of life to a patient is priceless. Please consider this when calculating cost per quality adjusted life years.

It has also been licensed in Europe the UK should not be left out. The FDA have also approved its use in the US.

# 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 your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

**About you**

**Your name:** [redacted]

**Name of your organisation: The Prostate Cancer Charity**

**Are you (tick all that apply):**

- ✓ an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)

  **Director of Operations**

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

We conducted a paper and online survey of people affected by prostate cancer about their opinions on cabazitaxel and access to the drug. 30 people replied to the survey and quotes from the respondents are included in this submission.[ii]

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

**What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?**

1. **Advantages**

(a) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make.

The main expected benefits of the technology are increased overall survival and progression-free survival. There are currently no other licensed second line treatments for men with metastatc castration-resistant prostate cancer (mCRPC) that have been shown to increase overall and progression-free survival once the cancer has progressed on or following docetaxel treatment. Cabazitaxel would make a difference to these patients by providing an additional treatment option that may significantly extend their lives at a point where the only other treatments available are palliative.

It would be desirable to increase the range of clinically effective treatment options available for patients with mCRPC that no longer responds to docetaxel. Should the STA recommend that cabazitaxel is effective for the above indication, it will help to provide standardised access and increased choice to a group of patients who currently have no other licensed treatments available to them and are facing a very limited lifespan.

(b) Please list any short-term and/or long-term benefits that patients expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example family, friends, employers)
- other issues not listed above.

Of the 30 people affected by prostate cancer who responded to our survey, 19 identified that the possibility of extended life that cabazitaxel offers was its most important benefit, particularly when no other treatment options are available. 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 quality of life and potentially reduce distress. The increased survival was also seen by some as an opportunity for these patients to be able to spend more time with family and friends. It is difficult to comment on impact on quality of life as this data is not available.

## NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

Comments included:

"The research report regards the extension of life as significant, although it only appears to be a few months, but if that is all one has it buys time (possibly longer) and with it hope."
Man diagnosed with prostate cancer

"I think if it improves disease control and extends life and as long as the quality of the extended life is good that is a massive benefit."
Relative of man who died of prostate cancer

**What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition? (continued)**

2. **Disadvantages**
Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

It is concerning that there were an excess number of deaths, mainly due to neutropenia, in the cabazitaxel arm of the Phase III trial compared to the mitoxantrone arm. The higher probablility of grade 3 adverse events in men taking cabazitaxel is also a disadvantage. However, of the 30 people we surveyed, only 7 highlighted that the side effects of cabazitaxel were a serious concern to them. Of these, most commented that all treatments had side effects and patients need balanced information to weigh up the pros and cons of cabazitaxel (if offered it) for themselves.

Thought must be given to how clear and balanced information on both the benefits and the likelihood of serious adverse events can be best provided to patients so that they are able to make an informed choice if offered this agent. Proactive management of side effects such as neutropenia will also be very important.

No survey respondent appeared to have any concerns that cabazitaxel treatment required repeat hospital visits for administration, but this may be seen by some patients as a disadvantage, or a barrier to receiving treatment where access to the hosiptal is difficult for them.

## NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe 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.

4. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

We have no information to enable us to answer this question.

**Comparing the technology with alternative available treatments or technologies**

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.

There are currently no other treatments licensed for men with mCRPC that have been shown to be clinically effective once the cancer has progressed following docetaxel treatment. Mitoxantrone is often offered as a palliative treatment but there is no evidence that it has any benefit to survival. Therefore there are not strictly any current alternatives to cabazitaxel available to these patients.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

The main advantage for eligible patients is that cabazitaxel is likely to increase progression-free and overall survival at a point where no other clinically effective options exist.

## NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

Cabazitaxel has significant serious adverse effects, but it is difficult to make comparisons as there are no equivalent standard practices for these patients. Eligible patients who are offered cabazitaxel treatment will be given the alternative of palliative care to improve quality of life. They must weigh up the potential pros and cons of both options, with support from a healthcare professional.

**Research evidence on patient or carer views of the technology**

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine NHS care reflects that observed under clinical trial conditions.

No patient who has had experience of cabazitaxel responded to our survey.

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?

Cabazitaxel has only been licensed since March 2011 and so this evidence is not yet available to us.

Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.

Our survey is the only relevant survey of attitudes to cabazitaxel that we are aware of. Details of the survey are provided in the notes at the end of this document.

In 2010 we surveyed people affected by prostate cancer on their views on the NHS in England[iii]. 129 people responded. When asked for their priorities for prostate cancer

care, 18% highlighted improved life expectancy for men with prostate cancer and 14% commented they wanted better choice and availability of treatments.

**Availability of this technology to patients in the NHS**

What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

Of the 30 people affected by prostate cancer we surveyed, the most common benefits of making cabazitaxel available on the NHS were identified as extending the lives of men with mCRPC and providing an additional treatment option for these men. Men who have this type of cancer and who no longer respond to docetaxel treatment have no other clinically effective treatment options available to them. They should be offered the choice of a life-extending agent that can allow them a few extra months to spend with family and friends and should be able to access that drug on the NHS if it has been prescribed by their doctor and they make an informed choice to take it.

Comments from the survey include:

"To be given another option when all other treatments have been unsuccessful is a huge step forward and I think the patients and carers will get some comfort knowing that it is available to them on the NHS"
Relative of man who died of prostate cancer

"I feel we would be grateful to know our lives could be extended as time is precious"
Man with advanced prostate cancer

What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

Comments from respondents suggested that if cabazitaxel was not made available, the main implication for these patients would be the loss of a chance to increase their survival and increased distress associated with not being able to access a clinically relevant drug. Other respondents identified that patients with mCRPC would feel deprived and would lose hope. A few were concerned that people would spend a lot of money trying to access the drug privately, or that only wealthy people would be able to have access to the treatment.

Comments included:

"Knowing that there is a drug that could extend your life but not having access to it would be extremely distressing for the patient and their carer. It would make you feel

like your life was not valued. It could cause financial difficulty if the drug is only available privately and it would cause a lot of resentment towards our NHS."
Relative of man who died of prostate cancer

"Denial of treatment when available is always emotive, although I understand there must be priorities. But prostate cancer is not sufficiently publicised so the importance of this treatment option could be too easily dismissed."
Man diagnosed with prostate cancer

"The consequences to patients and family if this was not available on the NHS would be a feeling of despair… there should not be one treatment available if you are rich and nothing if you are poorer"
Partner of man with prostate cancer

Are there groups of patients that have difficulties using the technology?

We do not have enough information to enable us to answer this question

**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?

It will be important to ensure that access to this technology is equitable and discrimination does not occur solely on the basis of age, ethnicity or socio-economic status. Prostate cancer is more common in men aged over 60 and African Caribbean men are three times more likely to develop prostate cancer than white men of the same age in the UK. Furthermore, men from lower socioeconomic backgrounds are less likely to survive prostate cancer than men from more affluent backgrounds. It will be important to ensure that eligible patients from these populations are not denied access to this technology (if approved) because of factors related to their age, ethnicity and socio-economic status. Information and communication strategies must also be considered and patients consulted to ensure that access can be as equitable as possible.

Respondents to our survey also felt that there were few options available for younger men with mCRPC. One respondent commented:

"The medical profession is facing a position where it is running out of treatments for

## NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

men in their forties & fifties... We need effective forms of chemo available. Not just palliative."
Man with locally advanced prostate cancer

**Other Issues**

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.

It is important that health-related quality of life and adverse effects are considered with an equal standing to the other outcomes, such as patient-reported outcomes. Consideration of patient-reported outcomes will ensure that the agent is not only clinically effective but also improves outcomes of importance to this patient population, such as the extension of life.

---

[i] Transforming the future for prostate cancer: The Prostate Cancer Charity's 2020 goals and 2008-2014 strategy. The Prostate Cancer Charity 2008. Available at: http://www.prostate-cancer.org.uk/about-us/what-we-do/our-strategy

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

[iii] Between 25th August and 8th September 2010, The Prostate Cancer Charity surveyed people affected by prostate cancer living in England for their views to the proposals in "Equity and excellence: liberating the NHS". 129 people responded to an online and paper survey.

# 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 your views on the technology and the way it should be used in the NHS.

Primary Care Trusts (PCTs) provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a PCT perspective on the issues you think the committee needs to consider, are what we need.

**About you**

Your name:
[redacted]

Name of your organisation
NHS Warwickshire

Please indicate your position in the organisation:

- commissioning services for the PCT in general?
- commissioning services for the PCT specific to the condition for which NICE is considering this technology?
- responsible for quality of service delivery in the PCT (e.g. medical director, public health director, director of nursing)?
- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)?
- other (please specify)

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## 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 the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in 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?

NICE CG 58 followed.

The aim of treatment for men with metastatic HRPC that has progressed during or after a docetaxel-based treatment is to improve symptoms, slow progression of the disease and prolong life. Clinical management is acknowledged to be multimodal rather than sequential, and patients may receive a combination of palliative treatments.

Alternatives to cabazitaxel include:

- Additional hormonal therapy (e.g. diethylstilbestrol)
- Mitoxantrone with or without steroids - widely used for patients who are fit for chemotherapy (but not licensed for this indication)
- Docetaxel re-challenge in patients initially responsive to docetaxel

To what extent and in which population(s) is the technology being used in your local health economy?

- is there variation in how it is being used in your local health economy?
- is it always used within its licensed indications? If not, under what circumstances does this occur?
- what is the impact of the current use of the technology on resources?
- what is the outcome of any evaluations or audits of the use of the technology?
- what is your opinion on the appropriate use of the technology?

Cabazitaxel is not currently used in our local health economy.

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

**Potential impact on the NHS if NICE recommends the technology**

What impact would the guidance have on the delivery of care for patients with this condition?

If used it may delay disease progression and improve survival.

In the TROPIC trial there was increased incidence of neutropenia and febrile neutropenia compared to mitoxantrone. This may lead to increased admissions to hospital which is not ideal for a palliative treatment. It may also lead to increased use of growth factors to support patients during neutropenia.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

Secondary care. May increase number of daycase attendances if increases time to progression compared to comparators.

## NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

Unable to estimate as price not known.

Cost of drug but also cost of adverse reactions, e.g. use of GcSF, admissions due to febrile neutropenia

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

If the technology costs more than mitoxantrone it will lead to the loss of funds to other services.

Would there be any need for education and training of NHS staff?

It is unlikely that there would be training issues associated with the use of cabazitaxel

# 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?

Unaware of any issues.

**Other Issues**

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.

The pivotal study suggests that the side effect profile of cabazitaxel is not as good as that of mitoxantrone. Patients in the cabazitaxel group experienced more haematological and non-haematological side effects than patients in the mitoxantrone group. There were 17 deaths as a result of cabazitaxel treatment compared to 3 as a result of mitoxantrone treatment. This seems inappropriate considering the aim of treatment is palliation, not cure.

Questions remain about the dosing regimen chosen in the TROPIC study. Could toxicity have been mitigated by starting on a lower dose as utilised in the phase II trials?

If abiraterone is likely to be licensed for the same indication. Would it be worth considering an MTA?

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

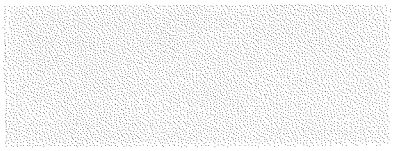
Please sign and return to:

Jennifer Heaton, Technology Appraisal Administrator
**Email:** TACommB@nice.org.uk
**Fax:** +44 (0)20 7061 9830
**Post:** NICE, MidCity Place, 71 High Holborn, London, WC1V 6NA

I confirm that:

- I agree with the content of the statement submitted by **NCRI/RCP/RCR/ACP/JCCO** and consequently I will not be submitting a personal statement.

Name: Dr Simon Crabb

Signed: 

Date: 5th July, 2011

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

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

Jennifer Heaton, Technology Appraisal Administrator
**Email:** TACommB@nice.org.uk

**Fax:** +44 (0)20 7061 9830
**Post:** NICE, MidCity Place, 71 High Holborn, London, WC1V 6NA

I confirm that:

- I agree with the content of the statement submitted by **Prostate Cancer Support Federation** and consequently I will not be submitting a personal statement.

Name: W.G. GLOVER

Signed: [redacted]

Date: 23 August 2011

## Appendix K - NHS Commissioning expert statement declaration form

### NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

### Single Technology Appraisal (STA)

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

Please sign and return by email to:
TACommB@nice.org.uk

If email is not possible, please return by fax to Jeremy Powell, Project Manager **on** 020 7061 9830

or by post to: NICE, MidCity Place, 71 High Holborn, London WC1V 6NA

I confirm that:

- I agree with the content of the statement submitted by **NHS Warwickshire** and consequently I will not be submitting a personal statement.

Name: Miss Suzanne Heafield

Signed:

Date: 2-9-11

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

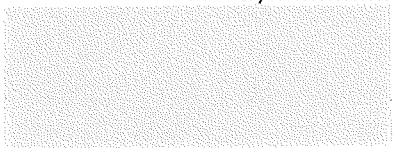
## Cabazitaxel for the second line treatment of hormone refractory, metastatic prostate cancer

Jennifer Heaton, Technology Appraisal Administrator
**Email:** TACommB@nice.org.uk
**Fax:** +44 (0)20 7061 9830
**Post:** NICE, MidCity Place, 71 High Holborn, London, WC1V 6NA

I confirm that:

- I agree with the content of the statement submitted by **The Prostate Cancer Charity** and consequently I will not be submitting a personal statement.

Name: ....Ms Ruth Holdaway.....

Signed:  .....

Date: .....23/01/11.....

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

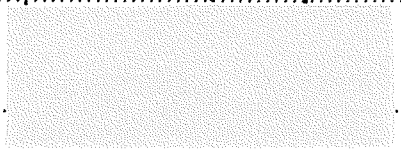
Please sign and return to:

Jennifer Heaton, Technology Appraisal Administrator
**Email:** TACommB@nice.org.uk
**Fax:** +44 (0)20 7061 9830
**Post:** NICE, MidCity Place, 71 High Holborn, London, WC1V 6NA

I confirm that:

- I agree with the content of the statement submitted by **British Uro-Oncology Group** and consequently I will not be submitting a personal statement.

Name: HEATHER PAYNE

Signed: 

Date: 15/07/2011

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

Please sign and return to:

Jennifer Heaton, Technology Appraisal Administrator
**Email:** TACommB@nice.org.uk
**Fax:** +44 (0)20 7061 9830
**Post:** NICE, MidCity Place, 71 High Holborn, London, WC1V 6NA

I confirm that:

- I agree with the content of the statement submitted by **The Prostate Cancer Charity** and consequently I will not be submitting a personal statement.

Name: Lauren Wiggins

Signed: .....  .....

Date: 15 July 2011

**Cabazitaxel for the second-line treatment of hormone refractory, metastatic prostate cancer: A single technology appraisal**


| | |
|---|---|
| **Produced by** | School of Health and Related Research (ScHARR), The University of Sheffield |
| **Authors** | Matt Stevenson, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA<br>Myfanwy Lloyd Jones, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA<br>Ben Kearns, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA<br>Chris Littlewood, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA<br>Ruth Wong, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA |
| **Correspondence to** | Matt Stevenson, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA |
| **Date completed** | 17th August 2011 (following the Fact Check Process) |



**Source of funding**: This report was commissioned by the NIHR HTA Programme as project number 10/49/01.


**Declared competing interests of the authors**

None.

**Acknowledgements**

Dr Stéphane Larré, Senior Clinical Lecturer and Consultant Urological Surgeon, Nuffield Department of Surgical Science, University of Oxford, John Radcliffe Hospital, Oxford, and Dr Satish Kumar, Consultant Medical Oncologist, Velindre Cancer Centre provided clinical advice and commented on draft materials during the project.

We would also like to thank Andrea Shippam and Gill Rooney, Programme Administrators, ScHARR, for their help in preparing and formatting the report.

**Declared competing interests of the clinical advisors**

None declared.

**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.

**This report should be referenced as follows:**

Stevenson M, Lloyd Jones M, Kearns B, Littlewood C, Wong R. Cabazitaxel for the second-line treatment of hormone refractory, metastatic prostate cancer: A Single Technology Appraisal. ScHARR, The University of Sheffield, 2011.

**Contributions of authors**

Matt Stevenson and Ben Kearns critiqued the manufacturer's economic evaluation and contributed to the writing of the report. Myfanwy Lloyd Jones and Chris Littlewood critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Ruth Wong commented on the searches included in the manufacturer's submission and contributed to the writing of the report. Matt Stevenson acted as project lead.

**TABLE OF CONTENTS**

**List of Tables and Figures**

**List of abbreviations**

| | |
|---|---|
| ADT | Androgen-Deprivation Therapy |
| AE | Adverse Event |
| AIC | Akaike Information Criterion |
| AS | Analgesic Score |
| ASCO | American Society of Clinical Oncology |
| BAUS | British Association of Urological Surgeons |
| BIC | Bayesian Information Criterion |
| BNF | British National Formulary |
| BSA | Body Surface Area |
| BSC | Best Supportive Care |
| CEAC | Cost-Effectiveness Acceptability Curve |
| CI | Confidence interval |
| CR | Complete Response |
| EAP | Early Access Programme |
| ECOG | European Cooperative Oncology Group |
| EQ-5D | EuroQol 5-Dimension |
| 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 |
| IQR | Interquartile Range |
| ITT | Intention To Treat |
| KM | Kaplan-Meier |
| LHRH | Luteinising Hormone-Releasing Hormone |
| mCRPC | Metastatic Castration-Resistant Prostate Cancer |
| mHRPC | Metastatic Hormone Refractory Prostate Cancer |
| MS | Manufacturer's Submission |
| NCDB | National Cancer Data Base |
| OS | Overall Survival |
| PD | Progressive Disease |
| PFS | Progression-Free Survival |
| PPI | Present Pain Intensity |

| | |
|---|---|
| PR | Partial Response |
| PS | Performance Status |
| PSA | Prostate-Specific Antigen |
| QALY | Quality Adjusted Life Years |
| RCT | Randomised Controlled Trial |
| RD&TC | Regional Drug and Therapeutics Centre |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| SAE | Serious Adverse Event |
| SD | Stable Disease |
| SRE | Skeletal-Related Event |
| VAS | Visual analogue scale |

**Glossary**

| | |
|---|---|
| Analgesic score | Mean daily patient-recorded analgesic use expressed in morphine equivalents. |
| European Cooperative Oncology Group (ECOG) performance status (PS) | Criteria used to assess a patient to determine appropriate treatment and prognosis. Performance is graded from 0 to 5, where:<br>0 = fully active, able to carry on all predisease performance without restriction<br>1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work<br>2 = ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours<br>3 = capable of only limited self-care, confined to bed or chair more than 50% of waking hours<br>4 = completely disabled. Cannot carry on any self-care. Totally confined to bed or chair<br>5 = dead. |
| Hazard ratio | A measure of relative risk used in survival studies. |
| Karnofsky performance status score | A performance measure used to rate a person's ability to perform normal activities. It can be used to determine a patient's suitability for therapy, or to evaluate the impact of a therapeutic procedure. It is commonly used in patients with cancer. The health care professional assesses the patient's ability to perform certain ordinary tasks on a scale of 0-100%, where:<br>100% is normal; 90% is able to carry on normal activity but with minor signs or symptoms of disease; 80 is able to carry on normal activity with effort and with some signs or symptoms of disease; 70% cares for self but unable to carry on normal activity or to do active work; 60% requires occasional assistance but is able to care for most needs; 50% requires considerable assistance and frequent medical care; 40% is disabled and requires special care and assistance; 30% is severely disabled and hospitalisation is indicated although death not imminent; 20% hospitalisation is necessary, very sick, active supportive treatment necessary; 10% moribund, fatal processes progressing rapidly; 0% dead. |
| Neutropenia | An abnormally low level in the blood of neutrophils, cells which are important in fighting infections within the body. |
| Prostate-specific antigen | A protein produced by the prostate gland. It is found in small quantities in the serum of men with healthy prostates, but is often elevated in men with prostate cancer or other prostate disorders. The PSA level should fall following curative therapy for prostate cancer; a subsequent rise is likely to indicate cancer recurrence. |
| Skeletal-related event | Adverse events associated with bone metastases, and including pathological fractures, spinal cord compression, hypercalcaemia, and severe pain requiring bone surgery, radiation therapy or opioid analgesics |
| Visual analogue scale (VAS) | A simple measurement scale frequently used for the assessment of an attitude or characteristic, e.g. pain. |

# 1. SUMMARY

## 1.1 Scope of the manufacturer's submission

The manufacturer's submission (MS) to NICE sought to provide evidence relating to the clinical and cost effectiveness of cabazitaxel used within its licensed indication in combination with prednisolone for the second-line treatment of metastatic hormone refractory prostate cancer (mHRPC) which has progressed following or during docetaxel therapy.

The NICE final scope identified two relevant comparators - mitoxantrone plus prednisolone, and chemotherapy without cabazitaxel (e.g. 5-fluorouracil, cyclophosphamide and carboplatin/etoposide). However, the MS limited the comparator to mitoxantrone plus prednisolone on the basis that mitoxantrone plus prednisolone is the active treatment most commonly used in the UK as second-line treatment in patients with mHRPC, and that other chemotherapy agents were not relevant to the decision problem because they are seldom used for this purpose and therefore cannot be considered part of standard UK clinical practice. The ERG's clinical advisors concurred with this view.

The MS addressed the outcomes specified within the NICE final scope.

## 1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The MS included a systematic review of all randomised controlled trials (RCTs) of cabazitaxel versus any comparator. This identified only one relevant study: the TROPIC study, a multinational open-label active-controlled randomised trial designed to compare the efficacy and safety of cabazitaxel plus prednisone or prednisolone against mitoxantrone plus prednisone or prednisolone in patients with mHRPC which has progressed following or during docetaxel therapy. (Prednisone, which is widely used outside the UK, appears to be functionally interchangeable with prednisolone.)

*Efficacy*

The TROPIC study found that, relative to mitoxantrone plus prednisone/prednisolone, cabazitaxel plus prednisone/prednisolone was associated with a median overall survival (OS) gain of 2.4 months (15.1 vs. 12.7 months; hazard ratio (HR) 0.70, 95% CI 0.59-0.83, $p<0.0001$). An updated analysis found that the median values were unchanged, but the HR was 0.72 (95% CI 0.61-0.84, $p<0.0001$). Cabazitaxel was associated with statistically significant improvements in median progression-free survival (PFS) (2.8 vs 1.4 months; HR 0.74, 95% CI 0.64-0.86, $p<0.0001$), and in Prostate-Specific Antigen (PSA) response, time to PSA progression, objective tumour response, and time to tumour progression, but was not associated with statistically significant differences in pain response or pain progression. Quality of life data comparing cabazitaxel with mitoxantrone were not available.

*Safety*

In the TROPIC study, the most common adverse events (AEs) associated with cabazitaxel were haematological: the incidence of grade $\geq$ 3 neutropenia and leukopenia were both noticeably higher with cabazitaxel than with mitoxantrone (82% vs 58%, and 68% vs 42%, respectively). The incidence of diarrhoea of any grade, and of grade $\geq$ 3 gastrointestinal disorders of all types, were also substantially higher with cabazitaxel (47% vs 11%, and 12.4% vs 1.6%, respectively). The risk of most AEs was substantially increased in patients aged 65 and over.

Deaths within 30 days of the last dose of study drug were more common with cabazitaxel (5% vs 2%). The most common causes of such deaths were neutropenia in patients receiving cabazitaxel, and disease progression in patients receiving mitoxantrone. Cardiac and renal complications other than deaths appear to be poorly reported.

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

The MS appears to be complete in that it includes the only RCT of cabazitaxel plus prednisone/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 assessment of subjective outcomes such as pain and symptomatic disease progression; PFS, a composite endpoint which incorporates pain progression, is also susceptible to bias, although OS (the primary outcome), and tumour response, both of which are objective measures, are unlikely to have been affected. Pain outcomes may also have been affected by the lower prevalence of bone metastases in patients randomised to cabazitaxel than in those randomised to mitoxantrone (80% vs 87%).

The assessment of clinical AEs is also susceptible to bias because of lack of blinding, although the assessment of laboratory AEs is unlikely to have been affected. Despite this, concern has been expressed about the raised incidence of neutropenic complications (febrile neutropenia and infection), renal failure, haematuria, and cardiac toxicity associated with cabazitaxel. There is particular concern that deaths were attributed to cardiac and renal failure even though the TROPIC study's inclusion criteria included adequate cardiac and renal function.

Because the TROPIC study used more stringent criteria relating to dose modifications and discontinuations of cabazitaxel therapy than are included in the product specification, the incidence of AEs associated with cabazitaxel may be higher in clinical practice than observed in TROPIC.

### 1.4 Summary of cost effectiveness submitted evidence by the manufacturer

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.

In the manufacturer's base case analysis, costs and transition probabilities are based on a subgroup of the TROPIC study, namely 'European patients who received ≥225mg/m2 of first-line docetaxel and with European Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1'. Transition probabilities are time-varying and based on Kaplan-Meier data, until the point when they are judged (by the manufacturer) to be too unreliable and are then replaced with transition rates calculated from parametric curves. In the absence of data relating to health-related quality of life from controlled trials of cabazitaxel, the manufacturer utilised interim results from the early access programme (EAP) for cabazitaxel, which allow comparison with baseline but not with mitoxantrone or any other comparator therapy. Data from the EAP was only available for a relatively small number of patients with stable disease; an estimation of the decreased utility for patients with progressive disease was taken from published literature.

In their base case the manufacturer estimated a deterministic cost per quality adjusted life year (QALY) gained of £74,938. Probabilistic sensitivity analysis (2,000 simulations) indicated that this value ranged from £45,760 to £890,372. Univariate sensitivity analyses showed that the main drivers for this variation are changes in utility estimates for both disease states and the time point from which the parametric curve were used. If the parametric curves were used for the entire modelling period the incremental cost-effectiveness ratio (ICER) became £82,950.

There is uncertainty regarding whether the deaths observed within 30 days of randomisation in TROPIC could be preventable with more vigilant treatment of neutropenia. 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. Following this, no new neutropenic deaths were reported. Accordingly the manufacturer conducted an exploratory analysis evaluating the change in the ICER were the deaths associated in the first 30 days not considered. This increased the ICER to £78,319 per QALY gained.

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

The ERG did not concur with the manufacturer in the choice of patient population and regarding the use of the Kaplan-Meier data that constitute the base case. These are discussed in turn.

Compared with the full TROPIC trial population, the patient population used within the economic model is filtered in three ways: it is restricted to European patients; patients who did not receive at least 225mg/m$^2$ of first-line docetaxel were excluded; and patients with an ECOG PS of 2 were excluded. Whilst the ERG (following discussions with its clinical advisors) believes that the last two filters have clinical validity, the restriction to just European patients is less justified. Given that there were no *a priori* reasons for considering just this population, and that a statistical test of treatment interaction by region gave a non-significant result, the ERG feels that the arguments for making this geographic restriction are not sufficiently compelling, and that all regions should be included.

The ERG feels that 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, which ranged from £72,184 to £90,786 dependent on when the Kaplan-Meier data were considered unreliable.

It is additionally noted that the ICER is sensitive to the choice of utility values and fuller data from the EAP are required before a robust ICER can be provided.

## 1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

### *1.6.1 Strengths*

The manufacturer undertook a systematic review of the evidence for cabazitaxel as second-line treatment of mHRPC. The one study which was identified and included in this review used cabazitaxel within its licensed indication in the relevant population, and measured outcomes which were appropriate and clinically relevant. The study's methodological quality appeared to be generally good. However, because of lack of blinding, it incorporated some risk of bias.

The conceptual model used appears robust and transparent, allowing both variability and uncertainty in the model inputs to be altered and assessed. The model contained the functionality to assess the impact of changing parameters and structural uncertainties on the ICER, and included a number of built-in alternative scenarios.

### *1.6.2 Weaknesses and areas of uncertainty*

The adverse event data observed within the TROPIC RCT was of concern, the Food and Drug Administration recommended a review of renal toxicity and a submission of updates from active RCTs for three years after the US approval date (2010); data are currently not available. Therefore, caution may be prudent until these data emerge.

There is dispute (and hence corresponding uncertainty in the ICER) regarding the correct population from which to estimate transition probabilities, and whether parametric curves should be used throughout the modelling horizon. The ERG has a different view on these issues than the manufacturer.

A key uncertainty relates to the utility values that should be assigned to stable and progressive disease, as the available data is not sufficiently robust. The importance of this is highlighted by the sensitivity of the results to the utility values used. It is noted that more data should soon be made available from the EAP.

Updated data from the TROPIC study (based on 585 deaths rather than 513) is available that were not used in the submission. During the clarification process the manufacturer indicated that this has little impact on the ICER (using the population in the manufacturer's base case and when the parametric curves are used throughout the modelling horizon) although it is unclear what effect would be observed using the population constituting the ERG base case.

There is also uncertainty in whether the deaths observed within 30 days of randomisation in TROPIC could be prevented with more vigilant treatment of neutropenia. If so, exploratory analyses indicate that the ICER may increase.

## 1.7 Summary of additional work undertaken by the ERG

The ERG made 3 amendments to the manufacturer's base case.

- Estimating the transition probabilities from all patients who received ≥225mg/m2 of first-line docetaxel and with ECOG PS 0 or 1, rather than just European patients
- Using the parametric curves throughout the modelling horizon
- Making a small change to the discount rate used

This increased the ICER to £89,684, which was calculated from probabilistic sensitivity analyses. It was seen that the choice of utility values had a marked impact on the ICER and these are currently

highly uncertain. There is also residual uncertainty regarding whether the deaths observed within 30 days of randomisation in TROPIC may be preventable.

# 2. BACKGROUND

This report provides a review of the evidence submitted by sanofi-aventis in support of cabazitaxel for the second-line treatment of metastatic hormone refractory prostate cancer (mHRPC) which has progressed following or during docetaxel therapy. It considers both the original manufacturer's submission (MS) received on 10th June 2011[1] and subsequent addenda supplied on 13th July 2011.[2]

## 2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's description of mHRPC which has progressed following or during docetaxel therapy is appropriate and relevant to the decision problem under consideration. It defines metastatic prostate cancer as stage IV cancer. Prostate cancer may be classified either by the tumour-node-metastasis (TNM) system or by numbered Stages I-IV; the latter defines Stage IV cancer as cancer which has either invaded local adjacent structures (the bladder or rectum) or has spread to the lymph nodes or other parts of the body such as the bones, liver, or lungs.[3] The MS then follows the NICE guideline[4] in stating that, while there is no universally accepted definition of hormone refractory prostate cancer, prostate cancer may be considered to be hormone refractory when androgen withdrawal therapy or combined androgen blockade no longer controls the prostate-specific antigen (PSA) or the symptoms of the disease, or when there is radiological evidence of progression. However, the guideline notes that such cancer may still respond to agents such as oestrogens or corticosteroids which probably work via the androgen receptor, and that luteinising hormone-releasing hormone (LHRH) therapy is usually continued even when the disease becomes hormone refractory.

The MS states in section 6.4.1 that metastatic prostate cancer is associated with a range of symptoms which substantially affect quality of life: these symptoms are said to include lymphoedema, weight loss, pain, and skeletal-related events (SREs) associated with bone metastases. It also states, in section 2.1, that bone metastasis is a common form of metastatic disease in prostate cancer; that bone metastases often lead to SREs including fractures, spinal cord compression, and severe pain; and that bone metastases, and the associated pain, contribute substantially to the burden of disease in patients with metastatic prostate cancer.[1] However, it should be noted that lymphoedema is not common in prostate cancer. Furthermore, although Cancer Research UK states that bone pain is the biggest problem associated with mHRPC,[5] the Prostate Cancer Charity notes that not all men with metastatic prostate cancer will have pain.[6] Moreover, the pathological fracture rate associated with bone metastases in prostate cancer is low relative to that associated with other metastatic cancers, and the rate of healing approaches that of normal bone, with surgical stabilisation required in only about a quarter of cases.[7]

Prostate cancer is common in England and Wales. There were 33,373 new cases in 2008, the most recent year for which data are available;[8] in that year, 9,150 deaths were attributed to prostate cancer.[9] Five-year survival with metastatic cancer is poor: although the overall five-year survival rate for patients diagnosed with prostate cancer in England and Wales in 2001-2006 was 77%, five-year survival in patients in England who presented with metastatic cancer in 1999-2002 was only around 30%.[10]

There are no published data for the incidence of mHRPC. The MS[1] estimates that 7,047 patients in England and Wales have mHRPC. This estimate is derived from an epidemiological model developed by sanofi-aventis which was not made available to the Evidence Review Group (ERG), but which was said to incorporate the following data:

- An estimated incidence of prostate cancer in England and Wales in 2011 of 36,105. This is based on the Cancer Research UK figure, noted above, of 33,373 new cases of prostate cancer in England and Wales in 2008,[8] uplifted for 2011 using an observed annual rate of increase of 2.6% which the MS claims to be based on Cancer Research UK data. However, the ERG has failed to find evidence within Cancer Research UK data to indicate that the incidence of prostate cancer has been rising at a rate of 2.6% per annum in recent years; rather, those data indicate that, in Great Britain as a whole, the age-standardised prostate cancer incidence rate fell from a peak of 103 per 100,000 males in 2004 to 97.7 in 2008. During the period from 2001-2010, the annual average population increase for England and Wales was only 0.6%.[11] Using this figure, and conservatively assuming the incidence rate of prostate cancer to be stable, the ERG suggests that the absolute incidence of prostate cancer in England and Wales in 2011 would be more appropriately estimated at 33,977 than at 36,105.
- Data from the British Association of Urological Surgeons (BAUS) indicating that, in 2009, 9.3% of patients with prostate cancer had metastatic disease at diagnosis
- Data from studies by Cooperberg *et al.*,[12] and Stephenson and Eastham[13] relating to the number of patients who progress to metastatic disease from earlier stages.
- An assumption that patients with metastatic disease would become hormone-refractory within 3 years, whatever primary therapy was used. Progression rates were assumed to be 80% at year 1 and 20% in following years, adjusted for patients dying before developing hormone-refractory disease according to US National Cancer Data Base (NCDB) survival reports.[1]

The MS notes that its estimate of 7,047 patients with mHRPC is supported by Cancer Research UK data that, in 2008, 9,150 men in England and Wales died from prostate cancer,[9] since most but not all deaths from prostate cancer will occur in patients with mHRPC.[1] However, the ERG suggests that, for the reasons indicated above, the number of patients in England and Wales with mHRPC might more appropriately be estimated at 6,632 than 7,047.

The MS then calculated that 1,938 patients with mHRPC would be eligible for cabazitaxel per annum on the basis that their disease had progressed following or during docetaxel therapy, and that they were fit to receive further chemotherapy.[1] This figure is calculated by applying to the estimate of 7,047 the following factors based on market research commissioned by sanofi-aventis:

- 50% of patients referred to an oncologist with mHRPC are eligible to receive first-line therapy with docetaxel
- 55% of these patients are fit to receive further chemotherapy following docetaxel.[1]

Application of these factors to the ERG's estimate of 6,632 patients with mHRPC results in a lower figure of 1,823 patients per annum who might be eligible for cabazitaxel (for details, see Table 1).

**Table 1: Manufacturer's and ERG's estimates of the number of patients with mHRPC who might be eligible for second-line therapy with cabazitaxel**

| Step | | Estimate contained in MS | ERG estimate |
|---|---|---|---|
| 1 | Incidence of prostate cancer in England and Wales, 2008 | 33,373 | 33,373 |
| 2 | Estimated 2011 incidence calculated by application of annual rate of increase by manufacturer of 2.6% and by ERG of 0.6% | 36,105 | 33,977 |
| 3 | BAUS figure of 9.3% for metastatic disease at diagnosis, plus data indicating numbers who progress from earlier stages | Not stated* | * |
| 4 | Assumption that metastatic disease will become hormone-refractory within 3 years, with progression rates of 80% at year 1 and 20% in years 2 and 3 | 7047 | 6632** |
| 5 | 50% eligible to receive first-line docetaxel | 3524 | 3316 |
| 6 | 55% fit to receive second-line chemotherapy | 1938 | 1823 |

* In the absence of the manufacturer's epidemiological model, these figures could not be calculated.

** Because it was not possible to calculate the figure for the preceding step in the calculation, this figure was derived by applying the same percentage change to the figure of 33,977 as is seen between steps 2 and 4 in the manufacturer's estimate.

### 2.2 Critique of manufacturer's overview of current service provision

The MS states that the initial approach to metastatic prostate cancer is generally medical castration using hormonal therapy to reduce levels of circulating testosterone and thus inhibit cancer growth; infrequently, surgical castration is used. In time, all patients become refractory to first-line hormonal

agents (LHRH agonists or antagonists). Second- and third-line hormonal approaches using anti-androgens followed by anti-androgen withdrawal are effective for only a minority of patients in the short-term only, estimated to be around four months.[1] This description of treatment options in metastatic prostate cancer is congruent with that presented by Khan and Partin.[14]

The MS correctly states that docetaxel in combination with prednisolone is the only chemotherapy regimen licensed in the UK for the first-line treatment of mHRPC. NICE recommends a maximum of ten cycles of docetaxel in patients with a Karnofsky performance-status score of 60% or more.[4] The aim of this chemotherapy is to slow disease progression and prolong survival.

There is currently no NICE-approved second-line chemotherapy for use in patients whose mHRPC has progressed on or after docetaxel. The MS states that such patients are frequently offered palliative therapy with mitoxantrone plus prednisolone,[1] although mitoxantrone is not licensed in the UK for use in this application; alternatively, they may receive best supportive care (BSC) which may involve corticosteroids, palliative radiotherapy, analgesics, and bisphosphonates.[4] However, section 5.10.4 of the MS states that, in an audit of five UK centres, [redacted] of patients with mHRPC which had progressed on or after docetaxel therapy received second-line treatment with cytotoxic chemotherapy; the manufacturer therefore anticipates that clinicians would consider these patients to be potentially eligible for second-line therapy with cabazitaxel.[1]

The MS notes that BSC is costly in patients with mHRPC, not least because of the need for surgery to treat medullar compression or fractures resulting from bone metastases.[1] However, as noted in section 2.1, the pathological fracture rate is relatively low in metastatic prostate cancer, healing is relatively good, and surgical stabilisation is required in only about a quarter of cases.[7]

# 3. CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem as issued by NICE and addressed by the MS is shown in Table 2.

**Table 2: Decision problem as issued by NICE and addressed by the MS**

| | **Final scope issued by NICE[15]** | **Decision problem addressed in the MS[1]** | **Rationale if different from the scope** |
|---|---|---|---|
| Population | Men who have hormone refractory metastatic prostate cancer which has progressed following or during docetaxel-based treatment | As in final scope | Not applicable |
| Intervention | Cabazitaxel in combination with prednisolone | As in final scope | Not applicable |
| Comparator(s) | • Mitoxantrone in combination with prednisolone<br>• Chemotherapy without cabazitaxel (e.g. 5-fluorouracil, cyclophosphamide and carboplatin/etoposide) | Mitoxantrone in combination with prednisone or prednisolone | • Prednisone is used in many countries in preference to prednisolone, which is used in the UK; the two may be regarded as equivalent<br>• The MS excluded the second comparator, citing as reasons the lack of clinical consensus on the choice of second-line cytotoxic agent; the absence of RCT evidence for any individual agent other than mitoxantrone; and the low frequency of use of such agents. |
| Outcomes | • Overall survival (OS)<br>• Progression-free survival (PFS)<br>• Response rate<br>• PSA level<br>• Adverse effects of treatment<br>• Health-related quality of life (HRQoL) | • Overall survival<br>• Progression-free survival<br>• Time to progression<br>• Response rate PSA response or progression<br>• Pain response or progression<br>• Grade 3/4 adverse events<br>• Cost-effectiveness<br>• HRQoL | The MS included pain outcomes on the basis that pain is an important outcome in mHRPC. |

| | | | |
|---|---|---|---|
| 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 (QALY).<br><br>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.<br><br>Costs will be considered from an NHS and Personal Social Services perspective. | The cost-effectiveness of cabazitaxel is expressed as a cost per QALY.<br><br>The base case time horizon is 747 weeks, which was assumed to be equivalent to the patient's lifetime.<br><br>Costs are considered from an NHS and Personal Social Services perspective. | Not applicable |
| Other considerations | If evidence allows, consideration will be given to subgroups defined by:<br>• baseline performance status<br>• duration of prior docetaxel exposure<br>• time since docetaxel treatment.<br><br>Guidance will only be issued in accordance with the marketing authorisation. | The TROPIC trial included pre-planned analyses of the primary outcome (OS) for subgroups defined by:<br>• baseline performance status<br>• total docetaxel dose<br>• time since docetaxel treatment | The MS includes subgroup analyses of OS by baseline performance status, by total docetaxel dose (which broadly equates to, and is proxy for, the duration of prior docetaxel exposure), and by time from last docetaxel treatment to randomisation. Further sub-grouping by geographical region has also been conducted. |

### 3.1 Population

The relevant patient population is patients with mHRPC which has progressed following or during docetaxel therapy. This population is appropriately defined in the MS.

### 3.2 Intervention

Cabazitaxel is a semi-synthetic taxane created by modifying 10-deacetylbaccatin III, a substance extracted from the European yew tree.[16] It binds to tubulin, inhibiting the disassembly of microtubules and thus inhibiting mitotic and interphase cellular functions, leading to tumour cell cytotoxicity.[17]

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.[17] It

received this marketing authorisation on 17th March 2011.[18] It is marketed in the UK by Aventis Pharma under the trade name Jevtana and supplied as a pack containing one 1.5 ml vial of liquid cabazitaxel concentrate (60 mg of cabazitaxel diluted in polysorbate 80 and citric acid), and one vial containing 4.5 ml of solvent (15% v/v ethanol 96% in water). Dosing is by body surface area (BSA) calculated in square metres; the recommended dose is 25 mg/m$^2$. The concentrate should first be mixed with the supplied solvent; the appropriate volume of concentrate-solvent mixture to produce the required dose for the patient should then be diluted to a concentration between 0.10 and 0.26 mg/ml in either 0.9% sodium chloride solution or 5% glucose solution. The dilution process must take place in controlled and aseptic conditions.[17] The list price of cabazitaxel is £3,696 per pack.[1] Because dosing is by BSA, some patients will require more than one pack per cycle. Unopened vials of cabazitaxel have a shelf-life of two years but, after opening, the concentrate and solvent should be used immediately.[17]

Cabazitaxel is administered as a 60-minute intravenous infusion every three weeks for a maximum of 10 cycles. Only one course of 10 cycles should be given. 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$^2$ [17] (for details, see Table 3).

**Table 3: Recommended dose modifications for adverse reactions in patients treated with cabazitaxel[17]**

| **Adverse reaction** | **Dose modification** |
|---|---|
| Prolonged (longer than 1 week) grade ≥3 neutropenia despite appropriate treatment including Granulocyte-Colony Stimulating Factors (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$^2$ |
| 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).[17]

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.[17]

Anti-emetic prophylaxis is recommended and can be given orally or intravenously as needed. Primary prophylaxis with G-CSF should be considered in patients with clinical features which put them at high risk of increased complications from prolonged neutropenia (i.e. age >65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities).[17] The MS suggests that G-CSF may also be used as secondary prophylaxis to prevent recurrent neutropenic complications.[1]

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.[17]

Oral prednisone or prednisolone, at a dose of 10 mg/day, should be taken throughout the course of treatment with cabazitaxel.[17] 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.[19] The MS notes that, in the UK, the majority of patients are medically rather than surgically castrated; when receiving cabazitaxel, medically castrated patients would also require ongoing therapy with luteinising hormone-releasing hormone (LHRH) agonists.[1]

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 such as hypotension and bronchospasm.[17]

### 3.3 Comparators

The NICE final scope stated that cabazitaxel in combination with prednisolone should be compared with:

- Mitoxantrone in combination with prednisolone
- Chemotherapy without cabazitaxel (e.g. 5-fluorouracil, cyclophosphamide and carboplatin/ etoposide).[15]

The MS is limited to one comparator: mitoxantrone in combination with prednisone or prednisolone. Mitoxantrone is an anthracycline derivative licensed for the treatment of metastatic breast cancer and other cancers.[19] Although it is not licensed in the EU for use in patients with mHRPC, the MS states that mitoxantrone plus prednisolone is the active treatment most commonly used in the UK in patients with mHRPC which has progressed after docetaxel. It states that it is used mainly for its palliative benefits on pain, and has not been shown to improve survival compared with corticosteroids alone in any indication.[1] This is consistent with its selection for use as the comparator in the TROPIC study because it "improves response but not OS and because of its beneficial effects on quality of life, including pain palliation".[16]

In section 2.5, the MS justifies its failure to include the second comparator specified in the NICE scope, chemotherapy without cabazitaxel, claiming its lack of relevance to the decision problem on the basis that chemotherapy agents other than mitoxantrone plus prednisolone are seldom used in the UK as second-line treatment for patients with docetaxel-resistant mHRPC, and therefore cannot be considered part of standard UK clinical practice.[1] The ERG's clinical advisors concurred with this view.

The MS further states that the manufacturer found no RCT evidence relating to the use of chemotherapy agents other than mitoxantrone plus prednisolone in second-line mHRPC, and that therefore the validity of comparisons against these agents would be limited.[1] The ERG agrees that there are no RCTs which compare cabazitaxel with chemotherapy agents other than mitoxantrone plus prednisolone although, as noted in section 5.10.3 of the MS, there are RCTs of other agents in the relevant population. In particular, there is a large RCT showing that abiraterone acetate, an androgen biosynthesis inhibitor not currently licensed for use in the UK, is effective in this group of patients.[20] The manufacturer claimed that, owing to the limited availability of abiraterone data at this time, further discussion was beyond the scope of the MS;[1] the ERG accepts that full publication of the abiraterone study postdated the manufacturer's searches, whilst considering it to be a relevant intervention in this population, however the ERG notes that abiraterone would not be considered a

comparator within this single technology appraisal as it is neither licensed nor in routine use within the UK.

### 3.4 Outcomes

As noted in Table 1, the outcomes reported in the MS are largely the same as those listed in the final scope.[15] They are discussed in more detail below.

*Overall survival (OS)*

The primary outcome measure, overall survival, is the gold standard efficacy outcome measure in this patient population.[21] The TROPIC study defined OS as the time from the date of randomisation to death. OS data were censored at the last date the patient was known to be alive, or at the data cut-off date, whichever was earlier.[22]

*Progression-free survival (PFS)*

PFS is a composite endpoint which has no standard definition. The TROPIC study defined it as the time from randomisation to tumour progression, PSA progression, pain progression, or death due to any cause, whichever occurred first.[22] The MS states that this is a conservative definition of PFS because it includes biochemical (PSA) progression, which frequently precedes symptomatic or radiological progression.[1] Consequently, it is likely to underestimate the clinical PFS experienced by patients with mHRPC who receive cabazitaxel therapy in clinical practice. The ERG notes that the TROPIC study's definition of PFS includes a subjective outcome, pain progression, which is susceptible to bias given the unblinded nature of the study. Treatment was discontinued following the identification of disease progression.[23]

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

In patients with measurable disease at baseline, tumour response rate was assessed according to RECIST (Response Evaluation Criteria in Solid Tumours) criteria.[22,24] 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. Smaller lesions are considered to be nonmeasurable, and a range of lesions including bone lesions are considered to be truly nonmeasurable. The RECIST criteria stipulate that all measurable lesions up to a maximum of 5 per organ and 10 in total, representative of all involved organs, should be regarded as target lesions and measured at baseline; if a patient has only one measurable lesion, it should be confirmed as neoplastic by cytology or histology.[24] The RECIST criteria define tumour responses as follows:

- Complete response (CR): disappearance of all target lesions
- Partial response (PR): decrease of at least 30% in the sum of the longest diameter of target lesions

- Progressive disease (PD): increase of at least 20% in the sum of the longest diameter of target lesions
- Stable disease (SD): neither sufficient decrease to qualify as partial response nor sufficient increase to qualify as progressive disease.[24]

In the TROPIC study, objective responses (CR and PR) had to be confirmed by repeat tumour imaging.[1] Although only 405 out of 755 patients (54%) in the TROPIC study had measurable disease,[22] this seems to be inconsequential in terms of the interpretation of the outcomes.

*Time to tumour progression*

Time to tumour progression was defined as the number of months from the date of randomisation to evidence of PD using the RECIST criteria.[22] Patients without PD were censored at their last tumour assessment.[1]

*PSA response (assessed only in patients with baseline PSA ≥ 20 ng/ml)*

PSA response was defined as a reduction in serum PSA concentration of ≥ 50% in patients with a baseline value of ≥20 ng/ml 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.[1,22]

*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.[22]
- 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 5 ng/ml).[1,22]

*Pain*

Pain is an important outcome in mHRPC because of the prevalence of considerable pain, mainly from bone metastases. In the TROPIC study, it was assessed using the present pain intensity (PPI) scale on the McGill-Melzack pain questionnaire.[25] Patients were asked to complete the PPI every day for the week prior to evaluation.[21] The use of the PPI aspect of the Short-Form McGill-Melzack pain questionnaire as a stand-alone tool has precedent in previous prostate cancer trials.

Pain was also assessed using an analgesic score (AS) defined as the mean daily patient-recorded analgesic use for the one-week period prior to each evaluation, expressed in morphine equivalents.[23]

As a subjective outcome measure, pain is susceptible to assessment bias in unblinded studies.

*Pain response (assessed only in patients with a median baseline PPI score of ≥ 2 and/or a mean baseline AS of ≥ 10 points)*

Pain response was defined as a two-point or greater reduction from baseline in median PPI with no concomitant increase in AS, or a reduction of more than 50% in analgesic use with no concomitant increase in PPI score. Either criterion had to be maintained for three or more weeks.[22]

*Pain progression (assessed in all patients)*

Pain progression was defined as any of the following:

- an increase of ≥ 1 point in the median PPI from its nadir noted on two consecutive three-week-apart visits
- an increase of ≥ 25% in the mean AS compared with the baseline score and noted on two consecutive three-week-apart visits
- a requirement for local palliative radiotherapy.[1,22]

In addition to the risk of assessment bias noted above, the Food and Drug Administration (FDA) reviewers observed that, in the TROPIC study, outcomes relating to pain were also susceptible to bias resulting from missing data: pain response was not evaluable if more than two PPI and/or AS values were missing for the week in question, while pain progression was not evaluable if more than two PPI and/or AS values were missing for that week unless a complete evaluation (i.e. at least five values) of PPI or AS showed a pain progression.[21] The TROPIC investigators stated that pain response was evaluable only in 174/378 patients randomised to cabazitaxel (46%) and 168/377 randomised to mitoxantrone (45%) who had pain at baseline;[22] there is no indication that any of these 342 patients were not evaluable because of missing data.

*Health-related quality of life (HRQoL)*

The TROPIC study did not collect data relating to HRQoL. For this outcome, the MS therefore utilised interim UK results from the early access programme (EAP) for cabazitaxel, a global study which includes nine active sites in the UK. In the UK sites only, EuroQol 5-Dimension (EQ-5D) questionnaires are 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 is also assessed using a visual analogue scale (VAS).[1] The use of data from the EAP is clearly potentially problematic as, while it

allows comparison with baseline, it does not allow for comparison with patients receiving mitoxantrone or any other comparator therapy.

*Adverse events (AEs)*

Adverse events were recorded in patients who had received at least one dose of study drug (the safety population).[22] AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 which classifies severe AEs as grade 3, and life-threatening or disabling AEs as grade 4, while grade 5 is used for deaths related to AEs.[26] The worst NCI grade was used for each AE per patient and per cycle.[1]

### 3.5 Other relevant factors

The MS claims that end-of-life considerations are relevant to cabazitaxel on the basis that it is indicated for patients with a life expectancy of ~12 months, and that, by their calculation, the population in England and Wales for which it is indicated would be fewer than 2000 patients.

In the UK, the risk of prostate cancer is approximately two to three times higher in black Caribbean and black African men than in white men, while the risk in Asian men is lower than the national average.[27]

Because the cabazitaxel infusion contains 15% v/v ethanol, equivalent to 14 ml of beer or 6 ml of wine, it may be harmful to patients suffering from alcoholism.[17]

# 4. CLINICAL EFFECTIVENESS

## 4.1 Critique of the methods used by the manufacturer to systematically review clinical effectiveness evidence

### *4.1.1 Objective of the systematic review, and description and critique of the manufacturer's search strategy*

The manufacturer performed three systematic searches, with the following aims and objectives:

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 of second-line therapy in patients with mHRPC which had progressed after first-line docetaxel, in order to identify any RCT evidence for comparators specified in the NICE scope which had not been directly compared with cabazitaxel
3. To identify all non-randomised studies of second-line therapy in patients with mHRPC 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.

The MS reports that a wide range of sources was searched. In addition to the core databases recommended by the NICE guidelines manual, there is evidence of searching for grey literature in governmental and HTA websites, gateways, conference proceedings sites, and research registers. Bibliographic reference tracking of included trials was also reported.

In relation to the manufacturer's first systematic review, of studies of cabazitaxel versus any comparator, the manufacturer's searches were comprehensive, and the ERG believes that no relevant studies which were available at the time of the manufacturer's review were missed. The ERG reproduced all of the manufacturer's database searches on 23rd June 2011. As expected, because these searches were undertaken at a later date, a higher number of unique records was retrieved (148, compared with the 52 identified by the manufacturer's searches, of which 68 were published in 2011). The ERG also ran slightly modified versions of the manufacturer's Medline and Embase searches; these retrieved 20 additional records in Embase (for details, see Table 4). One minor comment regarding the manufacturer's Embase search strategy is that the field limits applied could be broadened to "af" rather than "ti,ab,rn". When this was done by the ERG, it increased the sensitivity of the search, resulting in the retrieval of 18 (out of 20) more unique records. The ERG also conducted searches in the Web of Science, BIOSIS Preview, and TOXNET (a specialist adverse events database), none of which were included in the manufacturer's searches; an additional 8 unique records were identified. The ERG agrees with the manufacturer that the cabazitaxel searches are sufficiently comprehensive to retrieve all relevant studies pertaining to the intervention's adverse

events. The ERG also performed a citation search relating to the TROPIC study in Google Scholar; this identified 29 unique records.

**Table 4: Repeat database searches for the manufacturer's first systematic search, relating to cabazitaxel**

| Database | Search strategy | MS/ERG strategy | Comments |
|---|---|---|---|
| Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to Present> | 1 cabazitaxel.ti,ab,rn. (42)<br>2 (XRP 6258 or XRP6258 or RPR 116258A or rpr116258A).ti,ab,rn. (6)<br>3 jevtana.ti,ab,rn. (1)<br>4 1 or 2 or 3 (47) | MS strategy | 47 records in June 2011 compared to 14 in Sept 2010 |
| | 1 cabazitaxel.af. (42)<br>2 (XRP 6258 or XRP6258 or RPR 116258A or rpr116258A).af. (6)<br>3 jevtana.af. (1)<br>4 5 or 6 or 7 (47) | ERG strategy (all field search) | No difference in no of records retrieved |
| Embase <1980 to 2011 Week 24> | 1 cabazitaxel/ (94)<br>2 cabazitaxel.ti,ab,rn. (88)<br>3 (XRP 6258 or XRP6258 or RPR 116258A or rpr116258A).ti,ab,rn. (8)<br>4 jevtana.ti,ab,rn. (1)<br>5 1 or 2 or 3 or 4 (110) | MS strategy | 110 records in June 2011 compared to 15 in Sept 2010 |
| | 1 cabazitaxel.af. (106)<br>2 (XRP 6258 or XRP6258 or RPR 116258A or rpr116258A).af. (39)<br>3 jevtana.af. (25)<br>4 1 or 6 or 7 or 8 (130) | ERG strategy (all field search) | An extra 20 records retrieved |
| Cochrane Library | #1 (cabazitaxel)<br>#2 "XRP 6258" or XRP6258 or "RPR 116258A" or rpr116258A<br>#3 (jevtana)<br>#4 (#1 OR #2 OR #3) | MS strategy | CDSR = 0<br>CENTRAL = 1<br>DARE = 0<br>HTA = 2 records |
| Conference Proceedings Index (CPCI-S) <1990 to present> | TS=cabazitaxel<br>TS= ("XRP 6258" or XRP6258 or "RPR 116258A" or rpr116258A)<br>TS= jevtana<br>#1 or #2 or #3 | MS strategy | Statement 2 is not valid.<br>2 records |

| | | | |
|---|---|---|---|
| Science Citation Index Expanded (SCI-EXPANDED) <1899-present> | #1 Topic=(cabazitaxel)<br>#2 Topic=(jevtana)<br>#3 #2 OR #1 | ERG strategy | 42 records retrieved (only 5 unique) |
| BIOSIS Previews <1969 to present> | Topic=(cabazitaxel) | ERG strategy | 23 records retrieved (only 3 unique) |
| TOXNET (National Library of Medicine) | Cabazitaxel | ERG strategy | 13 results (already retrieved in previous searches) |
| HEED | AX=cabazitaxel<br>AX=("XRP 6258) or XRP6258 or (RPR 116258A) or rpr116258A<br>AX=jevtana<br>CS=1 OR 2 OR 3 | MS strategy | No records retrieved |
| EconLit | cabazitaxel.mp.<br>(XRP 6258 or XRP6258 or RPR 116258A or rpr116258A).mp.<br>jevtana.mp.<br>or/1-3 | MS strategy | No records retrieved |
| Citation search in Google Scholar | de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I *et al*. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010; **376:** 1147–1154 | ERG approach | 48 records (only 29 unique) |
| ClinicalTrials.gov | Cabazitaxel OR "XRP 6258" OR XRP6258 OR "RPR 116258A" OR rpr116258A OR jevtana | MS strategy | 11 records retrieved (for details, see Appendix 1) |

With respect to the manufacturer's second set of searches, for RCTs of second-line therapy in mHRPC, the manufacturer applied a sensitive RCT filter to the four core databases searched. The ERG could only use the Ovid platform instead of Embase.com for Medline and Embase. The ERG considers that it was unnecessary to apply an RCT filter to searches in Cochrane since the CENTRAL database consists entirely of clinical trial records. A number of criticisms could be made of the manufacturer's search strategies. It is not clear why duplicate EMTREE terms such as 'clinical trial'/exp or 'randomized controlled trials'/exp (statements 3, 6 & 7) appeared in several statements in the Embase and Medline strategy. Given the small number of records retrieved in statements 37-44, the proximity terms (NEAR/3 or NEAR/4) could be broadened by using 'NEAR/10' or even 'NEAR/20'. There was evidence of incorrect nesting of search terms within statement 22 in the CENTRAL searches (perhaps the Boolean operator 'AND' should read 'OR'). Translation of the strategy across databases from Medline was inconsistent: the first-line treatment term ('Taxotere') which was present in Medline was absent in Medline in Process and CENTRAL (if this term had been included, the searches would have retrieved 140 rather than 8 records); 'OR' was used to combine 'second line' with 'docetaxel' in Medline and Embase strategies, whereas 'AND' was used in Medline in Process and CENTRAL; and some word variants for disease terms (i.e. 'tumour' and 'oncolog*') were missing from the Medline in Process searches. However, the database searches were reproducible, and the ERG obtained a similar number of records.

The manufacturer's third set of systematic searches, intended to identify all non-randomised studies of second-line therapy in mHRPC, included duplication of search terms present in the non-RCT studies filter and the mHRPC RCT strategies. However, additional population terms were introduced which were not present in the RCT searches: these included 'hrpc', 'crpc', 'docetaxel-refractory' and 'taxane refractory'. The database searches in Medline and Embase were reproducible, but the ERG recommends that the manufacturer use a published observational studies filter for retrieval of non-RCT evidence.

For a quality assessment of the manufacturer's search strategies, see Appendix 2.

The MS states that study selection was performed independently by two reviewers as a two-step process, in accordance with the PRISMA guidelines. It presents, for each of the three reviews, a PRISMA flow diagram (http://www.prisma-statement.org/statement.htm) showing the number of studies included and excluded at each stage.

#### *4.1.2 Statement of the inclusion/exclusion criteria used in the study selection, and whether they were appropriate*

Details of the inclusion criteria used for study selection were presented in Table 5-1 of the MS; for convenience, this is reproduced here as Table 5. It was not clear why the inclusion criteria for the

second and third systematic reviews were limited to studies published in the English language, while no language restrictions were applied to the first systematic review: logically, the approach taken should have been consistent throughout and, if non-English language studies were to be excluded, this decision should have been justified. The manufacturer subsequently provided clarification indicating that the inclusion criteria differed in this respect because the three systematic reviews were conducted at different times with slightly different objectives, and also supplied details of all records excluded from the systematic review of RCTs in second-line chemotherapy as a result of the limitation of the search to studies published in the English language.[2] With the possible exception of two short papers for which abstracts were not available,[28,29] none of these studies would have met the inclusion criteria for that review.

The second and third systematic reviews were restricted to literature published in and after 2000, in order to focus on the most relevant, up-to-date, literature. This restriction seems appropriate in the relatively fast-moving field of cancer research.

Thus, with the exception of the inconsistent application of language restrictions, for which the manufacturer's clarification provided an explanation rather than a theoretical justification, the specified inclusion criteria appear to be appropriate.

**Table 5: Inclusion criteria used in study selection, as presented in the MS[1]**

| Review | 1. Systematic review of RCTs of cabazitaxel | 2. Systematic review of all RCTs in second-line mHRPC | 3. Systematic review of non-randomised studies in second-line mHRPC |
|---|---|---|---|
| Population | Men with mHRPC or mCRPC who had progressed following or during docetaxel-based treatment | | |
| Intervention(s) | Cabazitaxel with prednisone or prednisolone | Any active intervention (not best supportive care) | Any active intervention (not best supportive care) |
| Comparator(s): | Any | Any | Any or none |
| Outcome(s) of interest: | OS, PFS, time to progression, overall response rate, PSA response or progression, pain response or progression, Grade 3 or 4 AEs | | |
| Study design: | Phase II or III RCT or systematic review of Phase II or III RCTs; extension studies and cohort studies reporting AEs were also eligible for inclusion | | Non-randomised controlled studies, single-arm studies, case-control, cohort, cross-sectional studies |
| Language restrictions | There was no language restriction | English language only | |
| Publication timeframe: | Any date | 2000 – present (as the aim of these reviews was to provide a context for the cabazitaxel studies identified by the targeted systematic review, the date restriction was imposed for reasons of pragmatism, to focus on the most relevant, up-to-date literature) | |
| Publication status | Published, unpublished and grey literature (for example, conference abstracts) were eligible for inclusion | | |
| Exclusion criteria | Dosing studies were excluded, on the basis that they do not provide evidence of the effectiveness of cabazitaxel relative to relevant comparators | N/A | N/A |

Key: AE = adverse event; mCRPC = metastatic castration-resistant prostate cancer; mHRPC = metastatic hormone-resistant prostate cancer; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; RCT = randomised controlled trial

### *4.1.3 Studies included in the clinical effectiveness review, with a table of identified studies*

The manufacturer's systematic review of RCTs of cabazitaxel identified and included only one relevant study. This was the TROPIC study, 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 (for details, see Table 6).

**Table 6: Characteristics of the TROPIC study[1,22]**

| | |
|---|---|
| Design and clinical trial identification codes | Randomised, open-label, active-controlled, multicentre study<br>Protocol number: EFC6193<br>Clinicaltrials.gov identifier: NCT00417079 |
| Participants | *Inclusion criteria:*<br>• Pathologically proven prostate cancer<br>• Documented disease progression during or after completion of docetaxel treatment (for patients with measurable disease, documented disease progression by RECIST with at least one visceral or soft-tissue metastatic lesion; for patients with non-measurable disease, rising serum PSA concentrations (at least 2 consecutive increases relative to a reference value measured at least a week apart) or the appearance of at least 1 new demonstrable radiographic lesion)<br>• Age >18 years<br>• ECOG performance status 0-2<br>• Previous and ongoing castration by orchiectomy or LHRH agonists, or both<br>• Antiandrogen withdrawal followed by progression taken place at least 4 weeks (6 weeks for bicalutamide) before enrolment<br>• Adequate haematological, hepatic, renal, and cardiac function<br>• Left-ventricular ejection fraction of more than 50% assessed by multigated radionuclide angiography or echocardiogram<br>• Life expectancy >2 months<br>*Exclusion criteria*:<br>• Previous mitoxantrone therapy<br>• Radiotherapy to 40% or more of the bone marrow<br>• Cancer therapy (other than LHRH analogues) within 4 weeks before enrolment<br>• Active grade 2 or higher peripheral neuropathy or stomatitis<br>• Other serious illness<br>• History of hypersensitivity to polysorbate 80-containing drugs or prednisone<br>• Participation in another clinical trial with any investigational drug within 30 days prior to study enrolment<br>• For patients enrolled in the UK: patient with reproductive potential not implementing accepted and effective method of contraception |
| Intervention | Cabazitaxel 25 mg/m$^2$ intravenously over 1 hour on day 1 of each 21-day cycle plus oral prednisone 10 mg/d (or similar doses of prednisolone in countries in which prednisone was unavailable)<br>Premedication (single intravenous doses of an antihistamine, corticosteroid (dexamethasone 8 mg or equivalent), and histamine $H_2$-antagonist (except cimetidine)) administered 30 min or more before cabazitaxel. |
| Comparator | Mitoxantrone 12 mg/m$^2$ intravenously over 15-30 minutes on day 1 of each 21-day cycle plus oral prednisone 10 mg/d (or similar doses of prednisolone where prednisone was unavailable). |
| Concomitant therapy | Antiemetic prophylaxis given at the physician's discretion |
| Outcomes | *Primary outcome measure:*<br>Overall survival<br>*Secondary outcome measures:*<br>• Progression-free survival<br>• PSA response |

| | |
|---|---|
| | • PSA progression<br>• Objective tumour response (in patients with measurable disease)<br>• Time to tumour progression<br>• Pain response (in patients with a median PPI score of >2 or a mean AS of >10 points at baseline, or both)<br>• Pain progression<br>• Adverse events |
| Follow-up | Until death or the cut-off date for analysis (25.9.2009), whichever happened first. Overall median follow-up was 12.8 months (IQR 7.8-16.9) |

The manufacturer's broader systematic review of RCTs of all second-line agents in mHRPC identified six studies in addition to the TROPIC study which were carried out in the relevant population of men with mHRPC which had progressed after docetaxel therapy (for details, see Table 7). The manufacturer considered that these studies did not provide data relevant to the decision problem for the following reasons:

- Studies which compared mitoxantrone (the first comparator specified in the final scope) with other interventions were felt to be unnecessary given the existence of a head-to-head comparison of mitoxantrone with cabazitaxel (the TROPIC study)
- Studies of other forms of chemotherapy without cabazitaxel (the second comparator specified in the final scope) were not considered relevant on the basis that such agents cannot be considered part of standard UK clinical practice as they are seldom used in the UK as second-line treatment for patients with docetaxel-resistant mHRPC. The MS further claimed, in section 5.10.3, that the limited evidence available for such agents would limit the validity of any comparisons.[1] However, the latter argument is weak since the evidence for cabazitaxel itself rests on only one RCT, while two of the potentially relevant agents (abiraterone and satraplatin) are each supported by an RCT which included more patients than the TROPIC study (see Table 7); however, as noted earlier, the ERG recognises that full publication of the abiraterone study[20] post-dated the manufacturer's searches, which only found a conference abstract.

Reproduction of the searches related to the manufacturer's second systematic review did not yield any relevant studies other than the full publication of the abiraterone study.[20] For clarity, Table 7 has included the full publication rather than the conference abstract.

**Table 7: Intervention identified by the manufacturer's systematic review of all RCTs in second-line mHRPC which had progressed over docetaxel therapy (excluding the TROPIC study)**

| Trial name or identifier | Intervention | Comparator | Study references | Study design and number randomised | Study conclusion |
|---|---|---|---|---|---|
| COU-AA-301 | Abiraterone acetate plus prednisone | Placebo plus prednisone | de Bono 2011[20] | Phase III randomised double-blind placebo-controlled study<br>1195 | Abiraterone was associated with a significant improvement in OS and PFS |
| The SPARC trial | Satraplatin + prednisone | Placebo plus prednisone | Sternberg 2009,[30] Witjes 2009,[31] Sartor 2008,[32] Sartor 2009[33] Petrylak 2009* | Phase III randomised double-blind placebo-controlled study<br>950 | Satraplatin did not improve OS, but did improve PFS |
| Saad 2009 | Docetaxel + prednisone + custirsen | Mitoxantrone + prednisone + custirsen | Saad 2009*, Saad 2008[34] | Phase II randomised study; level of blinding not specified<br>42 | MS states that no statistical comparisons were reported, but that both regimens were well tolerated and associated with better-than-expected survival. Saad 2008[34] indicates that, while OS was the same in both groups, PSA response and pain response were better with docetaxel, which was also better tolerated than mitoxantrone. |
| de Bono 2010 | CNTO 328 + mitoxantrone | Mitoxantrone | de Bono 2010[35] | Phase II randomised open-label study<br>97 in efficacy study | CNTO 328 did not improve OS; PFS was better in the control group, but this may be misleading as enrolment was terminated after an interim analysis showed an imbalance in baseline patient characteristics which favoured the control group. |
| Fleming 2010 | Cetuximab + mitoxantrone | Mitoxantrone + prednisone | Fleming 2010[36] | Phase II randomised | Cetuximab did not improve PFS or OS |

| | | | | | |
|---|---|---|---|---|---|
| | + prednisone | | | study; level of blinding not specified<br>115 | and was not recommended for further study |
| Rosenberg 2007 | Ixabepilone | Mitoxantrone + prednisone | Rosenberg 2007[37] | Phase II randomised open-label study<br>82 | No difference was identified in OS |

* The MS did not include details of these publications, nor were they identified by the ERG's rerun searches

The objective of the manufacturer's third systematic review, of non-RCT studies of second-line therapy in patients with mHRPC which had progressed after first-line docetaxel, was to identify any non-randomised evidence for cabazitaxel or its comparators which might potentially be relevant to the decision problem. The searches identified 40 potentially relevant studies. None investigated cabazitaxel. Nine studies investigated mitoxantrone alone,[38,39] with prednisone,[40-43] or in combination with ixabepilone and prednisone[44,45] or GM-CSF and ketoconazole.[46] The manufacturer considered that, given the existence of a head-to-head comparison of mitoxantrone with cabazitaxel, these uncontrolled studies did not provide useful information. Thirteen studies investigated rechallenge with docetaxel, either alone[47-51] or in combination with other agents.[52-59] Finally, 19 studies investigated other drugs (pemetrexed,[60,61] vorinostat,[62] sunitinib,[63,64] sorafenib,[65,66] carboplatin plus etoposide,[67] carboplatin plus 5-fluorouracil plus epirubicin,[68] paclitaxel plus carboplatin plus estramustine,[69] ketoconazole plus doxorubicin,[70] cyclophosphamide plus dexamethasone,[71] bevacizumab plus satraplatin plus prednisone,[72] oxaliplatin plus capecitabine,[73,74] cisplatin plus prednisone,[75] paclitaxel poliglumex plus estradiol,[76] and TPI 287[77]). The MS considered these studies to be the only published evidence which could be used to address the second comparator specified in the final scope, namely 'chemotherapy without cabazitaxel'. However, it did not undertake any such comparisons because all the studies were small (<50 patients) and uncontrolled, and it was therefore felt that any comparisons would be associated with a high degree of uncertainty. The ERG agrees that, given their size and nature, these studies are unlikely to provide any useful data relating to either efficacy or safety. However, reproduction of the searches related to the manufacturer's third systematic review identified a conference abstract which provided some additional data relating to the TROPIC study.[78]

The MS did not identify any observational studies or publications of post-marketing surveillance data relating to the use of cabazitaxel in mHRPC. Given this paucity of safety data, the ERG felt that it would arguably have been appropriate to include safety data relating to the use of cabazitaxel in women with breast cancer - for example, the unreferenced phase II trial which the MS stated was not relevant to the systematic review or the decision problem because of the nature of its population. In

clarification, the manufacturer claimed that differences would be expected between the safety profile of cabazitaxel in the TROPIC study and in the breast cancer study because the populations differed not only in gender but also in age (the median age in the breast cancer study being 53, compared with 67-68 in TROPIC), prior therapy, and intended cabazitaxel dose.[2] The ERG comment that two deaths in the breast cancer study (one from cyanosis and one from dyspnoea) were deemed probably or possibly related to cabazitaxel; these represent 3% of the study population.[2] It is unclear whether this information can inform the evidence regarding use of cabazitaxel in mHRPC.

#### *4.1.4 Details of relevant studies not discussed in the MS*

The ERG is not aware of any relevant studies of cabazitaxel in mHRPC which were not discussed in the MS.

### 4.2 Summary and critique of submitted clinical effectiveness evidence

#### *4.2.1 Summary of submitted clinical evidence for each relevant trial*

The MS stated that the TROPIC study of cabazitaxel vs. mitoxantrone had been reported in the following journal article and conference abstracts or posters:

- de Bono JS *et al*. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010; 376: 1147–1154[22]
- Sartor AO *et al*. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: final results of a multinational Phase III trial (TROPIC). Conference abstract, American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium 2010 (San Francisco, CA)[79]
- de Bono JS *et al*. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: final results of a multinational Phase III trial (TROPIC). Conference abstract, American Society of Clinical Oncology (ASCO) 2010 (Chicago, IL)[80]
- Oudard S *et al*. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: estimating mean overall survival (OS) for health economics analyses from a phase III trial (TROPIC). Poster presentation at ASCO-GU 2011 (Orlando, FL).[81]

The MS also drew on an unpublished clinical study report which was made available to the ERG.[23]

The ERG identified the following publications in the public domain which contain additional data from the TROPIC study:

- the web appendix (http://www.sciencedirect.com/science/article/pii/S014067361061389X) to the article by de Bono *et al*;[22] this was not mentioned in the MS

- the FDA medical review[21]
- an article by Oudard[16] which included an updated efficacy analysis whose full results were not included in the MS
- a conference abstract presenting data relating to clinical benefit and symptom control[78]
- a conference abstract presenting a subgroup analysis of survival by time from first docetaxel treatment in both arms of the study[82]
- a conference abstract presenting a subgroup analysis of survival by reason for discontinuation of docetaxel therapy[83]
- an analysis of the impact of G-CSF prophylaxis on the occurrence of neutropenia.[84]

### *4.2.2 Description and critique of the manufacturer's approach to validity assessment for each relevant trial*

The manufacturer's quality assessment of the TROPIC study (presented in Appendix 3 section 9.3.1 of the MS included criteria relating to both internal and external validity. The following internal validity criteria were used:

- Appropriateness of method of randomisation
- Adequate concealment of treatment allocation
- Baseline similarity of treatment groups in terms of prognostic factors
- Blinding of patients, care providers, and outcome assessors to treatment allocation
- Unexpected imbalances in dropouts between treatment groups
- Whether the authors appeared to have measured more outcomes than they reported
- Adequateness of follow-up
- Use of ITT analysis, and appropriate methods to account for missing data.

The manufacturer 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 manufacturer considered that the fact that the trial was unblinded was unlikely to have introduced bias into the assessment of the primary outcome (OS), 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 AEs.[1] The MS did not provide adequate justification for the study being open label rather than blinding participants and care providers using double dummy procedures. The ERG's clinical advisors indicated that the use of such double dummy procedures would have been complicated by differences in the nature of the treatments, and by the requirement for premedication of patients receiving cabazitaxel; moreover, the use of such procedures might have been considered to cause unnecessary discomfort or inconvenience to study participants.

However, the ERG notes that there appears to be no reason why outcome assessors should not have been blinded to treatment allocation.

The MS 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.[1] 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 external validity criteria used by the manufacturer were:

- Whether the RCT was conducted in the UK, or was a multinational RCT with one or more centres in the UK
- How participants included in the RCT compare with patients who are likely to receive the intervention in the UK
- Whether the dosage regimens used in the study were within those detailed in the summary of product characteristics.

The manufacturer considered all the external validity criteria to be adequately met. However, the ERG notes that, whilst the first criterion was met, [redacted] of participants were recruited in the UK. In relation to the second criterion, the NHS Regional Drug and Therapeutics Centre notes that participants in the TROPIC study may have been younger is typical of patients with docetaxel-resistant mHRPC who are generally seen in the UK, and may have fewer co-morbidities than would be expected in clinical practice.[85]

### *4.2.3 Description and critique of the statistical approach used within each relevant trial*

The statistical analyses used in the TROPIC trial are summarised in Table 8. The ERG did not believe that the statistical tests undertaken were inappropriate.

**Table 8: Summary of statistical analyses used in the TROPIC trial[1,22]**

| | |
|---|---|
| Objective | The study objective was to evaluate whether cabazitaxel plus prednisone improved overall survival compared with mitoxantrone plus prednisone in patients with mHRPC which had progressed during or after docetaxel treatment |
| Statistical analysis | • Analysis of OS and PFS was by ITT (i.e. all patients randomly allocated to treatment groups)<br>• The final analysis was planned to take place when 511 deaths had occurred<br>• The safety analyses included all patients who had received at least one dose of study medication<br>• The Kaplan-Meier method was used to analyse OS, with log-rank comparisons stratified according to disease measurability (measurable vs. non-measurable) and ECOG status (0-1 vs. 2).<br>• OS data were censored at the last date the patient was known to be alive or at the analysis cut-off date (25.9.2009), whichever was the earliest.<br>• PFS, tumour progression, PSA, and pain were compared between treatments using log-rank comparisons stratified according to disease measurability (measurable vs. non-measurable) and ECOG status (0-1 vs. 2).<br>• Hazard ratios and 95% CIs were calculated using a Cox proportional hazards model<br>• Proportions were compared using the $\chi^2$ test or Fischer's exact test.<br>• SAS version 9.1.3 was used for all analyses. |
| Sample size, power calculation | Assuming a median overall survival in the mitoxantrone group of 8 months, it was calculated that a total of at least 511 deaths in the 2 groups would be needed to detect a 25% reduction in the hazard ratio for death in the cabazitaxel group relative to the mitoxantrone group with 90% power, using a 2-sided log-rank test at a significance level of 0.05. To achieve the target of 511 deaths within 30 months of the first patient enrolment, approximately 720 patients (360 per group) had to be randomised. |
| Data management, patient withdrawals | • For time to event analyses, missing data were handled based on censoring rules.<br>• For categorical data, missing data were reported as missing.<br>• Patients in the mitoxantrone group were not allowed to cross over to cabazitaxel following progression; however, 44 (12%) received treatment with tubulin-binding drugs at progression |

| | |
|---|---|
| | • Patients in the cabazitaxel group were allowed to cross over to mitoxantrone at progression; it was assumed that this would not affect the survival curves as mitoxantrone has not been associated with an effect on survival. |

*Subgroup analyses*

The MS states that pre-specified subgroup analyses of OS were performed in the ITT population. The prognostic factors which were considered were:

- ECOG performance status
- Disease measurability
- Number of prior chemotherapy regimens
- Age
- Geographical region
- Pain at baseline
- PSA status
- Time from last docetaxel to randomisation
- Total docetaxel dose received
- Time of progression from last docetaxel.[1]

The MS also states that post-hoc subgroup analyses were performed using combinations of these factors. The three key subgroups presented in the economic evaluation section included one which was based on a pre-specified factor, namely region (i.e. the subgroup of European patients who formed [redacted] of the study population), and two subgroups which used post-hoc combinations of factors:

- All patients with an ECOG performance status of 0-1 who received ≥ 225 mg/m$^2$ docetaxel
- European patients with an ECOG performance status of 0-1 who received ≥ 225 mg/m$^2$ docetaxel.

The MS states that the last of these three subgroups was presented as the base-case because it was considered the most representative of patients who will receive cabazitaxel in UK practice. This subgroup was justified as follows:

- The restriction to European patients is justified on the basis that the benefits demonstrated in the European region were considered most likely to represent those which might be expected in UK practice. The TROPIC trial recruited from a number of countries where the manufacturer felt that treatment patterns differed from UK clinical practice in ways which might be expected to affect treatment outcomes with cabazitaxel, and differences in the point estimates were identified by geographic region both in the hazard ratio for overall survival and in rates of AEs.

- The restriction to patients with an ECOG performance status of 0-1 reflects clinical opinion that it is extremely unlikely that, in the UK, patients with an ECOG status of 2 would be considered for cabazitaxel treatment
- The restriction to patients who had received ≥ 225 mg/m$^2$ docetaxel is justified on the basis that NICE guidance recommends docetaxel as first-line chemotherapy for mHRPC, and therefore it is unlikely that UK patients would be considered for second-line chemotherapy before receiving sufficient exposure to docetaxel.

The base case subgroup is said to form [redacted] of the total population of the TROPIC study.[1]

The ERG has concerns as to whether the manufacturer's selected base case is the most appropriate population. In order to avoid repetition, this discussion is contained only in section 5.2.12; the text is placed in that section as the choice of base case population impacts on the cost-effectiveness ratios.

### *4.2.4 Description and critique of the manufacturer's approach to outcome selection within each relevant trial*

The MS listed the following clinical outcomes observed within TROPIC which were perceived to be relevant to the decision problem:

- Overall survival
- Progression-free survival
- Tumour response rate
- Time to tumour progression
- PSA response
- PSA progression
- Pain response
- Pain progression
- Adverse events.

These differ from the outcomes listed in the final scope by the inclusion of pain response or progression, and the exclusion of health-related quality of life.

### *4.2.5 Discussion of the extent to which relevant trial includes the patient population(s), intervention(s), comparator(s) and outcomes as defined in the final scope*

The TROPIC study is substantially similar to the final scope in terms of its patient population, intervention, and outcomes (see Table 9).

Although the population of the TROPIC study is defined as men with castration-resistant rather than hormone-refractory prostate cancer, it should be noted that the terms 'castration-resistant' and 'hormone refractory' have been used interchangeably in the literature to describe prostate cancer which no longer responds to androgen withdrawal therapy or combined androgen blockade, whether

caused by medical or surgical castration. However, it has been suggested that the term 'endocrine-resistant' is more accurate than either 'castration-resistant' or 'hormone-refractory'.[86] The MS anticipates that cabazitaxel would not be used in all patients whose cancer had progressed during or following docetaxel therapy, but only in the subset with good performance status that were able and willing to tolerate further chemotherapy. The population of the TROPIC study was considered representative of that subset since over 91% in each arm had an ECOG performance status of 0-1. The MS also anticipates that, in line with NICE guidance, UK patients would receive at least 3 cycles (equating to 225 mg/m$^2$) of docetaxel before being considered for second-line chemotherapy; again, the TROPIC population reflects this, since over 92% of participants had received at least 225 mg/m$^2$ of docetaxel.

The population was further defined in the final scope as having mHRPC which has progressed following or during docetaxel-based treatment. The MS notes that, in the absence of a clear definition of disease progression in patients with mHRPC, such progression often incorporates a number of measures including rising serum PSA concentrations, new or enlarging radiological lesions, or the appearance of symptoms.[1] In the TROPIC study, disease progression was defined as follows:

- In patients with measurable disease: documented disease progression by RECIST criteria with at least one visceral or soft-tissue metastatic lesion
- In patients with non-measurable disease, either rising serum PSA concentrations (at least two consecutive increases relative to a reference value, measured at least one week apart) or the appearance of at least one new demonstrable radiographic lesion.[22]

The intervention evaluated in the TROPIC study is essentially that defined in the final scope. The cabazitaxel dosing schedule is the same as that in the licensed indication. Patients received the study treatment until disease progression, death, unacceptable toxicity, or for a maximum of 10 cycles.[23] The scope stipulates the use of cabazitaxel plus prednisolone, which is licensed in the UK, whereas the TROPIC study used prednisone rather than prednisolone in countries where the former was available. However, the two drugs appear to be functionally interchangeable, and the HTA report by Collins *et al.,* sets a precedent for treating them as such in a systematic review.[87] However, the TROPIC study only includes one of the comparators specified in the final scope (mitoxantrone plus prednisone/prednisolone).

The TROPIC study includes all the outcomes specified in the final scope with the exception of health-related quality of life. It includes additional pain-related outcomes which the MS considers to be to some extent surrogates for HRQoL.

**Table 9: Comparison of key aspects of the final scope and the TROPIC study**

| | **Final scope issued by NICE[15]** | **TROPIC study[22]** |
|---|---|---|
| Population | Men with metastatic hormone refractory prostate cancer which has progressed following or during docetaxel-based treatment | Men with metastatic castration-resistant prostate cancer which had progressed following or during docetaxel-based treatment |
| Intervention | Cabazitaxel in combination with prednisolone | Cabazitaxel in combination with prednisone (prednisolone in countries where prednisone was unavailable) |
| Comparator(s) | • Mitoxantrone in combination with prednisolone<br>• Chemotherapy without cabazitaxel (e.g. 5-flourouracil, cyclophosphamide and carboplatin/etoposide) | Mitoxantrone in combination with prednisone (prednisolone in countries where prednisone was unavailable) |
| Outcomes | • Overall survival (OS)<br>• Progression-free survival (PFS)<br>• Response rate<br>• PSA level<br>• Adverse effects of treatment<br>• Health-related quality of life | • Overall survival (OS)<br>• Progression-free survival (PFS)<br>• PSA response rate<br>• PSA progression<br>• Objective tumour response<br>• Time to tumour progression<br>• Pain response<br>• Pain progression<br>• Adverse effects of treatment |

### *4.2.6 Description and critique of any meta-analysis, indirect comparisons and/ or mixed treatment analysis carried out by the manufacturer*

The manufacturer could not undertake a meta-analysis because only one RCT of cabazitaxel was identified.

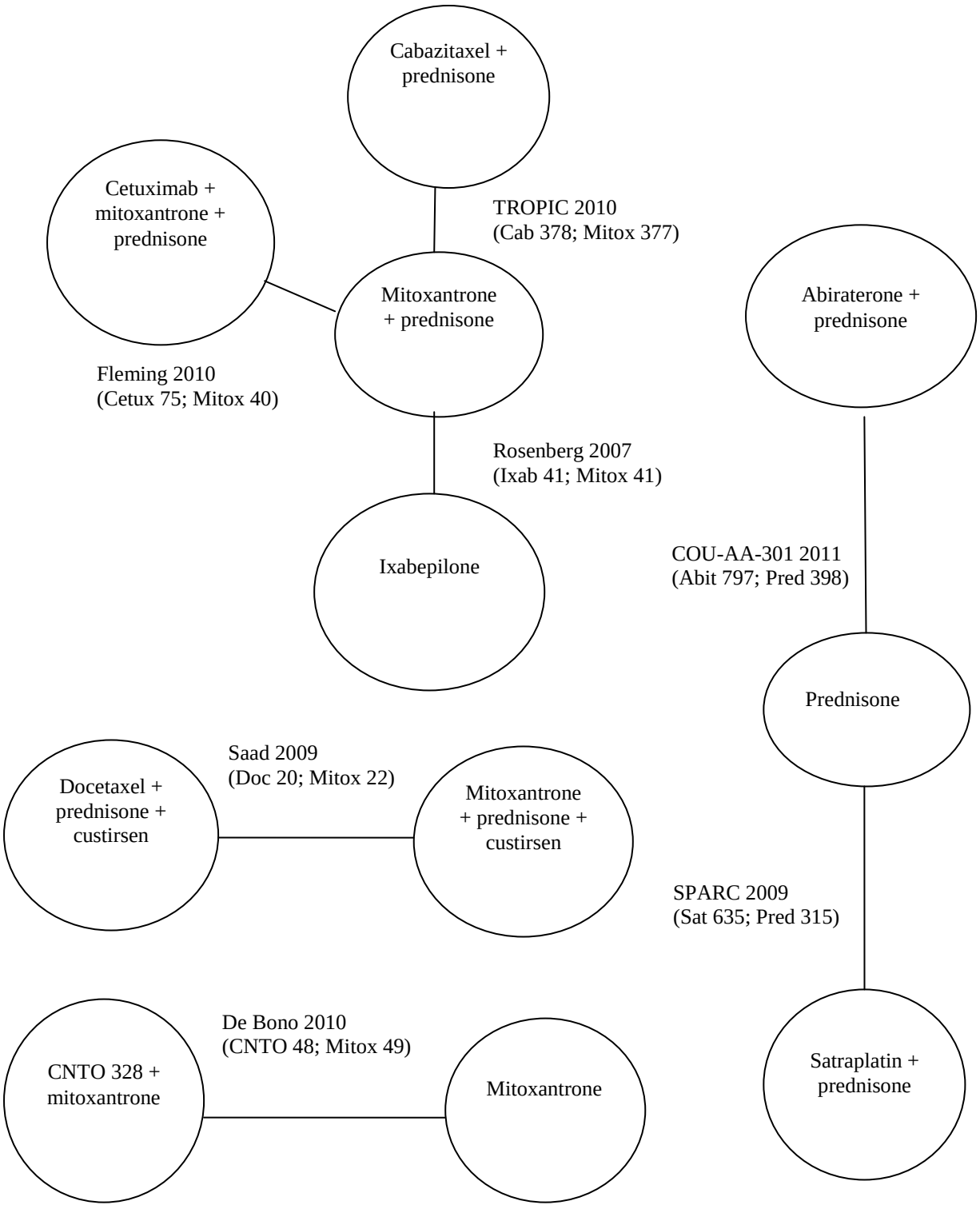
The MS states that indirect comparisons were not performed for the following reasons:

- indirect comparison was not necessary in relation to mitoxantrone, the first comparator identified in the final scope, because the one RCT of cabazitaxel took the form of a head-to-head comparison with mitoxantrone
- indirect comparisons were not considered relevant in relation to the second comparator identified in the final scope, chemotherapy without cabazitaxel. This was because, although RCTs were identified which investigated the use of docetaxel,[34] ixabepilone[37], and satraplatin[30] in the specified patient group, they were considered to be irrelevant to the decision problem for the following reasons:
    - Docetaxel rechallenge was not considered to be a suitable comparator for an agent designed to overcome docetaxel resistance
    - Ixabepilone was not reported to be used in the UK
    - Satraplatin failed to improve survival.[1]

However, in section 5.2.4, the MS indicates that the manufacturer's searches also identified RCTs of a further three agents: abiraterone, cetuximab, and CNTO 328. It is understood that none of these three agents are chemotherapy agents according to the usual interpretation of the term in oncology. The ERG believes that it is possible to conduct an indirect comparison of cabazitaxel against ixabepilone and cetuximab, but that such a comparison would be of limited value; this is discussed in more detail below. In section 5.10.3, the MS acknowledges that abiraterone has been shown to be effective in second-line therapy of patients with mHRPC, but claims that, as it has a different mechanism of action from cabazitaxel, in future the two drugs will probably be used to complement each other rather than as alternatives. As previously noted, it states that further discussion is beyond the scope of the MS because of the limited availability of data relating to abiraterone; full publication of the abiraterone study post-dated the manufacturer's searches. The MS also notes that abiraterone is not yet licensed in the UK for use as second-line therapy in patients with mHRPC.

The ERG has produced a schematic of the RCTs identified by the manufacturer (see Figure 1).

**Figure 1: Evidence networks for RCTs of second-line therapy in mHRPC**



Furthermore, the manufacturer did not undertake a mixed treatment comparison on the basis that:

- An MTC comparing cabazitaxel with mitoxantrone would not be helpful.[1] The reasons given were the small size of the two studies other than TROPIC which had mitoxantrone plus prednisolone as their comparator (Fleming's study of cetuximab plus mitoxantrone and prednisolone[36] and Rosenberg's study of ixabepilone,[37] which had total populations of 115 and 82 respectively), and the fact that the cetuximab trial did not report OS.
- An MTC comparing cabazitaxel with 'chemotherapy without cabazitaxel' was rejected by the manufacturer on the grounds that their searches only identified RCTs of three chemotherapy agents other than cabazitaxel or mitoxantrone (docetaxel,[34] ixabepilone[37], and satraplatin[30]). These studies were considered to be irrelevant to the decision problem for the reasons noted above. However, as also noted above, the manufacturer's searches also identified RCTs of abiraterone, cetuximab, and CNTO 328.

Figure 1 demonstrates that there are no closed networks which would allow a mixed treatment comparison to be conducted. However, as noted above, the manufacturer's review of all RCTs in second-line mHRPC identified two studies in addition to the TROPIC study which were carried out in the relevant patient group and which used mitoxantrone plus prednisolone as the comparator: Fleming's study of cetuximab plus mitoxantrone and prednisolone[36] and Rosenberg's study of ixabepilone[37] (for details, see Table 10, and Figure 2). Thus an indirect comparison with cetuximab in addition to mitoxantrone and with ixabepilone appeared possible. However, the cetuximab RCT concluded that further study was not recommended, and the ixabepilone RCT was relatively small; furthermore, the manufacturer reported that this intervention is not used in the UK. The clinical advisors to the ERG concurred with the manufacturer that comparisons with treatments other than mitoxantrone were not appropriate.

#### *4.2.7 Additional clinical work conducted by the ERG*

No additional clinical work was conducted by the ERG.

### 4.3 Conclusions

#### *4.3.1 Summary and critique of submitted clinical effectiveness evidence*

The manufacturer's systematic review identified one relevant RCT. This was the TROPIC study, a multinational open-label active-controlled randomised trial designed to compare the efficacy and safety of cabazitaxel plus prednisone/prednisolone with mitoxantrone plus prednisone/prednisolone in patients with mHRPC which has progressed following or during docetaxel therapy. Its primary outcome measure was overall survival.[22] For details of study design, see Table 6. The baseline characteristics of patients in the intervention and control groups are presented in Table 10. The NHS Regional Drug and Therapeutics Centre (RD&TC) report draws attention to the notable difference

between treatment groups in baseline median PSA serum concentration (143.9 μg/L in the cabazitaxel group vs 127.5 μg/L in the mitoxantrone group) but adds that, as both levels are hugely elevated from the reference range of 2-5 μg/L, the difference may not be clinically important. However, the RD&TC report also notes that fewer patients randomised to cabazitaxel had bone metastases (80% vs 87%), and that this may have implications for the pain scores.[85]

**Table 10: Baseline characteristics of patients in the TROPIC study[22]**

| | **Cabazitaxel + prednisone (n=378)** | **Mitoxantrone + prednisone (n=377)** |
|---|---|---|
| Age (years) | | |
| Median (IQR) | 68 (62-73) | 67 (61-73) |
| 75 and above | 69 (18%) | 70 (19%) |
| Ethnic origin | | |
| White | 317 (84%) | 314 (83%) |
| Asian | 26 (7%) | 32 (8%) |
| Black | 20 (5%) | 20 (5%) |
| Other | 15 (4%) | 11 (3%) |
| ECOG performance status 0 or 1 | 350 (93%) | 344 (91%) |
| Extent of disease | | |
| Metastatic | 364 (96%) | 356 (94%) |
| Bone metastases | 303 (80%) | 328 (87%) |
| Visceral metastases | 94 (25%) | 94 (25%) |
| Loco-regional recurrence | 14 (4%) | 20 (5%) |
| Unknown | 0 | 1 (<1%) |
| PSA | | |
| Number of patients | 371 | 370 |
| Median (IQR) serum PSA (ng/l) | 143.9 (51.1–416.0) | 127.5 (44.0–419.0) |
| Serum PSA concentration $\geq$ 20 ng/l | 329 (87%) | 325 (86%) |
| Measurable disease | 201 (53%) | 204 (54%) |
| Pain at baseline[†] | 174 (46%) | 168 (45%) |
| Previous therapy: | | |
| Hormonal | 375 (99%) | 375 (99%) |
| 1 chemotherapy regimen | 260 (69%) | 268 (71%) |
| 2 chemotherapy regimens | 94 (25%) | 79 (21%) |
| >2 chemotherapy regimens | 24 (6%) | 30 (8%) |
| Radiation | 232 (61%) | 222 (59%) |
| Surgery | 198 (52%) | 205 (54%) |
| Biological agent | 26 (7%) | 36 (10%) |
| Number of previous docetaxel regimens | | |
| 1 | 316 (84%) | 327 (87%) |
| 2 | 53 (14%) | 43 (11%) |
| >2 | 9 (2%) | 7 (2%) |
| Median (IQR) total previous docetaxel dose ($mg/m^2$) | 576.6 (408.4-761.2) | 529.2 (380.9-787.2) |
| Disease progression relative to docetaxel administration | | |
| During | 115 (30%) | 104 (28% |
| < 3 months from last dose | 158 (42%) | 181 (48%) |
| $\geq$ 3 months from last dose | 102 (27%) | 90 (24%) |
| Unknown | 3 (1%) | 2 (1%) |
| Median time in months from last docetaxel dose to disease progression (IQR) | 0.7 (0.0-2.9) | 0.8 (0.0-3.1) |

*4.3.2 Summary of results*

This section summarises the main clinical efficacy evidence from the TROPIC study.

*Overall survival*

At 25th September 2009, the cut-off date stipulated for analysis, 513 deaths had occurred, 234 in patients randomised to cabazitaxel and 279 in patients randomised to mitoxantrone.[1] Median overall survival was 15.1 months in the cabazitaxel group and 12.7 months in the mitoxantrone group; the hazard ratio (HR) was 0.70 (95% CI 0.59-0.83, p<0.0001)[22] (for details, see Table 11). Thus, cabazitaxel plus prednisone/prednisolone was associated with a median survival gain of 2.4 months relative to mitoxantrone plus prednisone/prednisolone. The mean survival gain, reported only in the MS, was 4.2 months.[1]

The MS states that an updated analysis was presented at ASCO in 2010, after 585 deaths had occurred. This analysis found that, while the median survival values were unchanged, the HR was 0.72.[1] The reference which is supplied in the MS, to an abstract by de Bono *et al*,[80] does not relate to these data. However, they are presented in an article by Oudard,[16] who states that this updated analysis was performed on 10th March 2010, and gives confidence intervals (CI) for the HR (for details, see Table 11).

**Table 11: The TROPIC study: overall survival[1,22]**

| | Cabazitaxel | Mitoxantrone | HR (95% CI) | P value |
|---|---|---|---|---|
| **Analysis at 25.9.2009 ('final' analysis) [1,22]** | | | | |
| Total deaths, safety population | 227/371 (61%) | 275/371 (74%) | NR | NR |
| Total deaths, ITT population | 234/377 (61.9%) | 279/378 (74.0%) | NR | NR |
| No of patients censored[1,2] | 144, including 7 lost to follow-up before cut-off | 98, including 3 lost to follow-up before cut-off | | |
| Median overall survival (months) | 15.1 (95% CI 14.1-16.3) | 12.7 (95% CI 11.6-13.7) | 0.70 (0.59-0.83) | <0.0001 |
| **Analysis at 10.3.10 (updated efficacy analysis)[16]** | | | | |
| Median overall survival (months) | 15.1 | 12.7 | 0.72 (0.61-0.84) | <0.0001 |
| **Data from MS[1]** | | | | |
| [redacted] | [redacted] | [redacted] | NR | NR |
| [redacted] | [redacted] | [redacted] | NR | NR |

| | | | | |
|---|---|---|---|---|
| [redacted] | | | | |

OS is the only outcome for which subgroup data are available. The final scope stated that, if the data permitted, three subgroup analyses should be considered: by baseline performance status, duration of prior docetaxel exposure, and time since docetaxel treatment. If total docetaxel dose may be assumed to be equivalent to duration of prior docetaxel exposure, then De Bono *et al.*,[22] published data relating to the first two of these subgroups; updated analyses were later published by Oudard.[16] Data relating to time from last docetaxel treatment to randomisation are available only in the MS.[1] These subgroup analyses are summarised in Table 12. Data contained in this table have been obtained from the following sources:

- The 2010 Lancet paper by de Bono *et al*.[22] (the 'final' analysis)
- A 2011 article by Oudard[16] (the updated analysis)
- The MS[1]
- A 2011 conference abstract by de Bono *et* al. which presented a subgroup analysis of survival by reason for discontinuation of docetaxel therapy.[83]

**Table 12: The TROPIC study: overall survival by subgroup**

| | **Cabazitaxel No (%)** | **Mitoxantrone No (%)** | **HR (95% CI)** |
|---|---|---|---|
| ECOG status 0-1<br>'Final' analysis (n=694)[22]<br>Updated analysis (n=694)[16] | NR | NR | 0.68 (0.57-0.82)<br>0.71 (0.60-0.84) |
| ECOG status 2<br>'Final' analysis (n=61)[22]<br>Updated analysis (n=61)[16] | NR | NR | 0.81 (0.48-1.38)<br>0.78 (0.46-1.33) |
| Total docetaxel dose <225 mg/m$^2$<br>'Final' analysis (n=59)[22]<br>Updated analysis (n=59)[16] | NR | NR | 0.96 (0.49-1.86)<br>1.02 (0.55-1.87) |
| Total docetaxel dose 225-450 mg/m$^2$<br>'Final' analysis (n=206)[22]<br>Updated analysis (n=206)[16] | NR | NR | 0.60 (0.43-0.84)<br>0.61 (0.44-0.84) |
| Total docetaxel dose 450-675 mg/m$^2$<br>'Final' analysis (n=217)[22]<br>Updated analysis (n=217)[16] | NR | NR | 0.83 (0.60-1.16)<br>0.81 (0.59-1.10) |
| Total docetaxel dose 675-900 mg/m$^2$<br>'Final' analysis (n=131)[22]<br>Updated analysis (n=131)[16] | NR | NR | 0.73 (0.48-1.10)<br>0.77 (0.52-1.12) |
| Total docetaxel dose >900 mg/m$^2$<br>'Final' analysis (n=134)[22]<br>Updated analysis (n=134)[16] | NR | NR | 0.51(0.33-0.79)<br>0.57 (0.39-0.84) |
| Time from last docetaxel to randomisation <6 months (n=504)[1] | NR | NR | 0.77 (0.63-0.94) |
| Time from last docetaxel to randomisation >6 months (n=250)[1] | NR | NR | 0.64 (0.46-0.89) |
| Discontinued docetaxel due to disease progression[83] | NR | NR | 0.70 (0.57-0.87) |
| Discontinued docetaxel for reasons other than disease progression (n=286)[83] | NR | NR | 0.63 (0.46-0.85) |
| Discontinued docetaxel due to an adverse event (n=26)[83] | NR | NR | 0.63 (0.30-1.33) |

With the exception of patients who received a total docetaxel dose less than 225 mg/m$^2$, these analyses consistently favour cabazitaxel, suggesting that there were generally no significant interactions between the prognostic factors of interest and treatment response. Moreover, a post-hoc

subgroup analysis relating OS to the reason for discontinuation of prior docetaxel therapy suggested that the survival benefit associated with cabazitaxel was maintained irrespective of whether prior docetaxel therapy was discontinued due to disease progression (see Table 12).[83]

*Progression-free survival*

Cabazitaxel was associated with a statistically significant improvement in median PFS, a composite endpoint including tumour, PSA, or pain progression, or death. Further data available in the FDA reviewers' report[21] indicate that the majority (43-49%) of progression events related to PSA progression (for details, see Table 13).

**Table 13: Progression-free survival**

| | **Cabazitaxel (n=378)** | **Mitoxantrone (n=377)** | **HR (95% CI)** | **P value** |
|---|---|---|---|---|
| Median progression-free survival (months)[22] | 2.8 (2.4-3.0) | 1.4 (1.4-1.7) | 0.74 (0.64-0.86) | <0.0001 |
| No of patients with PFS events (%)[21] | 364 (96.3%) | 367 (97.3%) | NR | NR |
| 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%) | NR | NR |
| Symptom deterioration | 10 (2.6%) | 14 (3.7%) | NR | NR |
| No of patients censored (data censored at last available assessment) | 14 (3.7%) | 10 (2.7%) | NR | NR |

*PSA response*

Cabazitaxel was associated with a statistically significant improvement in PSA response rate, relative to mitoxantrone (for details, see Table 14).

**Table 14: PSA response rate[22]**

| | **Cabazitaxel** | **Mitoxantrone** | **HR (95% CI)** | **P value** |
|---|---|---|---|---|
| No of evaluable patients | 329 | 325 | | |
| Response rate (%) | 39.2% (33.9-44.5) | 17.8% (13.7-22.0) | NR | 0.0002 |

*PSA progression*

In an ITT analysis, cabazitaxel was associated with a statistically significant improvement in time to PSA progression, relative to mitoxantrone (for details, see Table 15).

**Table 15: Time to PSA progression[22]**

| | Cabazitaxel (n=378) | Mitoxantrone (n=377) | HR (95% CI) | P value |
|---|---|---|---|---|
| Median time to PSA progression (months) | 6.4 (2.2-10.1) | 3.1 (0.9-9.1) | 0.75 (0.63-0.90) | 0.001 |

*Objective tumour response*

In patients with measurable disease, cabazitaxel was associated with a statistically significant improvement in objective tumour response, relative to mitoxantrone.[22] The MS notes that all responses were partial rather than complete. However, the FDA reviewers consider that the fact that 65 of the 405 potentially evaluable patients were actually not evaluable because of missing data could potentially affect this result because the number of patients with missing data exceeds the number of patients who displayed a response.[21] Consequently, this result may not be robust. An additional analysis which combined complete response, partial response, and stable disease to form a measure of disease control found that disease control was significantly better in the cabazitaxel group,[78] (for details, see Table 16) but the robustness of this result is presumably also open to some doubt.

**Table 16: Objective tumour response[22,78]**

| | Cabazitaxel (n=378) | Mitoxantrone (n=377) | HR (95% CI) | P value |
|---|---|---|---|---|
| No of evaluable patients | 201 | 204 | | |
| Response rate[22] | 14.4% (9.6-19.3) | 4.4% (1.6-7.2) | NR | 0.0005 |
| Disease control[78] | 61.7% | 47.5% | NR | 0.004 |

*Time to tumour progression*

An ITT analysis indicated that cabazitaxel was associated with a statistically significant improvement in time to tumour progression, relative to mitoxantrone (for details, see Table 17).

**Table 17: Time to tumour progression[22]**

| | Cabazitaxel (n=378) | Mitoxantrone (n=377) | HR (95% CI) | P value |
|---|---|---|---|---|
| Median time to tumour progression (months) | 8.8 (3.9-12.0) | 5.4 (2.3-10.0) | 0.61 (0.49-0.76) | <0.0001 |

*Pain response (measured in patients with a median PPI score of ≥2 points and/or a mean AS of ≥10 points at baseline)*

Pain response (defined as a ≥ 2-point reduction from baseline in median PPI with no increase in AS, or a ≥50% reduction in analgesic use with no increase in PPI score) could only be evaluated in the 342/755 patients (45%) whose baseline PPI or AS scores enabled this outcome to be measured. There was no significant difference in pain response rate between treatment groups. However, on the basis of a comparison of the mean cumulative area under the curve of the PPI curves over the treatment period, Oudard suggested that there was a trend towards a reduction in pain in the cabazitaxel group[16] (for details, see Table 18). As noted earlier, the RD&TC report[85] drew attention to the higher baseline prevalence of bone metastases in the mitoxantrone group than in the cabazitaxel group, and suggested that this might have an impact on pain outcomes. Such an imbalance would presumably favour cabazitaxel.

**Table 18: Pain response rate**

| | **Cabazitaxel** | **Mitoxantrone** | **P value** |
|---|---|---|---|
| No of evaluable patients[22] | 174 | 168 | |
| Pain response rate (95% CI)[22] | 9.2% (4.9-13.5) | 7.7% (3.7-11.8) | 0.63 |
| Patients with improvement in pain from baseline[16] | 21.3% | 18.2% | NR |
| Patients with deterioration in pain from baseline[78] | 32% | 32% | NR |

*Pain progression*

An ITT analysis found no significant difference between treatment groups in relation to median time to pain progression (for details, see Table 19). Data for 265 patients in the cabazitaxel group and 279 in the mitoxantrone group were censored because of missed assessments.[22]

**Table 19: Pain progression[22]**

| | **Cabazitaxel (n=378)** | **Mitoxantrone (n=377)** | **HR (95% CI)** | **P value** |
|---|---|---|---|---|
| Median time to pain progression (months) | 11.1 (2.9-not reached) | Not reached | 0.91 (0.69-1.19) | 0.52 |

*Quality of life*

As noted earlier, the TROPIC study did not collect quality of life data. The MS therefore uses pain as a partial surrogate for HRQoL, and suggests that, as the TROPIC study showed no significant difference between cabazitaxel and mitoxantrone in terms of pain response and time to pain progression, cabazitaxel may be similar to mitoxantrone at least in relation to this aspect of quality of life.[1] However, as noted above, the pain results may have been affected by the imbalance in baseline prevalence of bone metastases. The MS also refers to interim UK results from the early access

programme (EAP) for cabazitaxel. An analysis performed in May 2011 using a cut-off date of 29th April 2011 included EQ-5D data from [redacted] patients who had received at least one dose of cabazitaxel, and indicated [redacted]. The MS suggests that this result indicates that cabazitaxel therapy is not associated with a significant negative effect on utility, and may even improve it.[1] Unfortunately, however, no EQ-5D data were identified relating to patients with mHRPC receiving mitoxantrone.

### *4.3.3 Critique of reported efficacy data*

The MS appears to be complete in that it includes the only RCT of cabazitaxel plus prednisone/prednisolone which has been undertaken in the relevant population.

The reported efficacy data indicate that, relative to mitoxantrone plus prednisone/prednisolone, the use of cabazitaxel plus prednisone/prednisolone is associated with improved overall survival, progression-free survival, PSA response, time to PSA progression, objective tumour response, and time to tumour progression. It is not associated with improved pain outcomes. Comparative data are not available in relation to quality of life.

However, as the MS recognises, as an open label study, the TROPIC study is susceptible to ascertainment bias in the assessment of pain and symptomatic progression, both of which are subjective outcomes. PFS, a composite endpoint which incorporates pain progression, is therefore also susceptible to bias. However, as the MS also notes, the lack of blinding is unlikely to have biased the assessment of OS (the primary outcome), or tumour response.[1]

### *4.3.4 Safety and tolerability*

Evidence for the safety and tolerability of cabazitaxel in patients with mHRPC appears to be limited to the data on adverse events, discontinuations, dose reductions, and treatment delays available from the TROPIC study. This study was not said to be powered to detect differences between treatment arms in relation to the incidence of specific adverse events. Moreover, even if that study had sufficient power to detect significant differences in common adverse events, it should be noted than an RCT cannot form the best source of evidence for rarer adverse events.

Data relating to selected adverse events reported from the TROPIC study are summarised in Table 20. As may be seen, the most common AEs were haematological, and the incidence of grade $\geq$ 3 neutropenia and leukopenia were both noticeably higher in the cabazitaxel group than in the mitoxantrone group. The incidence of diarrhoea was also very substantially higher in the cabazitaxel group. The MS notes that the incidence of grade $\geq$ 3 gastrointestinal disorders of all types was

substantially higher in patients receiving cabazitaxel than in those receiving mitoxantrone (12.4% vs 1.6%).[1]

**Table 20: The TROPIC trial: numbers of patients suffering selected adverse events[22]**

| | Cabazitaxel (n=371) | | Mitoxantrone (n=371) | |
|---|---|---|---|---|
| | **All grades** | **Grade ≥3** | **All grades** | **Grade ≥3** |
| **Haematological AEs** | | | | |
| Neutropenia | 347 (94%) | 303 (82%) | 325 (88%) | 215 (58%) |
| Febrile neutropenia | - | 28 (8%) | - | 5 (1%) |
| Leukopenia | 355 (96%) | 253 (68%) | 343 (92%) | 157 (42%) |
| Anaemia | 361 (97%) | 39 (11%) | 302 (81%) | 18 (5%) |
| Thrombocytopenia | 176 (47%) | 15 (4%) | 160 (43%) | 6 (2%) |
| **Selected non-haematological AEs** | | | | |
| Diarrhoea | 173 (47%) | 23 (6%) | 39 (11%) | 1 (<1%) |
| Fatigue | 136 (37%) | 18 (5%) | 102 (27%) | 11 (3%) |
| Asthenia | 76 (20%) | 17 (5%) | 46 (12%) | 9 (2%) |
| Back pain | 60 (16%) | 14 (4%) | 45 (12%) | 11 (3%) |
| Nausea | 127 (34%) | 7 (2%) | 85 (23%) | 1 (<1%) |
| Vomiting | 84 (23%) | 7 (2%) | 38 (10%) | 0 |
| Haematuria | 62 (17%) | 7 (2%) | 14 (4%) | 2 (1%) |
| Abdominal pain | 43 (12%) | 7 (2%) | 13 (4%) | 0 |

In the web appendix to their article (http://www.sciencedirect.com/science/article/pii/S014067361061389X), de Bono *et al.*,[22] present data suggesting that the incidence of neutropenia and diarrhoea may vary by age, previous radiotherapy, and geographical region (for details, see Table 21). These subgroup analyses suggest that the incidence of diarrhoea and neutropenia is significantly higher in older patients; the incidence of diarrhoea also appears to be significantly higher in patients who have undergone previous radiotherapy. Regional differences were also identified in the incidence of neutropenia, and these may reflect differences in patterns of care. No differences in the incidence of neutropenia and diarrhoea were found in subgroups defined by race, baseline liver function, baseline renal function, ECOG performance status, or prior chemotherapy.

However, as may be seen from Table 21, de Bono *et al.*, used different age-related subgroups for diarrhoea and neutropenia. No justification was provided for this, prompting the suspicion that the use of the same age bands for both AEs would have made one or other result non-significant. This is supported by the statement in the MS[1] that, in patients treated with cabazitaxel, the following AEs occurred at rates ≥ 5% higher in patients aged 65 and over than in those aged under 65:

- fatigue (40.4% versus 29.8%)

- neutropenia (24.2% versus 17.6%)
- asthenia (23.8% versus 14.5%)
- pyrexia (14.6% versus 7.6%)
- dizziness (10.0% versus 4.6%)
- urinary tract infection (9.6% versus 3.1%)
- dehydration (6.7% versus 1.5%).

It is noticeable that, while this list includes neutropenia, it does not include diarrhoea. The MS also states that the incidence of Grade ≥ 3 neutropenia based on laboratory abnormalities (86.3% versus 73.3%), clinically complicated neutropenia (23.8% versus 16.8%), and febrile neutropenia (8.3% versus 6.1%) were all higher in patients aged ≥ 65 years than in younger patients.[1]

**Table 21: Incidence of neutropenia and diarrhoea (all grades) in subgroups of patients treated with cabazitaxel in the TROPIC study**

| | AE rate (all grades) % of patients | P value (by logistic regression) |
|---|---|---|
| Diarrhoea by age (years) | | <0.1 |
| <75 (N=301) | 44.5% | |
| ≥75 (N=70) | 55.7% | |
| Diarrhoea by prior radiotherapy | | <0.1 |
| Yes (N=226) | 50.0% | |
| No (N=145) | 41.4% | |
| Neutropenia by age | | <0.1 |
| <65 (N=131) | 17.6% | |
| ≥65 (N=240) | 24.2% | |
| Neutropenia by region | | <0.1 |
| North America (N=109) | 25.7% | |
| Europe (N=205) | 16.1% | |
| Other* (N=57) | 35.1% | |

* Argentina, Brazil, Chile, India, republic of Korea, South Africa, Taiwan, Turkey

27 deaths were reported within 30 days of the last dose of study drug. 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[22] (for details, see Table 22). The FDA reviewers considered 5 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. A further death occurred in a patient who did not have documented infection at the time of death, and who had

developed febrile neutropenia despite the use of prophylactic G-CSF. The FDA reviewers also attributed 4 deaths to renal failure,[21] rather than the three reported by de Bono *et al*.[22]

**Table 22: Deaths occurring within 30 days of last dose of study drug[22]**

| | **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%) | 0 |
| Dyspnoea (apparently related to disease progression) | 0 | 1 (<1%) |
| Dehydration/electrolyte imbalance | 1 (<1%) | 0 |
| Renal failure | 3 (1%) | 0 |
| Cerebral haemorrhage | 1 (<1%) | 0 |
| Unknown cause | 1 (<1%) | 0 |
| Motor accident | 0 | 1 (<1%) |

Some indication of relative toxicity may also be gained from data relating to discontinuation of treatment. 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 (for details, see Table 23).

**Table 23: Treatment received and reasons for discontinuation in the TROPIC study[22]**

| | Cabazitaxel (n=378) | Mitoxantrone (n=377) |
|---|---|---|
| Median number of treatment cycles (assessed in patients who received study treatment, i.e. 371 in each arm) | 6 (3-10) | 4 (2-7) |
| No of patients completing planned 10 cycles of study treatment | 105 (28%) | 46 (12%) |
| 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* | 45 (12%) | 15 (4%) |
| Treatment delays, no of patients* | 104 (28%) | 56 (15%) |

* Data from MS[1]

*4.3.5 Critique of reported safety data*

The lack of blinding in the TROPIC study may have biased the assessment of clinical AEs. However, as the MS notes, it is unlikely to have biased the assessment of laboratory AEs.[1]

In the TROPIC study, new cycles of therapy started when absolute neutrophil counts were $\geq$1500/mm$^3$, the platelet count was $\geq$75,000/mm$^3$, and non-haematological toxicities (except alopecia) had recovered to baseline levels. A maximum of two weeks' delay was allowed between two treatment cycles, and patients were removed from the study treatment if treatment was delayed for more than two weeks.[21] As these criteria appear more stringent than the EMEA recommendations for dose modifications,[17] the number of AEs reported in the TROPIC study may be lower than that which might be expected in clinical practice.

Despite the use of these stringent criteria, the TROPIC study found that cabazitaxel was associated with a higher incidence of AEs than was mitoxantrone. The FDA reviewers considered that the AEs of interest in cabazitaxel-treated patients included neutropenic complications (febrile neutropenia and infection), renal failure, haematuria, and cardiac toxicity.[21] The MS recognises that, since 8% of patients treated with cabazitaxel had febrile neutropenia, cabazitaxel treatment requires careful monitoring and management of emerging symptoms.[1] The TROPIC study reported haematuria as an AE, but did not report renal failure or cardiac toxicity other than as causes of deaths within 30 days of treatment.[22] The RD&TC report considers the deaths attributed to cardiac and renal failure to be of

particular concern given that the inclusion criteria for the TROPIC study included adequate cardiac and renal function.[85]

Because of its concerns about serious toxicity in general, and renal toxicity in particular, associated with the use of cabazitaxel at a dose of 25 mg/m$^2$, the FDA recommended four post-marketing requirements:

- A phase III RCT in patients with mHRPC to compare first-line docetaxel/prednisone with cabazitaxel 20 mg/m$^2$/prednisone and cabazitaxel 25 mg/m$^2$/prednisone, with overall survival as the primary endpoint, powered to detect a realistic difference in primary endpoint
- A phase III RCT in patients with HRPC previously treated with docetaxel to compare cabazitaxel 20 mg/m$^2$/prednisone with cabazitaxel 25 mg/m$^2$/prednisone, with overall survival as the primary endpoint, powered to preserve 50% of the treatment effect of cabazitaxel 25 mg/m$^2$
- A review and analysis by a group of renal experts of renal toxicity from all currently available cabazitaxel trials to identify aetiologies and provide recommendations for toxicity mitigation by patient selection or other measures; the group's recommendations and findings should be submitted within 9 months of the US cabazitaxel approval date of 17$^{th}$ June 2010
- The submission of updates on renal toxicity from all active randomised trials every 6 months for 3 years after the US cabazitaxel approval date.[21]

The ERG notes that 9 months have now passed since the FDA approved cabazitaxel, but that no publications have been identified which report the results of the expert review of renal toxicity. During the fact check process, the manufacturer indicated that they had information from the renal safety report, and also from a trial evaluating the effect of cabazitaxel on the QTc interval, which has relevance for cardiac toxicity, which could be provided. However, these data were not offered within the timescale of the ERG report.

The NHS RD&TC considers that further safety data are required before cabazitaxel can be recommended as it feels that a median gain of 2.4 months in overall survival may not be acceptable given cabazitaxel's AE profile.[85]

*Non-RCT evidence*

No non-RCT evidence has been identified relating to the adverse events of cabazitaxel.

### *4.3.6 Critique of submitted evidence analyses*

No evidence analyses were submitted.

### *4.3.7 Conclusions*

The clinical effectiveness evidence submitted by the manufacturer indicated that, relative to mitoxantrone plus prednisone/prednisolone, cabazitaxel at a dose of 25 mg/m$^2$ plus

prednisone/prednisolone is associated with improved overall survival, progression-free survival, PSA response, time to PSA response, objective tumour response, and time to tumour progression. However it is not associated with improvements in pain response or time to pain progression, and it is associated with an increased risk of adverse events such as neutropenia. Patients aged over 65 years appear to be at increased risk of many adverse events, and this is a matter for concern given that, in the UK, approximately 75% of new cases of prostate cancer occur in men aged over 65.[8]

# 5 ECONOMIC EVALUATION

## 5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

In the economic evaluation searches, the intervention terms for cabazitaxel were searched alone without the disease terms for mHRPC. Specialist databases such as NHS EED and HEED were searched by the manufacturer for economic evaluations. Note that any potentially relevant economic evaluations are likely to have been retrieved in the earlier clinical effectiveness review searches. The ERG believes that these searches were sensitive and reproducible.

The search strategy for HRQoL studies of prostate cancer consisted of the disease terms combined with a sensitive quality of life filter. By comparison to the disease terms used in the RCT and non-RCT search strategies in the clinical effectiveness review, fewer mHRPC terms were used and, unless tested by the manufacturer, this might affect the sensitivity of the searches for quality of life studies.

The manufacturer was unable to identify any previous economic evaluations of cabazitaxel. The ERG believes it unlikely that any studies have been overlooked. Therefore, the manufacturer developed a *de novo* model that is described in the MS.

## 5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

### *5.2.1 Adherence to the NICE reference case*

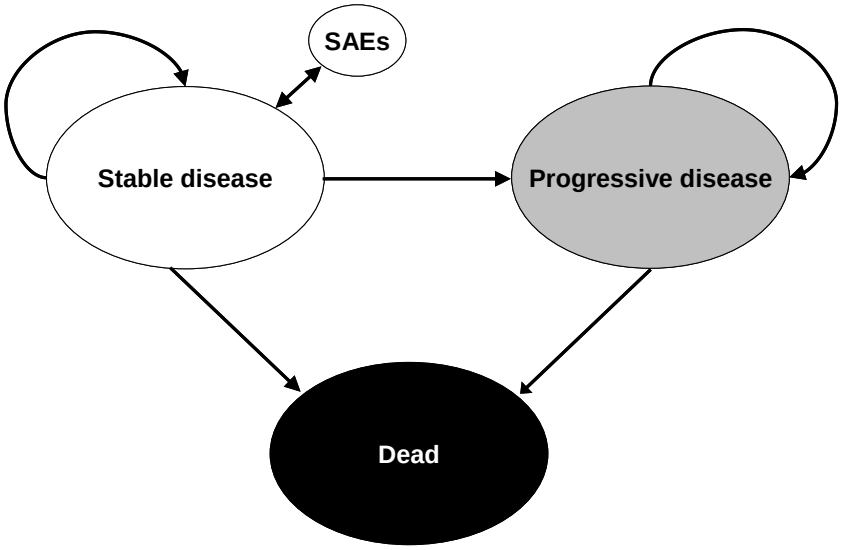
The MS is consistent with the principles of the NICE reference case.[88] The cost-effectiveness ratio is expressed in terms of cost per quality adjusted life year (QALY), the time horizon is that of assumed patient lifetime, utility has been estimated using the EuroQol 5-Dimension (EQ-5D), costs and benefits are discounted, and costs are taken from an NHS and Personal Social Services Perspective.

### *5.2.2 Model Structure*

The manufacturer supplied a *de novo* economic evaluation based upon a cohort Markov model constructed in Microsoft Excel©. The model includes three states: stable disease; progressive disease and death (an absorbing state). All patients begin in stable disease where transitions to progressive disease and death are possible. Following transition to progressive disease it was assumed that patients could not revert to stable disease, but would instead remain in this state until death.

In addition to these health states, the possibility of experiencing serious adverse events (SAEs), which incur costs and disutilities, whilst in the stable disease state has been modelled. A schematic of the model is shown in Figure 2 (reproduced from the MS (Figure 6-1 p 90)).

**Figure 2: A schematic of the manufacturer's model**




Separate transition probabilities are modelled for cabazitaxel and mitoxantrone, the sole comparator within the economic analysis. Data for these come from appropriate patients within the TROPIC trial, as described in Section 5.2.6.

The model uses a cycle length of three weeks to match the timing of treatment cycles for both drugs and an assumed lifetime horizon, set as 747 weeks (14.4 years). Half-cycle correction is employed.

Within the model clinical assumptions are based on patient experience within the TROPIC trial. The intervention and comparator being compared (cabazitaxel plus prednisolone and mitoxantrone plus prednisolone) are given only to patients with stable disease. Patients with progressive disease receive either post-second-line chemotherapy, a mix of treatments, or best supportive care, which are detailed in Section 5.2.8. It is assumed that neither post-second-line chemotherapy nor best supportive care affects either survival or utility. The utility within a given health state is assumed to be independent of time within that state. The ERG and the clinical advisors are satisfied that the model captures the main aspects of patient's clinical pathway of care.

Mitoxantrone was allowed to be provided as part of post-second-line chemotherapy. The manufacturer argues that, as mitoxantrone does not impact on survival, and as the results from TROPIC include the effects of cross-over, no adjustment is required, a logic that the ERG deems is reasonable.

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

*5.2.3 Patient population considered*

The MS present results for four patient populations:

- Base case: European patients within TROPIC who received ≥ 225mg/m$^2$ of first-line docetaxel and with an ECOG PS of 0 or 1
- Subgroup 1: The entire TROPIC population
- Subgroup 2: European patients within TROPIC
- Subgroup 3: Patients within TROPIC who received ≥ 225mg/m$^2$ of first-line docetaxel and with an ECOG PS of 0 or 1

The manufacturer has selected the base case claiming that it is the group most likely to reflect current practice within the United Kingdom. The ERG comment on the appropriateness of this choice in Section 5.2.12.

Following the round of clarifications the manufacturer also undertook analyses removing those patients who had died within 30 days of randomisation for the base case and for subgroup 1.

*5.2.4 Intervention and comparator*

The intervention was cabazitaxel (25 mg/m$^2$) given every three weeks plus 10 mg per day of prednisolone. The intervention could be given for a maximum of 10 cycles. The comparator was mitoxantrone (12 mg/m$^2$) given every three weeks plus 10 mg per day of prednisolone. These pharmaceuticals were directly compared in the TROPIC trial.

The decision scope also included chemotherapy without cabazitaxel. These comparators were not considered within the MS based on the following rationale: that the use of chemotherapy other than mitoxantrone was rare within the UK and could not be considered standard practice and that there was lack of evidence on efficacy for any other chemotherapy. The clinical advisors to the ERG believed that these statements were correct and did not consider other treatments than mitoxantrone to be appropriate.

*Intervention Costs*

Both cabazitaxel and mitoxantrone are provided in vials with the dosage required being dependent on body surface area (BSA) (25 mg/m$^2$ for cabazitaxel and 12 mg/m$^2$ for mitoxantrone). The average number of vials used per patient per infusion was calculated based on the distribution of BSA observed in the TROPIC trial (assumed to be normally distributed with a mean of 2.01 and a standard deviation of 0.21) and the observed relative dose intensity (0.928 for cabazitaxel and 0.941 for mitoxantrone). The cost per vial of cabazitaxel was taken from the MS[1] whilst the cost per vial of mitoxantrone was taken from the BNF61.[19] Both cabazitaxel and mitoxantrone are taken in

conjunction with prednisolone, which based on BNF61 costs and an assumption of 10 mg taken daily were costed at £1.55 per cycle.

**Table 24: Cabazitaxel and mitoxantrone costs assumed within the model**

| | Vial size (active ingredient) | Cost per vial | Average vials used per patient per infusion | Average cost per patient |
|---|---|---|---|---|
| Cabazitaxel | 60 mg | £3696 | 1.003 | £3707 |
| Mitoxantrone | 20 mg | £100 | 1.871 | £187 |

### *5.2.5 Perspective, time horizon and discounting*

The perspective of the evaluation was appropriately that of the NHS and personal social services. The time horizon, considering that there was a differential mortality rate between the intervention and the comparator, was also appropriate in approximating a patient's lifetime set as 747 weeks (14.4 years).

The manufacturer intended to use discount rates of 3.5% per year for both costs and benefits, in line with the NICE reference case [88] however a slight error (of no material significance) was made in implementation. More details are provided in section 5.2.12.

### *5.2.6 Treatment effectiveness*

The effectiveness of the treatment and the comparator were estimated from the TROPIC RCT and converted into time varying transition probabilities. The primary outcome of overall survival was used to model transition probabilities for moving to the death state. A secondary outcome, progression-free survival, was used to model the probability of those in the stable disease state moving to the progressed disease state. The probabilities (at any given time) of mortality are assumed to be the same for both the stable and the progressive disease states, which is unlikely to be correct, but the interaction with the probabilities for transitioning from stable disease to progressed disease ensures that the numbers in each health state are as intended.

The model supplied by the manufacturer has the flexibility to simulate disease progression and death using two alternative methodologies. The first methodology, and the one denoted the base case by the manufacturer, sets all transition probabilities to those observed in TROPIC, directly using the Kaplan-Meier (KM) curves, 'until the time when the small number of patients makes the curve erratic and unreliable' (p 97 of the MS) when transition probabilities calculated from fitted parametric curves are used instead. The times at which the curves became unreliable is made on a subjective examination of the KM curves and are discussed further in Section 5.2.12. In the base case the Kaplan-Meier data are used up until week 57 for progression-free survival and week 111 for overall survival (both inclusive). The second methodology uses the parametric curves for the entire time horizon.

The manufacturer considered a wide variety of parametric curves, basing their choice on a combination of information criteria and a visual inspection of goodness of fit. A Weibull distribution

was used to estimate the overall survival rates for both treatments. For progression-free disease rates a Weibull distribution was fitted to the cabazitaxel data whilst a log-normal distribution was fitted to the mitoxantrone data. The information criteria considered were the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), and these values are reproduced in Table 25; lower values are preferred, and the ERG has underlined the lowest estimate. 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.

**Table 25: Goodness of fit data for the parametric curve**

| **Overall Survival** | **Mitoxantrone** | | **Cabazitaxel** | |
|---|---|---|---|---|
| | **AIC** | **BIC** | **AIC** | **BIC** |
| Exponential | 379,18 | 382,25 | 421,46 | 424,66 |
| Weibull | <u>343,76</u> | <u>349,90</u> | 397,64 | 404,04 |
| Log-normal | 355,96 | 362,10 | 406,40 | 412,80 |
| Log-logistic | 350,50 | 356,64 | <u>396,96</u> | <u>403,36</u> |
| Gompertz | 351,13 | 357,27 | 406,33 | 412,73 |

| **Progression-Free Survival** | **Mitoxantrone** | | **Cabazitaxel** | |
|---|---|---|---|---|
| | **AIC** | **BIC** | **AIC** | **BIC** |
| Exponential | 456,60 | 459,67 | 510,38 | 513,58 |
| Weibull | 457,08 | 463,22 | <u>503,92</u> | <u>510,32</u> |
| Log-normal | <u>428,96</u> | <u>435,10</u> | 504,58 | 510,98 |
| Log-logistic | 439,30 | 445,44 | 508,30 | 514,70 |
| Gompertz | 458,14 | 464,28 | 507,29 | 513,69 |

The distribution with the lowest AIC and BIC was generally used within the modelling, although one exception exists, which is discussed.

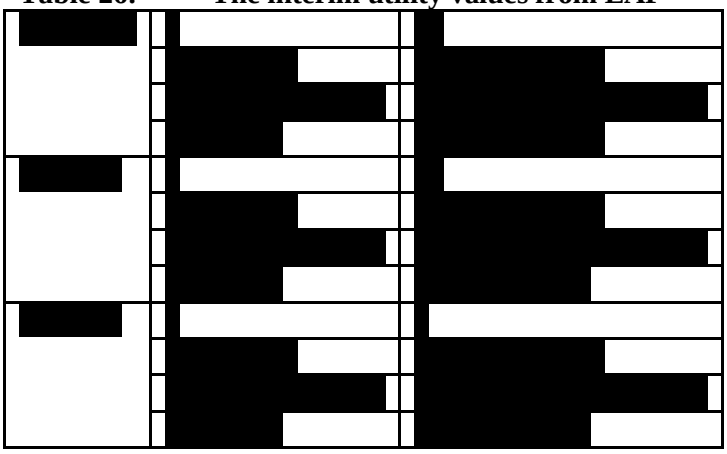
The manufacturer has assumed that the Weibull distribution is more appropriate to model OS for cabazitaxel than the Log-logistic distribution. The reasons for this choice, as explained in the clarification response A14,[2] are that 'Firstly, the Weibull is the best fit for the cabazitaxel OS in all the other patient subgroups and the whole TROPIC population, and also in the mitoxantrone arm. Given that both are a good fit, it seems reasonable to maintain consistency between analyses by using the same distribution for different patient subgroups. Secondly, graphically, the Log-logistic distribution appears to overestimate OS at the end of the curve. It was on this basis that the Weibull was chosen for the cabazitaxel arm. With the Log-logistic, the mean OS for cabazitaxel is 26.4 months, in comparison with 19.4 months with the Weibull distribution. This is much higher than that seen with the other subgroups and would be somewhat inconsistent with them. Thus the choice of Weibull distribution can be viewed as best reflecting the overall dataset.' The ERG believes this to be a reasonable approach.

The submitted model has the functionality to use the Weibull distribution for PFS for mitoxantrone in order that Weibull distributions are used throughout the modelling. The results when using the Weibull distribution are presented within the sensitivity analyses.

### *5.2.7 Health related quality of life*

Data on quality of life were not included in the TROPIC trial. EQ-5D utilities are being collected in the United Kingdom as part of the Early Access Programme (EAP) for cabazitaxel. As of July 2011, the EAP has only provided interim utility data for the stable disease state as only two patients had entered the progressive state. The EAP is an open-label, single-arm trial of cabazitaxel and thus does not include mitoxantrone. The model assumes that within any given health state the utilities are the same for both drugs. The clinical advisors to the ERG 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). The values that have been estimated from the EAP are provided in Table 26, together with the number of patients from which these values have been derived. The manufacturer reports that a further interim analysis will be performed in August 2011.

**Table 26: The interim utility values from EAP**



The manufacturer has assumed that the values from cycle 2 represent the most plausible value for stable disease. In response to clarification question A15, the manufacturer stated that "The baseline value in the EAP comes from patients who have been selected for cabazitaxel treatment on the basis of disease progression after first-line docetaxel treatment (but they have not yet begun second-line treatment). Therefore, the baseline value represents the utility for "first-line disease progression patients". It does not represent stable disease. Further, patients are not receiving cabazitaxel at this timepoint. Therefore, it is less appropriate than the Cycle 2 value. Cycle 4 data were not used due to the small number of patients ( ) for whom data were available."

This argument appears plausible, although the ERG notes both the relatively wide CIs around the means at baseline and cycle 2, and comment that the data are relatively uncertain. The exact values to

use in the evaluation, in addition to at which cycle utility should be measured, are therefore relatively uncertain

The manufacturer undertook a systematic review of health-related quality of life data to estimate the utility value within the progressed disease state. Only two studies met the manufacturer's inclusion criteria,[89,90] and of these, only one considered patients with metastatic hormone-refractory prostate cancer.[89] This study reports a similar baseline utility (0.715) to the EAP and reports a drop in utility of about 0.07 at about 3 months. This drop is maintained for the duration of the study (up to nine months). The manufacturer assumes that this drop reflects the disutility due to moving from the stable to progressive disease state and therefore have set the utility value of patients in the progressed state to be [redacted] ([redacted] minus 0.07) .

The second study[90] identified by the manufacturer reported a decline in utility between a point 16 months before death and a point eight months before death, assuming that these points approximated stable disease and progressed disease respectively. This estimated decline of 0.085 was subtracted from the estimated utility for stable disease from the EAP to produce a value of [redacted] for progressed disease. This value was used in sensitivity analyses.

### *5.2.8 Resources and costs*

General resource use (such as inpatient visits) is based on a mixture of expert clinical opinion and a retrospective UK-based audit of five major cancer centres, with costs taken from the National Schedule of Reference Costs (2009-10).[91] These costs are detailed in Tables 6-12 and 6-13 (pages 126-128) of the MS. The ERG and clinical advisors did not identify any issues with the values used.

Post-second-line interventions

The model assumes that a proportion of patients ([redacted]) would receive post-second-line chemotherapy following progression, with the complement ([redacted]) receiving best supportive care. These percentages were assumed the same for both cabazitaxel and mitoxantrone.

Table 27 shows the breakdown of drugs used in post-second-line chemotherapy in the economic model. Note that there was a typographical error in the MS, (confirmed by the manufacturer and corrected in Table 27) in that the numbers for cabazitaxel and mitoxantrone were transposed. Table 27 additionally shows the expected costs of post-second-line chemotherapy drugs for cabazitaxel and mitoxantrone.

**Table 27: Breakdown of drugs used in post-second-line chemotherapy in the economic model**

| Post-2nd line chemotherapy | Mean Duration | | Cost (per week) | Proportions | |
|---|---|---|---|---|---|
| | Cabazitaxel | Mitoxantrone | | Cabazitaxel | Mitoxantrone |
| Carboplatin | 9.11 | 10.32 | £118.13 | 2.82% | 8.45% |
| Cyclophosphamide | 20.89 | 9.23 | £16.21 | 8.45% | 10.56% |
| Docetaxel | 16.14 | 21.37 | £335.67 | 12.68% | 19.01% |
| Estramustine | 12.30 | 9.70 | £47.88 | 9.15% | 11.97% |
| Etoposide | 10.31 | 15.70 | £2.91 | 10.56% | 15.49% |
| Mitoxantrone | 12.72 | 12.96 | £40.20 | 38.02% | 8.45% |
| Paclitaxel | 6.07 | 2.80 | £261.27 | 3.52% | 1.41% |
| Vinorelbine | 7.58 | 9.49 | £116.58 | 4.93% | 11.27% |
| Cisplatin | 18.47 | 5.33 | £19.60 | 1.40% | 1.41% |
| Gemcitabine | 0 | 13.33 | £160.80 | 0% | 2.11% |
| Total Cost | | | | £1,754 | £2,422 |

It is noted that almost 40% of patients crossed from cabazitaxel to mitoxantrone following disease progression. Hence, if cabazitaxel is fully approved as a drug, it will not fully replace mitoxantrone.

The constituents of best supportive care (and percentage of patients assumed to require each) were taken from an audit of five major UK centres and were: analgesics ([redacted]); steroids ([redacted]); palliative radiotherapy ([redacted]) and bisphosphonates ([redacted]). These percentages were assumed to be the same for both cabazitaxel and mitoxantrone. This translated into a cost of £[redacted] per 3 week cycle. More details are provided in Table 6-12 and 6-13 (pages 126-128) of the MS.

*Costs at the end-of-life*

In addition, a cost associated with treatment at the end of life is incorporated. The assumptions behind this cost are provided in Table 6-12 of the MS, resulting in an estimated cost of [redacted] per patient.

### *5.2.9 Serious adverse events considered within the model*

SAEs were defined as grade 3 or higher adverse events that either occurred during the TROPIC trial in at least 2% of patients (on either treatment) or events which are of clinical significance (which were defined as either deep vein thrombosis or neuropathy). Table 28 lists the adverse events used within the model, along with their rates per patient. As the manufacturer has appropriately used the rate per patient (allowing for multiple events), these values do not match the percentage of patients experiencing the event, which is detailed in Table 5-10 (p 77) of the MS.

**Table 28: The adverse events incorporated within the manufacturer's model**

| Adverse Events (Grade ≥3) | Adverse Event rates | | Total cost per event |
|---|---|---|---|
| | Mitoxantrone arm | Cabazitaxel arm | (£) |
| Neutropenia | [redacted] | [redacted] | [redacted] |
| Febrile neutropenia | [redacted] | [redacted] | [redacted] |
| Diarrhoea | [redacted] | [redacted] | [redacted] |
| Fatigue | [redacted] | [redacted] | [redacted] |
| Asthenia (weakness) | [redacted] | [redacted] | [redacted] |
| Leukopenia | [redacted] | [redacted] | [redacted] |
| Back pain | [redacted] | [redacted] | [redacted] |
| Anaemia | [redacted] | [redacted] | [redacted] |
| Thrombocytopenia | [redacted] | [redacted] | [redacted] |
| Pulmonary embolism | [redacted] | [redacted] | [redacted] |
| Dehydration | [redacted] | [redacted] | [redacted] |
| Nausea / vomiting | [redacted] | [redacted] | [redacted] |
| Bone pain | [redacted] | [redacted] | [redacted] |
| Deep vein thrombosis | [redacted] | [redacted] | [redacted] |
| Neuropathy | [redacted] | [redacted] | [redacted] |

The total cost per event has been calculated based on a number of factors: the proportion of patients hospitalised (sourced from the TROPIC trial and adjusted by expert opinion); the total inpatient days per hospitalisation (sourced from the HRG data[91]); the cost per day whilst hospitalised (sourced from the National Schedule of Reference Costs (2009-10) [91]); and the cost of pharmaceuticals to treat the SAE (sourced from the BNF).[19] These data are provided in Tables 6.14 – 6.16 (pages 128 – 130) of the MS. The manufacturer assumed 'that AEs in patients who do not require hospitalisation will be managed through the outpatient visits that occur regularly throughout the treatment period – including both visits associated with chemotherapy administration and the regular visits not directly related to chemotherapy administration. This assumption was validated by clinical expert opinion' (clarification response A24). It is unclear whether this slightly underestimates resource use.

Disutilities due to adverse events were taken from a literature review with the assumption that disutilities in patients without mHRPC would be transferable to mHRPC patients. The disutilities used within the modelling are provided in Table 29. Details regarding the sources of these values are provided in Table 6.6 of the MS (pages 111 to 112) and in Section 6.4.8 of the MS. Table 29 also reports the standard errors used within the probabilistic sensitivity analyses. The manufacturer clarified that only the value for bone pain had an associated standard error and that the remaining standard errors were estimated assuming that the ratio between the point estimate and the standard error for bone pain was applicable to all SAEs type.

**Table 29: The disutilities associates with serious adverse events**

| SAE | Assumed Disutility | Assumed Standard Error |
|---|---|---|
| Neutropenia | -0.090 | 0.0157 |
| Febrile neutropenia | -0.120 | 0.0209 |
| Diarrhoea | -0.047 | 0.0082 |
| Fatigue | -0.094 | 0.0163 |
| Asthenia (weakness) | -0.094 | 0.0163 |
| Leucopenia | -0.090 | 0.0157 |
| Back pain | -0.069 | 0.0120 |
| Anaemia | -0.125 | 0.0217 |
| Thrombocytopenia | -0.090 | 0.0157 |
| Pulmonary embolism | -0.145 | 0.0252 |
| Dehydration | -0.151 | 0.0263 |
| Nausea/vomiting | -0.076 | 0.0131 |
| Bone pain | -0.069 | 0.0120 |
| Deep vein thrombosis | -0.160 | 0.0278 |
| Neuropathy | -0.116 | 0.0202 |

*5.2.10 Deterministic cost-effectiveness results presented by the manufacturer*

Following the clarification questions asked by the ERG the manufacturer altered the values of some parameters within the model: a value of 2.97 days for total inpatient days per neuropathy episode replaced the previous figure of 2.77; the value for the risk ratio for neutropenia prophylaxis, previously left blank, was updated to 0.077; the risk of AEs is now divided by 365.25 instead of 365; and the disutility for pulmonary embolism is corrected to 0.145 instead of 0.245. These changes had a marginal effect on the results, increasing the manufacturer's deterministic base case incremental cost effectiveness ratio (ICER) from £74,908 to £74,938 per QALY gained. It is commented that the change regarding the risk ratio for neutropenia prophylaxis would not affect the deterministic ICER, only the sensitivity analyses conducted.

Additionally, the manufacturer provided an updated model that allowed probabilistic sensitivity analyses to be conducted whilst using the Kaplan-Meier data. For each intervention, the methodology used the same 'random seed' to ensure coherence between PFS and OS; it is unclear what bias, if any, is introduced by this. Further details are provided in section 5.2.12.

Only the revised model will be detailed and critiqued.

Plots of the Markov trace for each intervention within the manufacturer's deterministic base case are provided in Figures 3 and 4.

**Figure 3: The Markov trace for cabazitaxel in the manufacturer's deterministic base case**

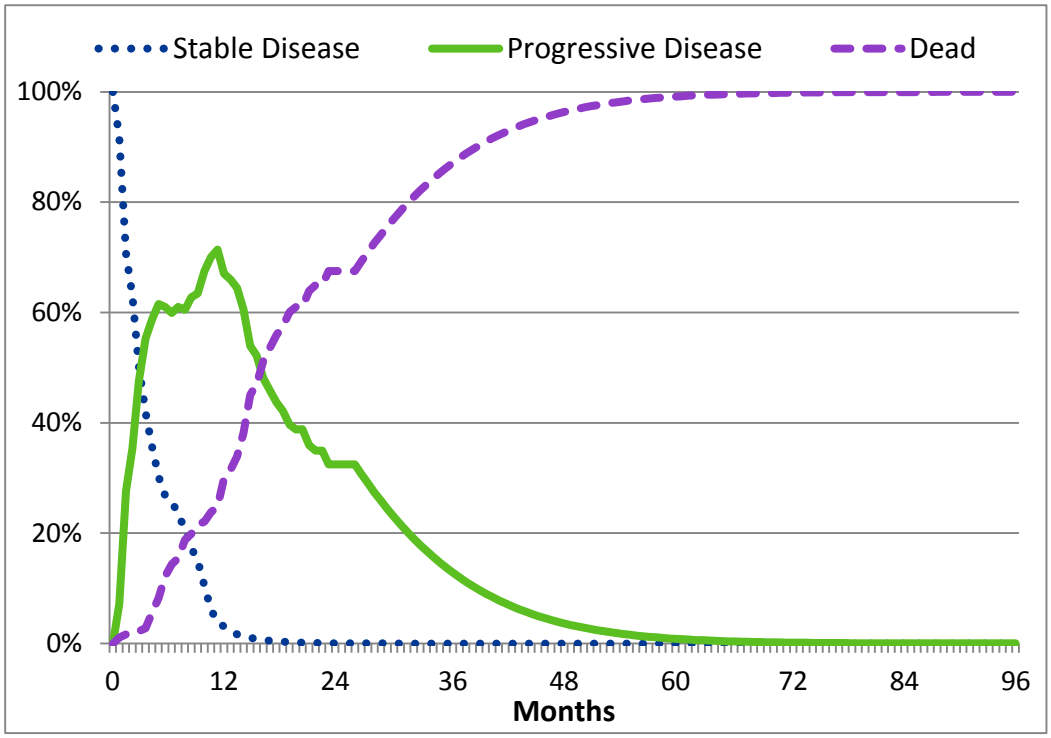
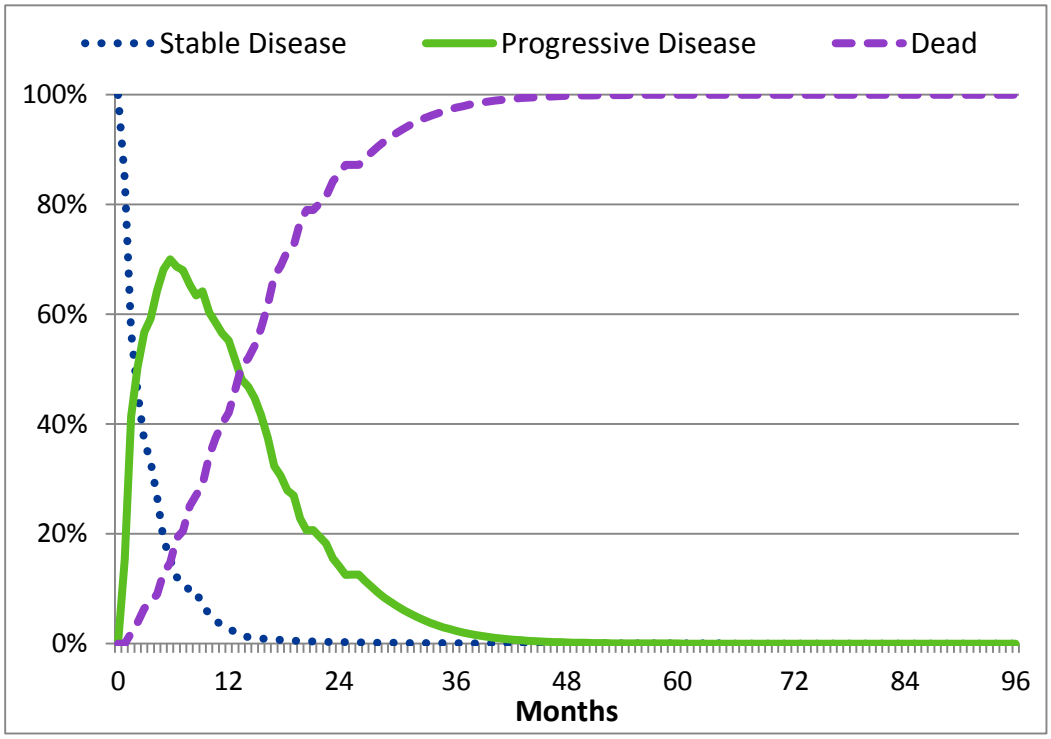



**Figure 4: The Markov trace for mitoxantrone in the manufacturer's deterministic base case**




The estimated costs and QALYs in the base case are provided in Table 30. Figures 5 and 6 show the constituent parts of costs and QALYs for the cabazitaxel and mitoxantrone arms in terms of SD, PD, and death.

**Table 30: Deterministic base case results**

| | Total Costs (£) | Total QALYs | Δ Cost (£) | Δ QALY | Cost per QALY (£) |
|---|---|---|---|---|---|
| Mitoxantrone | 13,047 | 0.849 | | | |
| Cabazitaxel | 35,372 | 1.147 | 22,325 | 0.298 | 74,938 |

**Figure 5: The breakdown of costs by constituent health state**

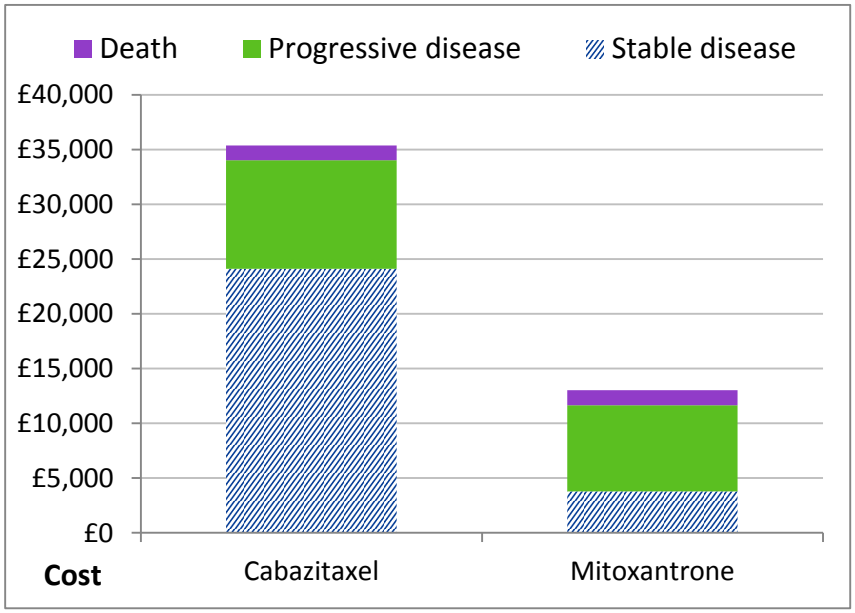
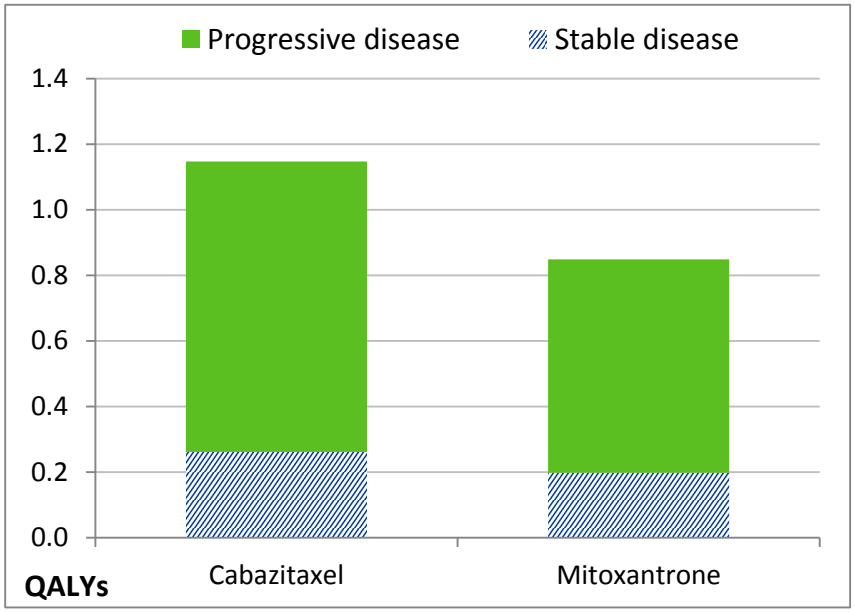



**Figure 6: The breakdown of QALYs by constituent health state**



*5.2.10 Sensitivity analyses presented by the manufacturer*

The manufacturer conducted scenario analyses (defined as using an alternative assumption for a parameter) and deterministic one-way sensitivity analyses (where the current value was subject to an increase or a decrease to assess the robustness of the ICER to changes in this parameter). A list of the alternative scenarios considered is provided on page 131 of the MS, whilst details of the one-way sensitivity analysis are on page 132. In addition, the model had the functionality to estimate the cost-effectiveness of cabazitaxel in the alternative population subgroups.

*Sensitivity analyses presented by the manufacturer regarding the modelled population*

The results produced from the alternative subgroups are provided in Table 31. These have been generated by the ERG using the submitted model.

**Table 31: Deterministic results using the alternative subgroups**

| | **Total Costs (£)** | **Total QALYs** | **Δ Cost (£)** | **Δ QALY** | **Cost per QALY (£)** |
|---|---|---|---|---|---|
| Base case | | | | | |
| Mitoxantrone | 13,047 | 0.849 | | | |
| Cabazitaxel | 35,372 | 1.147 | 22,325 | 0.298 | 74,938 |
| | | | | | |
| Subgroup 1 : The entire TROPIC population | | | | | |
| Mitoxantrone | 12,724 | 0.880 | | | |
| Cabazitaxel | 34,093 | 1.133 | 21,368 | 0.244 | 87,684 |
| | | | | | |
| Subgroup 2 : European patients within TROPIC | | | | | |
| Mitoxantrone | 12,736 | 0.875 | | | |
| Cabazitaxel | 34,703 | 1.174 | 21,966 | 0.260 | 84,540 |
| | | | | | |
| Subgroup 3 : Patients within TROPIC who received ≥ 225mg/m$^2$ of first-line docetaxel and with ECOG 0 or 1 | | | | | |
| Mitoxantrone | 13,085 | 0.916 | | | |
| Cabazitaxel | 34,493 | 1.190 | 21,408 | 0.259 | 82,538 |

*Sensitivity analyses presented by the manufacturer regarding an updated hazard ratio for overall survival*

On page 63 of the MS the manufacturer discusses the availability of a more recent HR for death than that used. 'The HR used was 0.70 (95% CI, 0.59–0.83) in favour of cabazitaxel corresponding to a 30% reduction in risk of death.[22] An updated analysis was performed almost six months later, after 585 (rather than 513) deaths had occurred, and has been presented at ASCO, but has not yet been published in a peer-reviewed publication. The updated analysis found identical median survival values with a HR of 0.72;[80] this submission uses the HR reported in the regulatory submissions and peer-reviewed Lancet publication'. The ERG asked the manufacturer to clarify the effect of using the updated HR on the ICER (Clarification Question A1).

The manufacturer provided a comparison of the original and updated OS data for the entire TROPIC population (reproduced in Table 32) and for the base case (reproduced in Table 33). The manufacturer reports that, for the base case, the use of the updated OS data had little effect on the ICER (assuming fitted curves used throughout), increasing the cost per QALY from £82,950 to £82,963.

**Table 32: Comparison of original and updated OS data for whole TROPIC population (N=755)**

| OS | MTX+PRED | | | CBZ+PRED | | | CBZ+PRED vs. MTX+PRED | | |
|---|---|---|---|---|---|---|---|---|---|
| | Number dead / N (%) | median survival (95% C.I.) | mean survival | Number dead / N (%) | median survival (95% C.I.) | mean survival | Hazard Ratio (HR) | Median difference | Mean difference |
| Updated OS | 308/377 (81.7%) | 12.7 (11.5–13.7) | 14.5 | 277/378 (73.3%) | 15.1 (14.0–16.5) | 18.5 | 0.72 (0.61–0.84) | 2.4 | 4.0 |
| Original OS | 279/377 (74.0%) | 12.7 (11.6–13.7) | 14.0 | 234/378 (61.9%) | 15.1 (14.1–16.3) | 18.2 | 0.70 (0.59–0.83) | 2.4 | 4.2 |

**Table 33: Comparison of original and updated OS data for European patients with ECOG PS 0, 1 and with ≥ 225 mg/m² of previous docetaxel ([redacted])**

| | MTX+PRED | | | CBZ+PRED | | | CBZ+PRED vs. MTX+PRED | | |
|---|---|---|---|---|---|---|---|---|---|
| | Number dead / N (%) | Median survival (95% C.I.) | Mean survival | Number dead / N (%) | Median survival (95% C.I.) | Mean survival | Hazard Ratio (HR) | Median difference | Mean difference |
| Updated data-set | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Original data-set used in submission | 117/159 (73.6%) | [redacted] | [redacted] | 109/181 (60.2%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*Scenario analyses undertaken by the manufacturer*

The scenario analyses undertaken by the manufacturer were conducted before the amendments to the model after the ERG clarification questions, and are therefore compared with a base case ICER of £74,908. The full breakdown of costs and QALYs are provided in pages 143 to 147 of the MS; for brevity, Table 34 only presents the incremental costs and QALYs, and the corresponding ICER for an evaluation of cabazitaxel and mitoxantrone.

**Table 34: The results from scenario analyses**

| | **Δ Cost (£)** | **Δ QALY** | **Cost per QALY (£)** |
|---|---|---|---|
| Base case | 22,325 | 0.298 | 74,908 |
| Fitted curves used throughout | 23,088 | 0.278 | 82,950 |
| Using a Weibull distribution for PFS in the mitoxantrone arm | 22,310 | 0.298 | 74,786 |
| Post-second-line treatment set to that of a UK audit rather than Tropic | 22,642 | 0.298 | 75,972 |
| No vial wastage assumed | 18,159 | 0.298 | 60,928 |
| Using UK-estimated BSA rather than that from Tropic | 22,354 | 0.298 | 75,003 |
| Using UK-specific G-CSF use | 22,146 | 0.278 | 74,387 |
| Using the decrement in utility between SD and PD estimated from Sandblom *et al*.[90] | 22,325 | 0.293 | 76,171 |
| Excluding SAE-related disutilities | 22,325 | 0.300 | 74,536 |
| Assuming equal costs post-progression for cabazitaxel and mitoxantrone treated patients | 20,329 | 0.298 | 68,210 |

The ERG believes that three of these scenarios (no vial wastage assumed, excluding SAE-related utilities, and assuming equal costs post-progression) are not appropriate. The clinical advisors to the ERG indicate that vial sharing would not be feasible given the proposed numbers of patients to be treated; the disutilities associated with SAE are tangible; and the prolonged survival associated with cabazitaxel will incur costs for those patients within the PD state.

For the remaining scenarios, which the ERG believes are plausible alternatives, it is seen that only the use of the fitted curve makes a marked impact on the ICER, increasing the value to £82,950 per QALY.

A scenario analysis was conducted by the manufacturer during the clarification process (A11) where patients dying within 30 days of randomisation were excluded from the analyses. This is possibly pertinent if it is believed that these deaths observed in TROPIC could be preventable with more vigilant treatment of neutropenia. The MS reports on pages 75 and 76 that 'The clinical consequences of neutropenia were the most frequent cause of 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. Following this, no new neutropenic 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.' In this analysis the manufacturer's base case ICER increased to £78,319 per QALY gained. The ERG speculates that the likely reason that the ICER increases is that the parameters for the Weibull distributions fitted to the overall survival data have altered, reducing the tail for cabazitaxel survival, which has resulted in a difference between the mean survival within the cabazitaxel and the mitoxantrone arms.

*Univariate analyses undertaken by the manufacturer*

Univariate sensitivity analyses were also conducted by the manufacturer. These were undertaken before the amendments to the model and are therefore compared with a base case ICER of £74,908. The results are provided on pages 141-142 of the MS. A reproduction of the incremental cost, incremental QALYs and the ICER are provided in Table 35.

**Table 35: The results from univariate sensitivities**

| Analysis | ΔCost (£) | ΔQALY | Cost per QALY (£) |
|---|---|---|---|
| **Base case** | **£22,325** | **0.30** | **£74,908** |
| | | | |
| **Costs** | | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| | | | |
| **Utilities** | | | |
| AE disutilities excluded | £22,325 | 0.30 | £74,536 |
| SD utility +20% | £22,325 | 0.31 | £71,764 |
| SD utility -20% | £22,325 | 0.28 | £78,341 |
| PD utility +20% | £22,325 | 0.34 | £64,733 |
| PD utility -20% | £22,325 | 0.25 | £88,878 |
| | | | |
| **Time horizon** | | | |
| 1 year | £19,699 | 0.05 | £425,106 |
| 2 years | £20,418 | 0.12 | £168,895 |
| 3 years | £21,520 | 0.23 | £93,882 |
| 5 years | £22,279 | 0.29 | £75,694 |
| 10 years | £22,325 | 0.30 | £74,908 |
| | | | |
| **Discount rates** | | | |
| Costs: 0%, Effects: 0% | £22,695 | 0.32 | £70,705 |
| Costs: 3.5%, Effects: 0% | £22,346 | 0.32 | £69,618 |
| Costs: 0%, Effects: 3.5% | £22,674 | 0.30 | £76,078 |
| Costs: 6%, Effects: 6% | £22,076 | 0.28 | £78,038 |
| | | | |
| **State costs** | | | |
| Caba & Mitox drug & adm cost -50% | £12,501 | 0.30 | £41,945 |
| Caba & Mitox post 2nd line (drugs & adm) cost -50% | £22,231 | 0.30 | £74,592 |
| Caba & Mitox other costs SD -50% | £22,150 | 0.30 | £74,320 |
| Caba & Mitox other costs PD -50% | £21,411 | 0.30 | £71,840 |
| AE costs -50% | £22,171 | 0.30 | £74,389 |
| | | | |
| **Proportion with G-CSF as primary prophylaxis** | | | |
| Caba & Mitox: 0% | £22,146 | 0.30 | £74,387 |
| Caba & Mitox: 20% | £22,128 | 0.30 | £74,268 |
| Caba & Mitox: 40% | £22,111 | 0.30 | £74,150 |
| Caba & Mitox: 60% | £22,094 | 0.30 | £74,031 |
| Caba & Mitox: 80% | £22,077 | 0.30 | £73,913 |

| | | | |
|---|---|---|---|
| Caba & Mitox: 100% | £22,060 | 0.30 | £73,795 |

The ERG does not believe that the univariate analyses undertaken by the manufacturer r[redacted].

The amounts by which the utilities have been varied within the scenario analyses are arbitrary. In addition, the utilities for stable disease and progressive disease have been varied separately, leading to improbable combinations of values. Of the four utility scenarios considered, two lead to the utility for progressive disease being larger than that for stable disease (utility of SD = [redacted], utility of PD = [redacted]; utility of SD = [redacted], utility of PD = [redacted]), whilst in the other two the difference between the two utility states is greater than [redacted] (utility of SD = [redacted], utility of PD = [redacted]; utility of SD = [redacted], utility of PD = [redacted]). However, the results show that the choice of utility values, in particular that of progressive disease, can have a large impact on the ICER, placing more emphasis on obtaining robust estimates from the EAP.

Consistent with evaluations of technologies where there is a relatively large cost borne in the initial stages, with a resulting elongated survival, the ICER decreases as the time horizon lengthens. The ERG believes that the time horizon used by the manufacturer in their base case is appropriate. Discounting has some effect on the ICER but the manufacturer provides no reason as to why different rates than 3.5% for both costs and benefits should be used. It is seen that altering the costs assumed post-second-line, or other costs accrued within stable disease or progressive disease, have little effect on the ICER; as before, the ERG do not consider a sensitivity analysis on the [redacted]. The assumed proportion of patients receiving prophylactic G-CSF treatment has minimal effect on the ICER.

*5.2.11 Probabilistic sensitivity analyses presented by the manufacturer*

For the manufacturer's probabilistic uncertainty analyses, the assumed distributions for the parametric curves and the utilities are shown in Table 36. The assumed uncertainties in the remaining parameters incorporated into the probabilistic uncertainty analyses are provided in Appendix 3. It is noted that the utilities for stable disease and progressive disease were sampled independently, which resulted in the utility for progressive disease being assumed to be greater than the utility for stable disease on over 3% of simulations.

**Table 36: The distributions for key variables within the manufacturer's probabilistic sensitivity analyses**

| Parametric Curves | Distribution | Shape* | Scale* | Mean (months) | 95% CI |
|---|---|---|---|---|---|
| OS: Cabazitaxel | Weibull | 1.587 | 0.0076 | [redacted] | See text |
| OS: Mitoxantrone | Weibull | 1.693 | 0.0089 | [redacted] | |
| PFS: Cabazitaxel | Weibull | 1.195 | 0.170 | [redacted] | |
| PFS: Mitoxantrone | Log-normal | 0.693 | 0.937 | [redacted] | |
| **Utilities** | **Distribution** | **Alpha** | **Beta** | **Mean** | **95% CI** |
| Stable Disease | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Progressive Disease | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

* Note that the values for the lognormal distribution represent mean and standard deviation

Where possible, standard errors for the variables are derived from the TROPIC trial. Simulated values for the parametric curves are taken from a Cholesky decomposition in order to maintain correlations. For proportions included in the TROPIC trial their standard error is calculated as:

$$SE = \sqrt{\frac{p(1-p)}{n}}$$

Proportions estimated using expert opinion have their standard error estimated by the Beta-Pert method; SE = (Maximum value – minimum value) / 6. The manufacturer assumed that these maximums and minimums were equal to the point estimate plus or minus 25%. This is the same as assuming that the standard error is equal to the expected value divided by twelve. The Beta-Pert methodology is also applied to average length of stay data.

Uncertainty in the Kaplan-Meier curves was not included in the initial model. However, in response to the ERG's clarification letter, it was incorporated in the manufacturer's revised model. To achieve this, the manufacturer used the observed data to model beta distributions at each time point (for a probability 'p', the alpha parameter is equal to p times the sample size, and the beta parameter is equal to 'one minus p' times the sample size). For each simulation of the probabilistic sensitivity analyses, a random percentile is simulated from these beta distributions. To account for the fact that the survival percentages at different time points are not independent, the same random percentile – which the manufacturer refers to as a 'random seed' – is simulated at all time points and for both OS and PFS (within a given probabilistic sensitivity analyses simulation and for a given drug). This methodology is likely to overestimate the uncertainty in the decision as extreme values for the random seed would be applied throughout the modelling horizon.

Whilst the manufacturer provided a cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC), the actual ICER was not reported (Clarification Response A13). The ERG ran 2,000 simulations to provide an estimate of the ICER. The mean ICER was £75,682, range (£45,760 - £890,372); 95% of all the ICERs fell into the range £54,749 to £148,647.

A cost-effectiveness plane and cost-effectiveness acceptability curve for the manufacturer's base case are shown in Figures 7 and 8.

**Figure 7: The cost-effectiveness plane comparing cabazitaxel with mitoxantrone**

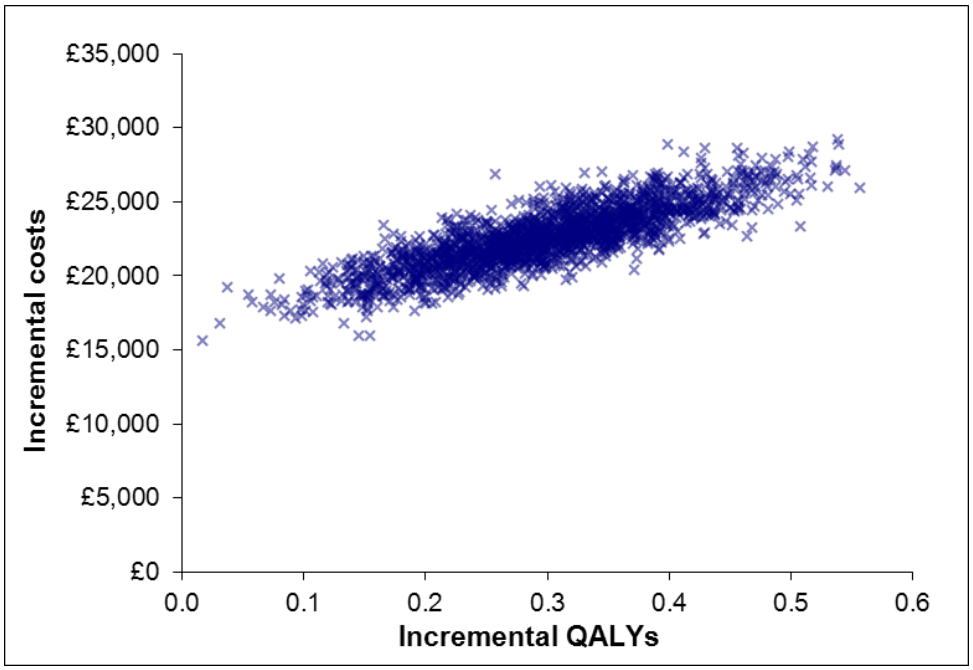
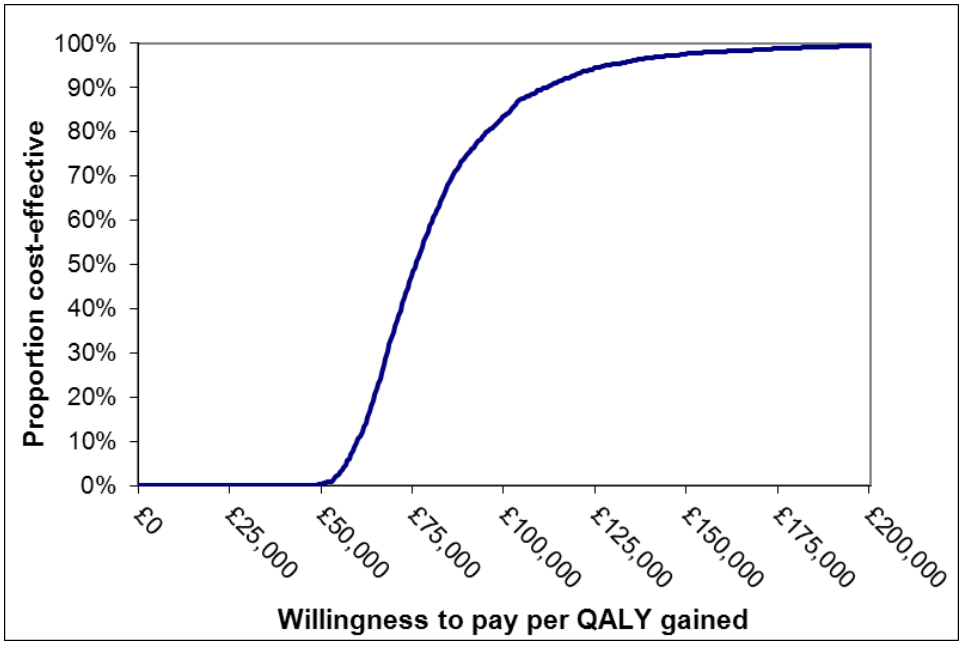



**Figure 8: The CEAC comparing cabazitaxel with mitoxantrone**




*5.2.12 ERG critique of the submitted model*

Generally, the ERG is satisfied with the model structure presented by the manufacturer. The use of a relatively simple model (employing only three states) enhances its transparency whilst the inclusion of additional costs (for example due to adverse events) reflects the clinical pathway likely to be encountered by patients on the drug.

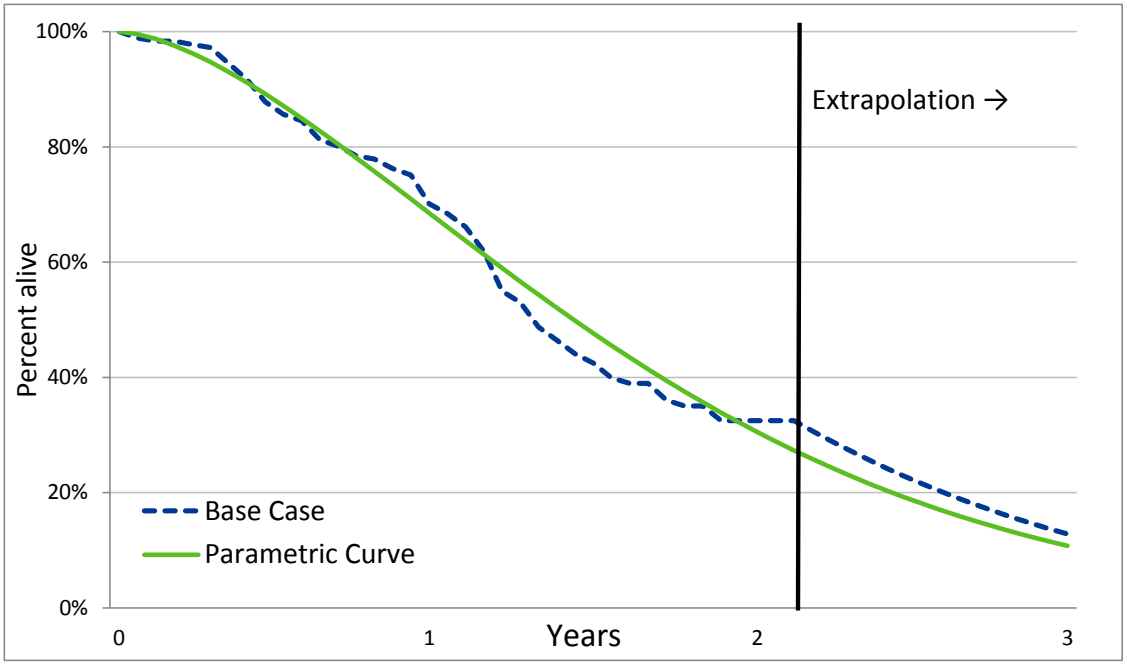
However, the ERG identified a number of concerns, of varying severity. These are discussed below.

*Discussion of the use of parametric curves versus the use of the Kaplan-Meier data*

The main source of data for the *de novo* model is the TROPIC trial, which only includes a small number of patients from England and Wales. The ERG recommends that parametric curves be used throughout instead of Kaplan-Meier curves for two reasons. First the Kaplan-Meier curves may over-fit the data, and thus model patterns that would not repeatedly occur whereas the use of parametric curves tries to avoid this by smoothing the data to an assumed underlying pattern, which is more likely to generalise to other populations.

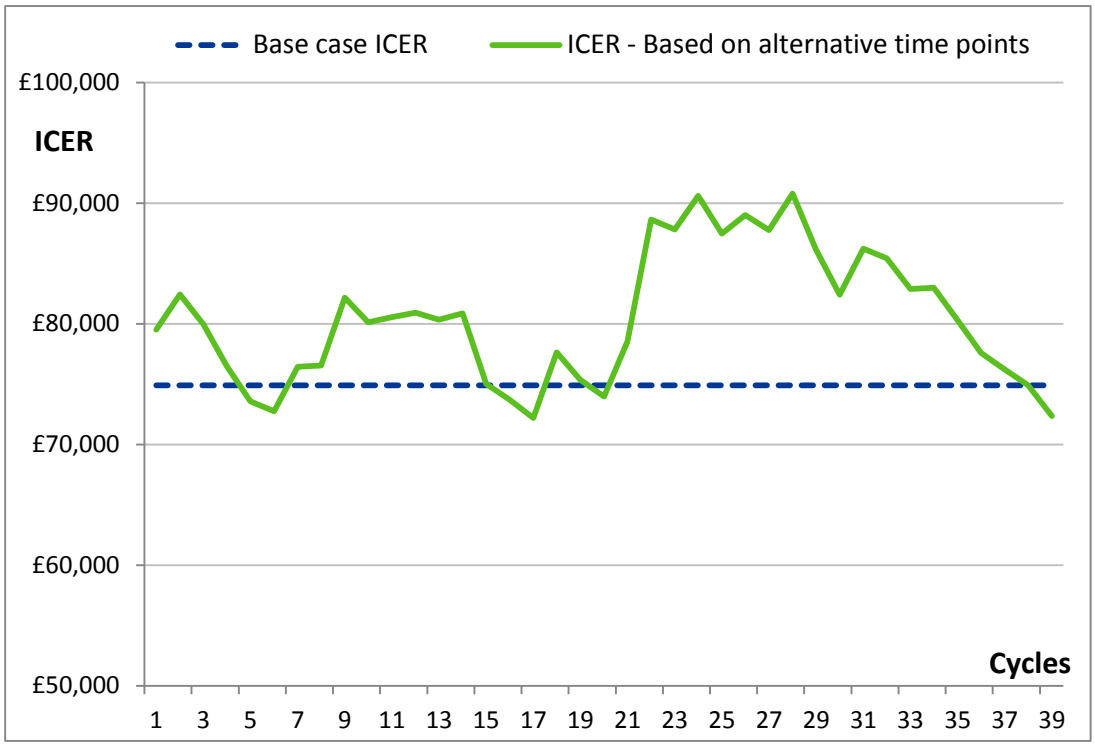
Second, the selection of the time point at which the proportions from the fitted curve is preferred to the Kaplan-Meier data is arbitrary, and can significantly affect the ICER. Figure 9 shows that, for OS in cabazitaxel, when the proportions from the parametric curve are adopted, the Kaplan-Meier data estimate that more patients are alive than would be estimated from the Weibull distribution. The discrepancy between the PFS data and the OS data for mitoxantrone is much less pronounced and has not been provided.

**Figure 9: The discrepancy in the parametric curve fit and the Kaplan-Meier data for overall survival in the cabazitaxel arm in the manufacturer's base case**




In response to a clarification request (A10), the manufacturer reported the change in the ICER when assuming different time points at which the parametric curve is used for overall survival. These data have been plotted in Figure 10 and show that the time point chosen has a marked effect on the ICER, with the time point chosen by the manufacturer (cycle 38) being one of the relatively lower values.

**Figure 10: The sensitivity of the ICER to the point at which the Kaplan Meier curves for overall survival are replaced with parametric curves**




Due to the instability of the ICER based on the time point at which the parametric curve is used and the possibility that directly using the Kaplan-Meier curves may overfit the data, the ERG believes that the use of the parametric curves throughout the model is a preferable approach, and do not concur with the manufacturer's rationale for using the Kaplan-Meier data (clarification response A9).[2]

The ERG believes, however, that, should the Kaplan-Meier data be used, the most appropriate time point in which to switch to the parametric curve would be at cycle 34 (week 102 or 1.96 years), where the Kaplan-Meier data and the Weibull data for OS in the cabazitaxel arm are approximately equal (Figure 9). In this instance, the deterministic ICER is £82,997, compared with £82,950 in the manufacturer's base case when the parametric distributions are used throughout; the ERG notes the similarity of these values.

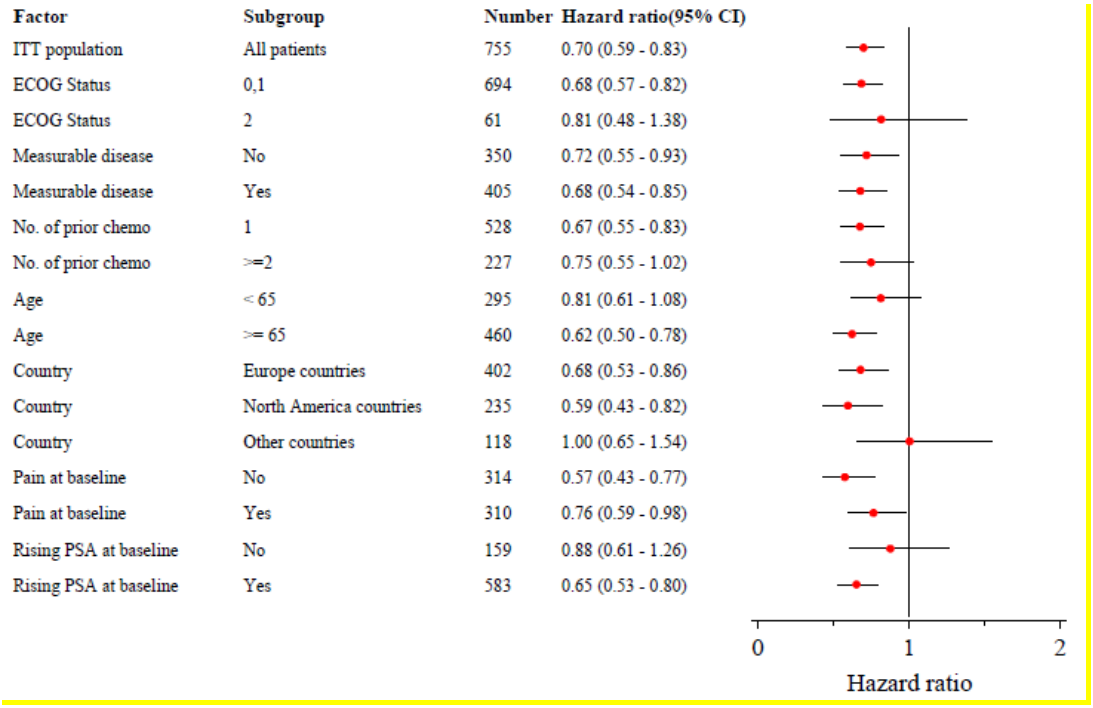
*The patient population*

The ERG believes that the patient population selected by the manufacturer within the base case is not the most appropriate. The entire TROPIC population was restricted by the manufacturer to patients 'with an ECOG performance status of 0 or 1, who have received at least 225 mg/m$^2$ docetaxel, and is based on European data from TROPIC'.

The manufacturer provided a Forest plot that detailed the hazard ratio by subgroup (replicated in Figure 11. Whilst it is seen that the midpoint value for 'other' countries is noticeably higher than

those for Europe and North America, it is conceivable that the hazard ratio may actually be lower in this region because of its wide associated CIs.

**Figure 11: Hazard ratio of overall survival for baseline data (cabazitaxel and prednisone/prednisolone versus mitoxantrone and prednisone/prednisolone; ITT population)**




The ERG believes that, in order to conduct sub-group analyses, there must be an *a priori* belief and rationale that the results may differ between subgroup, and that a formal statistical test of interaction between the outcome and the subgroup should be performed. In the manufacturer's response to the clarification question (A2) it was reported that 'There was no *a priori* clinical hypothesis for a difference in treatment effect by region. However, treatment practices vary between different countries and these different practices can affect treatment outcomes. The interaction of treatment by region is not statistically significant. This is true of the whole population (p value =0.1535)'. These statements combined do not convince the ERG that restricting the base case population to European patients can be justified.

The interaction test between those patients with an ECOG PS of 0 or 1 patients who received ≥ 225 mg/m$^2$ docetaxel was less statistically significant (p = 0.4098), although the ERG were more prepared to accept the validity of this sub-group. The advice provided by the clinical advisors to the ERG was that it was extremely unlikely those patients with an ECOG PS value of 2 would be treated. Additionally all patients should have received at least 225 mg/m$^2$ docetaxel prior to embarking on treatment with cabazitaxel and that it is plausible that the efficacy of cabazitaxel would be lower in patients who had received insufficient docetaxel. The *a priori* belief or this subgroup is also supported

by an amendment in the TROPIC protocol (after the recruitment of 59 patients) to exclude patients who had not received sufficient docetaxel. The ERG does not believe that restricting the population to this subgroup is inappropriate.

The ERG base case population is thus Subgroup 3 as defined by the manufacturer (patients who received ≥ 225 mg/m$^2$ of first-line docetaxel and with an ECOG PS 0 or 1).

*Estimates of Utility*

As of July 2011, only interim results from the EAP are available for patients with stable disease, which are associated with wide CIs, with no data reported for progressive disease. [redacted] In order to obtain a more robust ICER, it is imperative that more data regarding the utility in each health state is collected.

As previously reported, the utilities for stable disease and progressive disease were sampled independently, which resulted in the utility associated with the value for progressive disease being assumed to be greater than that for stable disease on over 3% of simulations. The violation of monotonicity appears implausible.

*Discounting*

A very minor error in the implementation of the discount rate was identified by the ERG. The manufacturer attempted to implement a continuous discounting rate (see Clarification Response A28) but used a value of 0.035. For continuous discounting, a rate of 0.0344 (calculated from ln (1.035)) should be used. This amendment made little difference to the results, reducing the manufacturer's deterministic base case from £74,938 to £74,865.

### 5.3 Additional work undertaken by the ERG

In order to provide an estimation of the ERG base case ICER, the ERG undertook analyses having altered the manufacturer's base case in the following manners:

- Using the parametric curves for the entire duration of the modelling horizon
- Altering the population to Subgroup 3 (patients who received ≥ 225 mg/m$^2$ of first-line docetaxel and with an ECOG PS 0 or 1)
- Ensuring monotonicity by calculating the utility of progressive disease from the value for stable disease, assuming a mean decrement of 0.07 as suggested by the Sullivan paper,[89] with an arbitrarily defined standard deviation of 0.02

- Correcting the discounting rate to use a continuous value of ln(1.035).

In addition, a number of sensitivity analyses have been conducted to determine the robustness of the base case ERG ICER to altering parameter values within the model.

The markov traces for the ERG base case are provided in Figure 12 for cabazitaxel and Figure 13 for mitoxantrone.

**Figure 12: Markov trace for cabazitaxel in the ERG base case**

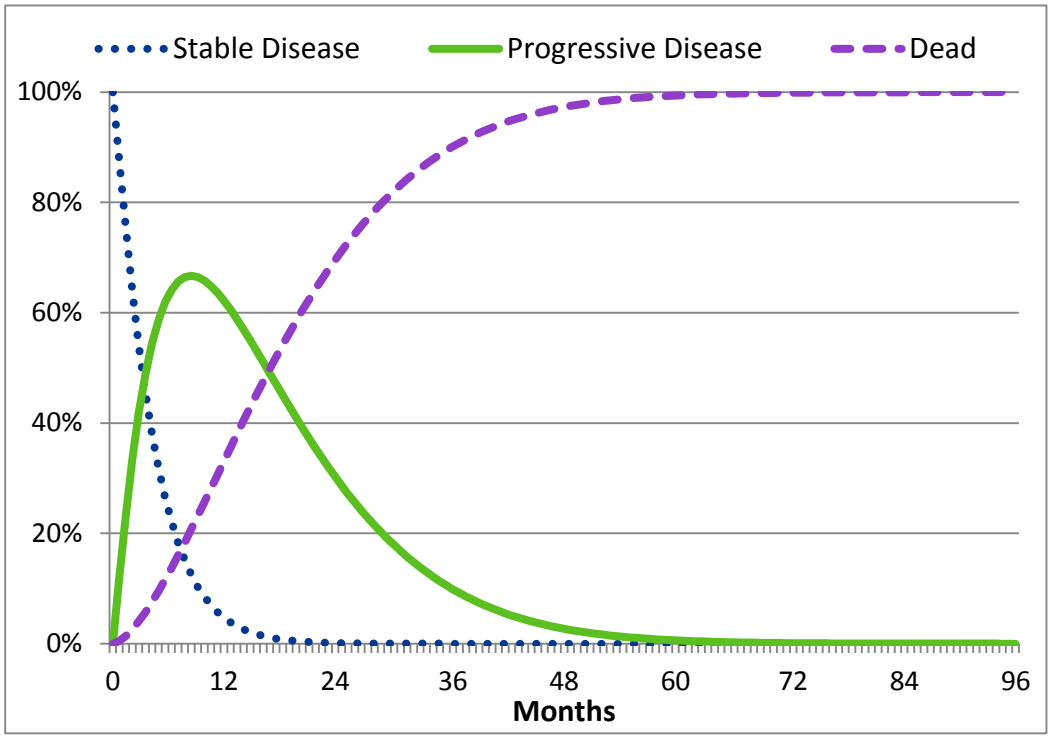
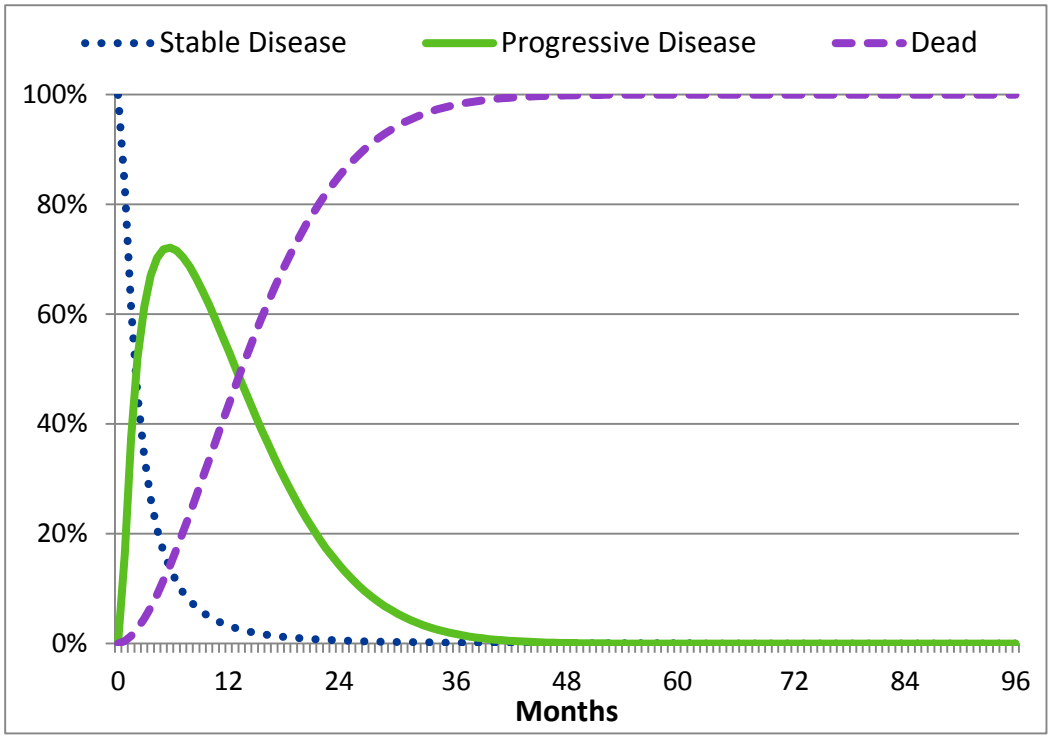


**Figure 13: Markov trace for mitoxantrone in the ERG base case**




## 5.4 Conclusions

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

The uncertainty in the ICER is mainly driven by choice of subgroup to use, the choice of whether to use the Kaplan-Meier data directly, and the availability of robust data regarding the utility in the stable and progressive disease states. The ERG has provided a commentary on these issues in section 5.2.12. Both the use of a parametric curve for the entire distribution and increasing the patient population by including non-European patients will increase the ICER and be less favourable to cabazitaxel. It is unclear what effect, if any, fuller data regarding the utility values associated with stable disease and progressive disease would have on the ICER.

A further uncertainty relates to the effect that the more recent OS data, which altered the HR from 0.70 to 0.72 for the entire TROPIC population, would have on the population used within the ERG base case.

An additional uncertainty is whether the deaths observed within TROPIC could be prevented if neutropenia is appropriately managed, particularly when patients are within the early stages of cabazitaxel treatment. If this is the case, then the ICER is likely to be greater than that estimated within the manufacturer's base case.

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

In order to provide an indication of the key drivers to the change in the ICER, three of the four amendments detailed in 5.3 were made independently to the deterministic base case, and then with all three made in combination. The amendment regarding monotonicity of utility values was not undertaken as this only affects the results from the probabilistic sensitivity analyses. Results are presented in Table 37. It is seen that the ICER is approaching £90,000.

**Table 37: Changes in deterministic ICER of cabazitaxel compared with mitoxantrone based on the ERG amendments**

| Amendment to the base case | ΔCost (£) | ΔQALY | Cost per QALY (£) |
|---|---|---|---|
| | | | |
| None (base case) | 22,325 | 0.298 | 74,938 |
| Using parametric curves for the entire time horizon | 23,088 | 0.278 | 82,986 |
| Using Subgroup 3 (patients who received ≥225 mg/m$^2$ of 1st line docetaxel and with ECOG PS 0 or 1) | 21,408 | 0.259 | 82,538 |
| Amending discount rate | 22,331 | 0.298 | 74,865 |
| | | | |
| All 3 amendments | 22,233 | 0.248 | 89,476 |

*Probabilistic sensitivity analyses undertaken by the ERG.*

The incremental cost of cabazitaxel was £22,439 with an incremental 0.250 QALYs accrued, resulting in an ICER of £89,684 per QALY gained. This ICER is similar to the deterministic result (£89,476). Note that the model supplied by the manufacturer only saves the incremental values. The cost-effectiveness plane and the CEAC are provided in Figures 14 and 15 respectively.

**Figure 14: The cost-effectiveness plane from the ERG probabilistic sensitivity analyses**

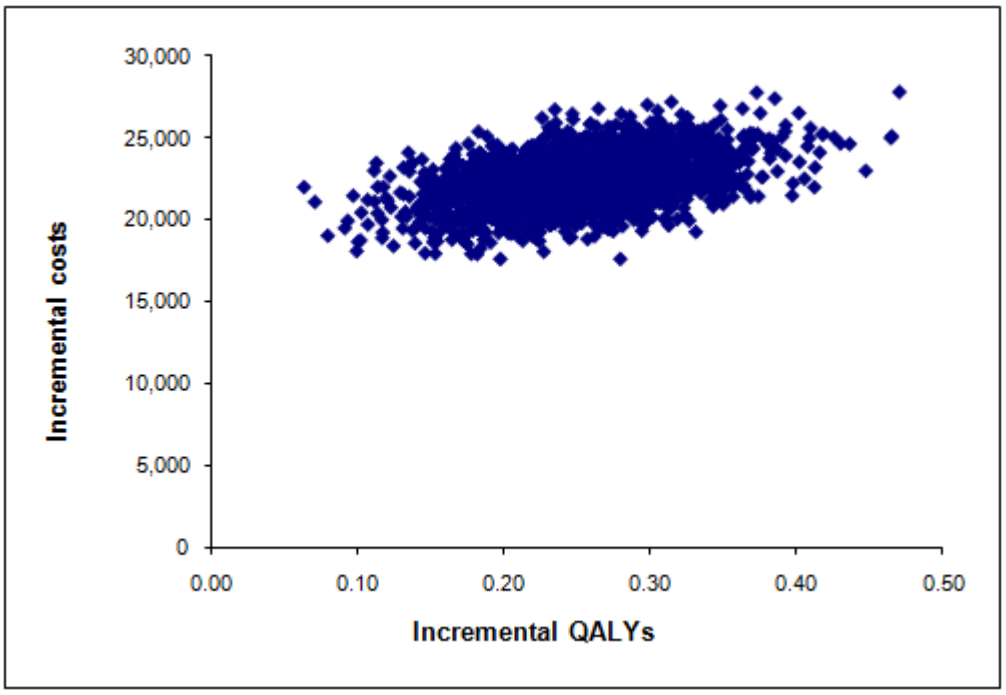
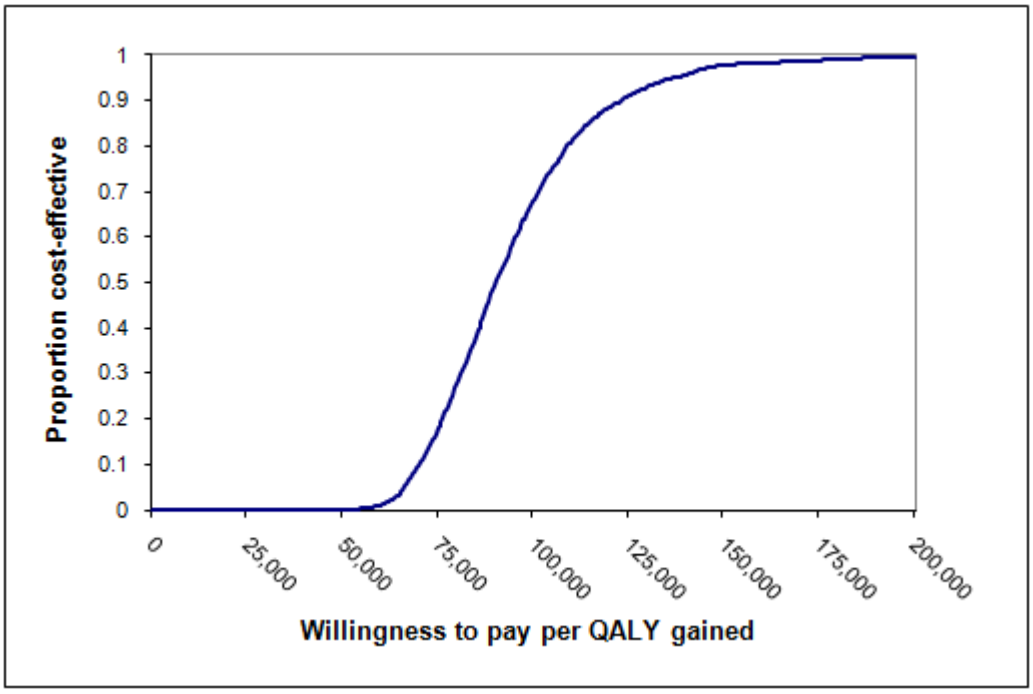



**Figure 15: The CEAC from the ERG probabilistic sensitivity analyses**



**Sensitivity analyses undertaken by the ERG**

The ERG undertook a number of sensitivity analyses to assess the robustness of the ERG-base case ICER to plausible changes. These sensitivities analyses were: using the entire TROPIC population; using the upper and lower 95% CIs for the utility of stable disease estimated from EAP at cycle 2; and using the utility decrement (0.085) taken from Sandblom[90] rather than the 0.070 estimated from Sullivan *et al*.[89] As the results from the deterministic and the probabilistic analyses were similar (£89,476 and £89,684 respectively), the impact of each change has, for computational time reasons, been undertaken only deterministically. It is seen that ICER can be changed markedly by the utility values assumed for PD and SD.

**Table 38: Sensitivity analyses undertaken by the ERG**

| Sensitivity analyses | ΔCost (£) | ΔQALY | Cost per QALY (£) |
|---|---|---|---|
| | | | |
| None (ERG base case) | 22,233 | 0.248 | 89,476 |
| Using Subgroup 1 (entire TROPIC population) | 22,283 | 0.239 | 93,177 |
| Upper 95% of SD from the EAP at cycle 2 ([redacted]) | 22,233 | 0.298 | 74,620 |
| Lower 95% of SD from the EAP at cycle 2 ([redacted]) | 22,233 | 0.199 | 111,719 |
| Utility difference between SD and PD estimated from Sandblom[90] | 22,233 | 0.245 | 90,865 |

The ERG note the sensitivity analyses undertaken by the manufacturer when patients dying within 30 days of randomisation were removed from the analysis which may be relevant if these deaths could be prevented by strictly following the protocol regarding dose modification and delay and treating neutropenia as per ASCO guidelines. This increased the manufacturer's base case ICER by approximately £3500 per QALY; the ICER increased by £8000 for the entire TROPIC population. Similar analyses conducted for the ERG base case led to a £2000 increase in the ICER, from £89,476 to £91,465.

The manufacturer has reported more recent OS data. The effect of this on the manufacturer's base case was limited, increasing the ICER from £82,950 to £82,963 when assuming fitted curves throughout. The effect of utilising the more recent data on the ERG's base case is unknown.

# 7. END OF LIFE

Within this section, the ERG provide relevant information regarding whether cabazitaxel is likely to meet the end of life criteria published by NICE.[93] It is recognised that this will be decided by the relevant NICE appraisal committee and this section may have no bearing upon their decision.

The criteria published by NICE are (numbers retained from original document):

2.1 This supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied:
2.1.1 The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
2.1.2 There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;
2.1.3 The treatment is licensed or otherwise indicated, for small patient populations.

Each criterion is evaluated in turn.

*Life Expectancy*
In the deterministic ERG base case, patients who do not receive cabazitaxel have a mean life expectancy of 1.17 years (approximately 14 months). As such, criterion 2.1.1 is likely to be fulfilled. It is noted that the probabilistic results only saved incremental life years and thus the corresponding results from probabilistic analyses were not available.

*Extension of Life*
In the probabilistic ERG base case, the mean extension of life is estimated to be 0.35 years (approximately 4 months). These results were relatively robust in that cabazitaxel produced a survival advantage in each of the 2000 probabilistic analyses run by the ERG (Figure 14). The median extension of life in the ERG base case was reported by the manufacturer to be [redacted]

*Licensed Indication*
Cabazitaxel (in combination with prednisolone) is licensed only for the treatment of mHRPC previously treated with docetaxel. The manufacturer estimates that fewer than 2,000 patients per year would be eligible following failure of docetaxel treatment. As such, although there is no formal

definition of a small patient population, it is likely that criterion 2.1.3 is fulfilled based on previous NICE guidance.

# 8. CONCLUSIONS

The ERG did not identify any issues relating to the manufacturer'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 manufacturer reported a deterministic base case ICER of £74,938. However, the ERG has concerns regarding two important assumptions used in formulating the manufacturer's base case:

- The use of Kaplan-Meier curves (where the data were deemed sufficiently reliable) in preference to parametric curves, and

- Restricting the economic evaluation to only European patients.

As detailed in section 5.2.12 the ERG believes that using parametric curves throughout and having a patient population of 'patients who received ≥ 225 mg/m$^2$ of first-line docetaxel and with an ECOG PS 0 or 1' represents a more accurate base-case.
Altering these two assumptions and slightly amending the discount rate (which has only a minor effect on the ICER) results in the ERG's deterministic base case ICER being £89,476; the probabilistic value was similar (£89,684). This is considerably higher than the manufacturer's base case estimate (£74,938).

An additional key source of uncertainty relates to the utilities for both progressive disease and stable disease. The ERG notes that the manufacturer has an on-going study aimed at collecting utility data, but at the present time the available evidence is weak. The choice of alternative, plausible, values was shown to have a considerable impact on the ICER.

There was additional uncertainty regarding whether the deaths observed in TROPIC within 30 days of randomisation could be preventable with more vigilant treatment of neutropenia; exploratory analyses indicate that this may slightly increase the ICER, by £2000 in the ERG base case.

Finally, the adverse event data observed within the TROPIC RCT was of concern, the FDA recommended a review of renal toxicity and a submission of updates from active RCTs for three years after the US approval date (2010); data are currently not available. Therefore, caution may be prudent until these data emerge.

### 8.1 Implications for research

The utility of patients with mHRPC in the stable disease and progressive disease state needs to be researched more fully. It is commented that the manufacturers are running such a study but it is unclear how many patients will ultimately be followed-up. These values have a considerable effect on the ICER.

Further research on the toxicity of cabazitaxel is required. The ERG notes that these trials have been requested by the FDA.

Further research may be required to investigate if there are any genuine variations in the treatment practices for cabazitaxel and mitoxantrone by geographical region

Additional research should be conducted (even if only through the collection of observational data) to ascertain whether more vigilant treatment of neutropenia can reduce the number of observed deaths in the period following initiation with cabazitaxel treatment.

**Appendix 1: Cabazitaxel trials identified by the ERG in ClinicalTrials.gov**

1 Recruiting A Study to Evaluate the Effects of Combining Cabazitaxel With Cisplatin Given Every 3 Weeks in Patients With Advanced Solid Cancer

**Condition:** Solid Cancer
**Intervention:** Drug: cabazitaxel (XRP6258)

2 Recruiting Dose-Escalation, Safety, Pharmacokinetics Study of Cabazitaxel With Gemcitabine In Patients With Solid Tumor

**Condition:** Neoplasms, Malignant
**Interventions:** Drug: cabazitaxel (XRP6258); Drug: gemcitabine; Drug: midazolam

3 Recruiting Safety and Pharmacokinetic Study of Cabazitaxel in Patients With Advanced Solid Tumors and Liver Impairment

**Condition:** Neoplasm Malignant
**Intervention:** Drug: Cabazitaxel (XRP6258)

4 Recruiting Early Access to Cabazitaxel in Patients With Metastatic Hormone Refractory Prostate Cancer Previously Treated With a Docetaxel-containing Regimen

**Condition:** Prostate Cancer Metastatic
**Intervention:** Drug: CABAZITAXEL

5 Not yet recruiting Study of Cabazitaxel Plus Bavituximab as Second-line Chemotherapy for Patients With Castration-resistant Prostate Cancer

**Conditions:** Prostate Cancer; Prostatic Neoplasms
**Intervention:** Drug: Cabazitaxel plus bavituximab

6 Active, not recruiting Effect of Cabazitaxel on the QTc Interval in Cancer Patients

**Condition:** Neoplasms, Malignant
**Intervention:** Drug: Cabazitaxel (XRP6258)

7 Completed
Has Results XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer (TROPIC)

**Conditions:** Neoplasms; Prostatic Neoplasms
**Interventions:** Drug: cabazitaxel (XRP6258) (RPR116258); Drug: mitoxantrone; Drug: prednisone

8 Not yet recruiting Chemotherapy for Patients With Gastroesophageal Cancers Who Have Progressed After One Prior Chemo Regimen

**Conditions:** Esophageal; Gastrooesophageal Cancer; Gastric Cancer
**Intervention:** Drug: jevtana

9 Recruiting Cabazitaxel at 20 mg/m² Compared to 25 mg/m² With Prednisone for the Treatment of Metastatic Castration Resistant Prostate Cancer

**Condition:** Prostate Cancer
**Interventions:** Drug: cabazitaxel (XRP6258); Drug: Prednisone

10 Recruiting Cabazitaxel Versus Docetaxel Both With Prednisone in Patients With Metastatic Castration Resistant Prostate Cancer

**Condition:** Prostate Cancer
**Interventions:** Drug: Cabazitaxel (XRP6258); Drug: Docetaxel (XRP6976); Drug: Prednisone

11 Recruiting Dose Escalation Study With Cabazitaxel in Combination With Daily Prednisolone in Patients With Hormone Refractory Prostate Cancer

**Condition:** Prostate Cancer
**Interventions:** Drug: Cabazitaxel (XRP6258); Drug: prednisolone

**Appendix 2: Quality assessment of the manufacturer's search strategies**

| Facet | Elements | Review | |
|---|---|---|---|
| | | **Clinical effectiveness** | **Cost effectiveness** |
| **Reporting** | Are the searches systematic? | Yes. | Yes. |
| | Are searches clearly reported? | Yes, database coverage dates, host platforms clearly provided. | Yes. |
| | Are all strategies given? | Yes, all reported search strategies were provided | Yes. |
| | Are all the appropriate searches carried out? | Yes, it is believed that the adverse events searches would be retrieved in the effectiveness search. The ERG did not find additional studies. | Yes. |
| | Are the searches reproducible? | Yes, despite the different host platforms used. | Yes. |
| | Are the results consistent with the PRISMA diagram? | Yes, clear PRISMA diagrams were given for the cabazitaxel, all RCT and non-RCT searches. | No PRISMA reported. |
| **Source** | Were the core databases searched? | Yes. | Yes including specialist economic evaluation databases e.g. HEED, NHS EED and EconLit |
| | Is the choice of database for the various searches consistent? | List of sources searched for cabazitaxel studies were extensive. Fewer databases were searched for all RCTs and non-RCT studies. | Search for cabazitaxel studies in the clinical effectiveness should have captured economic evaluations. |
| | Were other document type searches missing? | No, bibliographic reference follow-up, hand searching of conference proceedings, ongoing studies search were carried out by the manufacturer. | No. |

| | | | |
|---|---|---|---|
| **Items from the PRESS Checklist for search strategies[94]** | Translation: Is the search question translated well into search concepts? | Cabazitaxel searches (intervention terms only); all RCTs (mHRPC + first line disease + RCT filter); non-RCTs (mHRPC + intervention + non-RCT filter) | Cabazitaxel searches same as clinical effectiveness (intervention terms only); QoL searches (mHRPC + QoL filter) |
| | Operators: Are there any mistakes in the use of Boolean or proximity operators? | Inconsistent use of Boolean for mHRPC RCT searches (see text body). | No. |
| | Subject headings: Are any important subject headings missing or have any irrelevant ones been included? | No, some of the exploded MeSH subject headings/EMTREE terms may be overlapping. | No. |
| | Natural language: Are any natural language terms or spelling variants missing, or have any irrelevant ones been included? Is truncation use optimally? | No, but use of free-text terms should be used consistently between mHRPC RCT and non-RCT searches (see text body). | Inconsistencies of mHRPC terms between effectiveness reviews and QoL searches. |
| | Spelling & syntax: Does the search strategy have any spelling mistakes, system syntax errors, or wrong line numbers? | No. | Ambiguity of 'or sc.fs.' in statement 5 of the QoL Medline search. Minor typographical omission of statement 46 which should read '44 not 45' |
| | Limits: Do any of the limits used seem unwarranted or are any potentially helpful limits missing? | No. but justification for limiting searches since 2000 was not given for mHRPC RCT and non-RCT searches. | No. |
| | Adapted for database: Has the search strategy been adapted for each database to be searched? | The strategies should be adapted consistently between databases i.e. population and intervention term use differed between searches. It appears that the three searches were | Terms for mHRPC should be used consistently between effectiveness review searches. |

| | | | |
|---|---|---|---|
| | | performed independently. | |
| **Overall approach** | Are the search strategies adequate? | Yes. | Yes. |
| | Are strategies sensitive? | Yes. | Yes. |
| | Are strategies well designed? | Yes. | Yes. |
| | Are there any studies missing? | Despite the minor limitations mentioned, the ERG does not consider that any studies were missing at the time of the review. | Despite the minor limitations mentioned, the ERG does not consider that any studies were missing at the time of the review. |

**Appendix 3: The assumed distributions used within the probabilistic sensitivity analyses for parameters deemed non-key by the ERG**

| Variables following the Beta Distribution | Alpha | Beta | Mean | 95% CI |
|---|---|---|---|---|
| 'Normed' Body-Surface Area (mean = 2.01) | 66.77 | 82.72 | 2.01 | 1.89 - 2.12 |
| **Disutilities** | | | | |
| Neutropenia | 30.00 | 303.30 | 0.09 | 0.06 - 0.12 |
| Febrile Neutropenia | 28.98 | 212.48 | 0.12 | 0.08 - 0.16 |
| Diarrhoea | 31.46 | 637.93 | 0.05 | 0.03 - 0.06 |
| Fatigue | 29.86 | 287.81 | 0.09 | 0.06 - 0.12 |
| Asthenia (weakness) | 29.86 | 287.81 | 0.09 | 0.06 - 0.12 |
| Leukopenia | 30.00 | 303.30 | 0.09 | 0.06 - 0.12 |
| Back pain | 30.71 | 414.39 | 0.07 | 0.04 - 0.09 |
| Anaemia | 28.80 | 201.63 | 0.12 | 0.08 - 0.17 |
| Thrombocytopenia | 30.00 | 303.30 | 0.09 | 0.06 - 0.12 |
| Pulmonary embolism | 28.12 | 165.83 | 0.14 | 0.09 - 0.19 |
| Dehydration | 27.92 | 156.98 | 0.15 | 0.10 - 0.20 |
| Nausea | 30.49 | 373.36 | 0.07 | 0.05 - 0.10 |
| Bone pain | 30.71 | 414.39 | 0.07 | 0.04 - 0.09 |
| Deep vein thrombosis | 27.61 | 144.97 | 0.16 | 0.10 - 0.21 |
| Neuropathy | 29.11 | 221.85 | 0.11 | 0.07 - 0.15 |
| **Proportion patients per BSC type** | | | | |
| Analgesics | 14.62 | 19.38 | 0.43 | 0.27 - 0.59 |
| Steroids | 70.05 | 67.30 | 0.51 | 0.42 - 0.59 |
| Palliative Radiotherapy | 81.65 | 108.23 | 0.43 | 0.36 - 0.50 |
| Bisphosphonates | 119.35 | 582.71 | 0.17 | 0.14 - 0.19 |
| **Proportion patients per drug (BSC)** | | | | |
| Co-codamol | 71.50 | 71.50 | 0.50 | 0.41 - 0.58 |
| Diclofenac | 71.50 | 71.50 | 0.50 | 0.41 - 0.58 |
| Dexamethasone | 71.50 | 71.50 | 0.50 | 0.41 - 0.58 |
| Prednisone | 71.50 | 71.50 | 0.50 | 0.41 - 0.58 |
| Strontium-89 | 71.50 | 71.50 | 0.50 | 0.41 - 0.58 |
| External beam RT | 71.50 | 71.50 | 0.50 | 0.41 - 0.58 |
| **Proportion patients requiring inpatient care due to AEs** | | | | |
| Neutropenia | 15.08 | 738.92 | 0.02 | 0.01 - 0.03 |
| Febrile Neutropenia | 565.50 | 188.50 | 0.75 | 0.71 - 0.78 |
| Diarrhoea | 75.40 | 678.60 | 0.10 | 0.07 - 0.12 |
| Fatigue | 7.54 | 746.46 | 0.01 | 0.00 - 0.01 |
| Asthenia | 7.54 | 746.46 | 0.01 | 0.00 - 0.01 |
| Leukopenia | 15.08 | 738.92 | 0.02 | 0.01 - 0.03 |
| Back pain | 113.10 | 640.90 | 0.15 | 0.12 - 0.17 |
| Anaemia | 113.10 | 640.90 | 0.15 | 0.12 - 0.17 |
| Thrombocytopenia | 37.70 | 716.30 | 0.05 | 0.03 - 0.06 |
| Pulmonary embolism | 603.20 | 150.80 | 0.80 | 0.77 - 0.82 |
| Dehydration | 188.50 | 565.50 | 0.25 | 0.21 - 0.28 |
| Nausea | 0.00 | 0.00 | N/A | N/A |
| Bone pain | 15.08 | 738.92 | 0.02 | 0.01 - 0.03 |
| Deep vein thrombosis | 226.20 | 527.80 | 0.30 | 0.26 - 0.33 |
| Neuropathy | 0.00 | 0.00 | N/A | N/A |
| **End-of-life care (share of patients)** | | | | |
| Hospice home | 115.00 | 460.00 | 0.20 | 0.16 - 0.23 |
| Palliative care at home | 71.50 | 71.50 | 0.50 | 0.41 - 0.58 |

| | | | | |
|---|---|---|---|---|
| Nurse visits | 28.00 | 7.00 | 0.81 | 0.65 - 0.91 |
| GP visits | 115.00 | 460.00 | 0.20 | 0.16 - 0.23 |
| Palliative hospital outpatients visits | 71.50 | 71.50 | 0.50 | 0.41 - 0.58 |
| Palliative care - hospital inpatient | 0.00 | 0.00 | N/A | N/A |
| Share of patients on BSC post-2nd line – Caba | 19.74 | 23.26 | 0.46 | 0.31 - 0.60 |
| Share of patients on BSC post-2nd line – Mitox | 19.74 | 23.26 | 0.46 | 0.31 - 0.60 |
| Share of patients getting GCSF prophylaxis – Caba | 107.04 | 312.89 | 0.25 | 0.21 - 0.29 |
| Share of patients getting GCSF prophylaxis – Mitox | 129.95 | 1211.12 | 0.10 | 0.08 - 0.11 |

**REFERENCES**


1. sanofi-aventis. Cabazitaxel for the second-line treatment of metastatic hormone refractory prostate cancer. 2011.

2. sanofi-aventis. Manufacturer's clarification. 2011. 2011.

3. Cancer Research UK. The stages of prostate cancer. *Internet* 2010; Available from http://cancerhelp.cancerresearchuk.org/type/prostate-cancer/treatment/the-stages-of-prostate-cancer (accessed July 2011).

4. National Collaborating Centre for Cancer. Prostate cancer: diagnosis and treatment. Full guideline. 2008. National Collaborating Centre for Cancer. 2011.

5. Cancer Research UK. Prostate cancer - symptoms and treatment. *Internet* 2011; Available from http://info.cancerresearchuk.org/cancerstats/types/prostate/symptomstreatment/ (accessed July 2001).

6. The Prostate Cancer Charity. Living with prostate cancer. *Internet* 2011; Available from http://www.prostate-cancer.org.uk/information/living-with-prostate-cancer (accessed July 2011).

7. bonetumor.org. Metastatic prostate cancer. *Internet* 2001; Available from http://www.bonetumor.org/metastatic-tumors/metastatic-prostate-cancer (accessed July 2011).

8. Cancer Research UK. Prostate cancer - UK incidence statistics. *Internet* 2011; Available from http://info.cancerresearchuk.org/cancerstats/types/prostate/incidence/ (accessed July 2011).

9. Cancer Research UK. Prostate cancer - UK mortality statistics. *Internet* 2011; Available from http://info.cancerresearchuk.org/cancerstats/types/prostate/mortality/ (accessed July 2011).

10. Cancer Research UK. Prostate cancer - survival statistics. *Internet* 2011; Available from http://info.cancerresearchuk.org/cancerstats/types/prostate/survival/ (accessed July 2011).

11. Office for National Statistics. Annual mid-year population estimates. *Statistical Bulletin* 2011.

12. Cooperberg, M.R., Cowan, J., Broering, J.M., Carroll, P.R. High-risk prostate cancer in the United States, 1990-2007. *World Journal of Urology* 2008; 26:211-218.

13. Stephenson, A.J., Eastham, J.A. Role of salvage radical prostatectomy for recurrent prostate cancer after radiation therapy. *Journal of Clinical Oncology* 2005; 23:8198-8203.

14. Khan, M.A., Partin, A.W. Prostate cancer and chemotherapy. *Reviews in Urology* 2004; 6(3):167-169.

15. National Institute for Health and Clinical Excellence. Cabazitaxel for the second line treatment of hormone refractory, metastatic prostate cancer. Final scope. 2011.

16. Oudard, S. TROPIC: Phase III trial of cabazitaxel for the treatment of metastatic castration-resistant prostate cancer. *Future Oncology* 2011; 7(4):497-506.

17. European Medicines Agency. Jevtana: EPAR. *Internet* 2011; Available from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002018/WC500104764.pdf (accessed June 2011).

18. European Medicines Agency. Jevtana cabazitaxel authorisation details. *Internet* 2011; Available from http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002018/human_med_001428.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125&jsenabled=true (accessed June 2011).

19. Royal Pharmaceutical Society. British national formulary 61. *Internet* 2011; (accessed July 2011).

20. de Bono, J.S., Logothetis, C.J., Molina, A., Fizazi, K., North, S., Chi, K.N. et al. Abiraterone and increased survival in metastatic prostate cancer. *New England Journal of Medicine* 2011; 364(21):1995-2005.

21. FDA Center for Drug Evaluation and Research. Application number: 201023 Medical review(s). *Internet* 2011; Available from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201023s000MedR.pdf (accessed June 2011).

22. de Bono, J.S., Oudard, S., Ozguroglu, M., Hansen, S., Machiels, J.P., Kocak, I. et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010; 376(9747):1147-1154.

23. sanofi-aventis. Clinical study report: a randomized, open label multicenter study of XRP6258 at 25 mg/m$^2$ in combination with prednisone every 3 weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a taxotere®-containing regimen. 2009.

24. Therasse, P., Arbuck, S.G., Eisenhauer, E.A., Wanders, J., Kaplan, R.S., Rubinstein, L. et al. New guidelines to evaluate the response to treatment in solid tumors. *Journal of the National Cancer Institute* 2000; 92(3):205-216.

25. Melzack, R. The McGill pain questionnaire: major properties and scoring methods. *Pain* 1975; 1:277-299.

26. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). *Internet* 2006; Available from http://www.eortc.be/services/doc/ctc/ctcaev3.pdf (accessed July 2011).

27. Cancer Research UK. Prostate cancer - risk factors. *Internet* 2011; Available from http://info.cancerresearchuk.org/cancerstats/types/prostate/riskfactors/ (accessed July 2011).

28. Heidenreich, A. Satraplatin as a second-line therapy for castrate-refractory prostate cancer. *Onkologe* 2010; 16(3):314-315.

29. [Docetaxel enables initial survival time lengthening]. [German]. *Urologe (Ausg A)* 2004; 43(9):1183-1184.

30. Sternberg, C.N., Petrylak, D.P., Sartor, O., Witjes, J.A., Demkow, T., Ferrero, J.M. et al. Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. *Journal of Clinical Oncology* 2009; 27(32):5431-5438.

31. Witjes, J.A., Petrylak, D.P., Sartor, A.O., Wirth, M., Billiet, I., Petrone, M.E. et al. Radiologic progression predicts overall survival in patients (pts) with androgen independent prostate caoncer (AIPC) who received first line docetaxel; an analysis from the SPARC trial. *European Urology* 2009; 8(4 Suppl):133.

32. Sartor, A.O., Petrylak, D.P., Witjes, J.A., Berry, W.R., Chatta, G.S., Vaughn, D.J. et al. Satraplatin in patients with advanced hormone-refractory prostate cancer (HRPC): overall survival (OS) results from the phase III satraplatin and prednisone against refractory cancer (SPARC) trial. ASCO Annual Meeting, Chicago, IL, USA. 2008.

33. Sartor, A.O., Petrylak, D., Sternberg, C., Witjes, F., Halabi, S., Berry, W. et al. Use of pain at baseline and pain progression to predict overall survival (OS) in patients (pts) with docetaxel pretreated metastatic castration-refractory prostate cancer (CRPC): Results from the SPARC trial. *Journal of Clinical Oncology* 2009; 27(15 SUPPL. 1):5148. Available from http://meeting.ascopubs.org/cgi/content/abstract/27/15S/5148

34. Saad, F., Hotte, S.J., North, S., Eigl, B.J., Chi, K.N., Czaykowski, P. et al. A phase II randomized study of custirsen (OGX-011) combination therapy in patients with poor-risk hormone refractory prostate cancer (HRPC) who relapsed on or within six months of 1st-line docetaxel therapy. ASCO Annual Meeting, Chicago, IL. 2008.

35. de Bono, J.S., Fizazi, K., Flechon, A., Heidenreich, A., Voog, E., Davis, N.B. et al. Randomized phase II study of CNTO 328 (C), an anti-IL-6 monoclonal antibody, in combination with mitoxantrone (M) versus M alone in metastatic castration-resistant prostate cancer (CRPC). Genitourinary Cancers Symposium, San Francisco, CA. 2010.

36. Fleming, M.T., Kolodziej, M.A., Awasthi, S., Hutson, T.E., Martincic, D., Sonpavde, G. et al. Results of a randomized phase II study of mitoxantrone versus mitoxantrone with cetuximab in metastatic castrate-resistant prostate cancer (CRPC) previously treated with docetaxel-based chemotherapy. ASCO General Meeting, Chicago, IL, USA. 2010.

37. Rosenberg, J.E., Weinberg, V.K., Kelly, W.K., Michaelson, D., Hussain, M.H., Wilding, G. et al. Activity of second-line chemotherapy in docetaxel-refractory hormone-refractory prostate cancer patients: randomized phase 2 study of ixabepilone or mitoxantrone and prednisone. *Cancer* 2007; 110:556-563.

38. Morales, R., Valverde, C., Surez, C., Braa, I., Planas, J., Padros, O. et al. Mitoxantrone as second-line chemotherapy in patients with castrate-resistant prostate cancer (CRPC). *Annals of Oncology* 2010; 21:viii301.

39. El Demery M., Pouessel, D., Avances, C., Iborra, F., Rebillard, X., Faix, A. et al. [What is the objective of second-line chemotherapy after failure of first-line chemotherapy in hormone-resistant metastatic prostate?]. *Prog Urol* 2006; 16(3):320-323.

40. Michels, J., Montemurro, T., Murray, N., Kollmannsberger, C., Nguyen, C.K. First- and second-line chemotherapy with docetaxel or mitoxantrone in patients with hormone-refractory prostate cancer: does sequence matter? *Cancer* 2006; 106(5):1041-1046.

41. Ismail, J.R., Bystricky, B., Moylan, E., O'Reilly, S. Mitoxantrone-based treatment in taxane-refractory advanced hormone refractory prostate cancer: A community-based retrospective analysis. ASCO Annual Meeting, Chicago, IL, USA. 2010.

42. Thomas, C., Hadaschik, B.A., Thuroff, J.W., Wiesner, C. [Patients with metastatic hormone-refractory prostate cancer. Second-line chemotherapy with mitoxantrone plus prednisone]. [German]. *Urologe (Ausg A)* 2009; 48(9):1070-1074.

43. Berthold, D.R., Pond, G.R., de, W.R., Eisenberger, M., Tannock, I.F., TAX 327 Investigators. Survival and PSA response of patients in the TAX 327 study who crossed over to receive docetaxel after mitoxantrone or vice versa. *Annals of Oncology* 2008; 19(10):1749-1753.

44. Small, E., Harzstark, A., Weinberg, V.K., Smith, D.C., Mathew, P., Beer, T. et al. Ixabepilone, mitoxantrone, and prednisone in patients with metastatic castration-resistant

prostate cancer refractory to docetaxel-based therapy: A phase II study of the DOD Prostate Cancer Clinical Trials Consortium. *Journal of Clinical Oncology* 2009; 27(15 SUPPL. 1):5058. Available from http://meeting.ascopubs.org/cgi/content/abstract/27/15S/5058

45. Rosenberg, J.E., Ryan, C.J., Weinberg, V.K., Smith, D.C., Hussain, M., Beer, T.M. et al. Phase I study of ixabepilone, mitoxantrone, and prednisone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel-based therapy: a study of the department of defense prostate cancer clinical trials consortium. *Journal of Clinical Oncology* 2009; 27(17):2772-2778.

46. Doshi, G., Cen, P., Ramirez, P., Amato, R. Granulocyte macrophage: Colony stimulating factor (GM-CSF), ketoconazole, and mitoxantrone as second-line therapy in patients (Pts) with progressive hormone refractory prostate cancer (HRPC). *Journal of Clinical Oncology* 2009; 27(15 SUPPL. 1):e16033. Available from http://meeting.ascopubs.org/cgi/content/abstract/27/15S/e16033

47. Firek, P., Pfister, D.A., Thüer, D., Brehmer, B., Epplen, R., Heidenreich, A. Docetaxel rechallenge at PSA relapse after docetaxel chemotherapy at hormone-refractory prostate cancer. ASCO Genitourinary Cancers Symposium, San Francisco, CA, USA. 2010; Abstract 93.

48. Loriot, Y., Massard, C., Gross-Goupil, M., Di, P.M., Escudier, B., Bossi, A. et al. The delay from the last cycle of docetaxelbased chemotherapy to progression is a strong predictive factor of activity of second line docetaxel in castration-resistant prostate cancer. *Annals of Oncology* 2008; 19(S8):viii199.

49. Eymard, J.C., Oudard, S., Gravis, G., Ferrero, J.M., Theodore, C., Joly, F. et al. Docetaxel reintroduction in patients with metastatic castration-resistant docetaxel-sensitive prostate cancer: a retrospective multicentre study. *BJU International* 2010; 106(7):974-978.

50. Gernone, A., Pagliarulo, A., Calderoni, G., Pagliarulo, V. Elderly patients with metastatic castrate-resistant prostate cancer (mCRPC): safety and efficacy of docetaxel retreatment. Genitourinary Cancers Symposium, Washington, DC, USA. 2011.

51. Jankovic, B., Beardsley, E., Chi, K.N. Rechallenge with docextaxel as second-line chemotherapy in patients with metastatic hormone refractory prostate cancer (HRPC) after previous docetaxel: a population based analysis. Genitourinary Cancers Symposium, San Francisco, CA, USA. 2008; Abstract 196.

52. Gernone, A.G., Troccoli, G.T., Pagliarulo, V.P., Pagliarulo, A.P. Re-treatment with docetaxel in metastatic castration resistant prostate cancer (CRPC). *European Urology, Supplements* 2010; 9(2):283.

53. Ansari, J., Hussain, S.A., Zarkar, A., Tanguay, J.S., Bliss, J., Glaholm, J. Docetaxel chemotherapy for metastatic hormone refractory prostate cancer as first-line palliative chemotherapy and subsequent re-treatment: Birmingham experience. *Oncology Reports* 2008; 20(4):891-896.

54. Di Lorenzo, G., Buonerba, C., Faiella, A., Rescigno, P., Rizzo, M., Autorino, R. et al. Phase II study of docetaxel re-treatment in docetaxel pre-treated castration-resistant prostate cancer. *BJU International* 2011; 107:234-239.

55. Caffo, O., Sava, T., Comploj, E., Giampaolo, M.A., Segati, R., Valduga, F. et al. Estramustine plus docetaxel as second-line therapy in patients with hormone-refractory prostate cancer resistant to docetaxel alone. *Urologic Oncology* 2010; 28(2):152-156.

56. Gruenewald, A., Ivanyi, P., Winkler, T., Morgan, M., Fenner, M., Ganser, A. et al. Outcome of second-line chemotherapy with a combination of docetaxel and carboplatin (DC) in docetaxel-resistant (DR) hormone refractory prostate cancer (HRPC) patients. ASCO Annual Meeting, Chicoago, IL, USA. 2008; Abstract 16090.

57. Reuter, C.W., Morgan, M.A., Gruenwald, V., Fenner, M., Ivanyi, P., Ganser, A. Carboplatin plus weekly docetaxel as salvage chemotherapy in docetaxel-resistant and castration-resistant prostate cancer (DRPC). *Journal of Clinical Oncology* 2011; 29(Suppl 7):Abstract 172.

58. Sangal, A., Gulmi, F., Kim, H., Mooppan, U., Gu, Y., Saini, R. et al. Efficacy of combined docetaxel and bevacizumab treatment in hormone-refractory metastatic prostate cancer pretreated with docetaxel: A single institution experience. *Journal of Clinical Oncology* 2010; 28(15 SUPPL. 1):Abstract e15150.

59. Heidenreich, A., Thiier, D., Pfister, D., Bernhard, B. Docetaxel rechallenge versus docetaxel bevacizumab in castration-resistant prostate cancer following first line docetaxel. *European Urology, Supplements* 2010; 9(2):283-284.

60. Hahn, N.M., Zon, R.T., Yu, M., Ademuyiwa, F.O., Jones, T., Dugan, W. et al. A phase II study of pemetrexed as second-line chemotherapy for the treatment of metastatic castrate-resistant prostate cancer (CRPC); Hoosier Oncology Group GU03-67. *Annals of Oncology* 2009; 20(12):1971-1976.

61. Caffo, O., Fratino, L., Perin, A., Barbieri, R., Sava, T., Segati, R. et al. Permetrexed (P) in castration-resistant prostate cancer (CRPC) patients (pts) resistant to docetaxel (D): results of a multicentric phase II study. Genitourinary Cancers Symposium, San Franciso, CA. 2010; Abstract 98.

62. Bradley, D., Rathkopf, D., Dunn, R., Stadler, W.M., Liu, G., Smith, D.C. et al. Vorinostat in advanced prostate cancer patients progressing on prior chemotherapy (National Cancer Institute Trial 6862): trial results and interleukin-6 analysis: a study by the Department of Defense Prostate Cancer Clinical Trial Consortium and University of Chicago Phase 2 Consortium. *Cancer* 2009; 115(23):5541-5549.

63. Oudard, S.M., Caty, A., Rolland, F., Sevin, E., Gravis, G., Priou, F. et al. An open-label phase ii study of treatment with sunitinib in patients suffering from metastatic castrated refractory prostate cancer (CRPC) after progression with docetaxel-based regimen. *Annals of Oncology* 2010; 21:viii276.

64. Dror, M.M., Regan, M.M., Oh, W.K., Kaufman, D.S., Olivier, K., Michaelson, S.Z. et al. Phase II study of sunitinib in men with advanced prostate cancer. *Ann Oncol* 2009; 20(5):913-920.

65. Aragon-Ching, J.B., Jain, L., Draper, D., Gulley, J.L., Arlen, P.M., Wright, J.J. et al. Updated analysis of a phase II study using sorafenib (S) for metastatic castrate-resistant prostate cancer (mCRPC). ASCO Annual Meeting, Chicago, IL, USDA. 2008; Abstract 16026.

66. Dahut, W.L., Scripture, C., Posadas, E., Jain, L., Gulley, J.L., Arlen, P.M. et al. A phase II clinical trial of sorafenib in androgen-independent prostate cancer. *Clinical Cancer Research* 2008; 14:209-214.

67. Loriot, Y., Massard, C., Gross-Goupil, M., Di, P.M., Escudier, B., Bossi, A. et al. Combining carboplatin and etoposide in docetaxel-pretreated patients with castration-resistant prostate cancer: a prospective study evaluating also neuroendocrine features. *Annals of Oncology* 2009; 20(4):703-708.

68. Bezecny, P., Harland, S. Epirubicin, carboplatin and 5-fluorouracil (E-Carbo-F) after docetaxel and vice versa in castration resistant prostate cancer. *Clinical Oncology* 2009; 21(10):799.

69. Sella, A., Yarom, N., Kove, S. TEC (paclitaxel/estramustine/carboplatin) combination chemotherapy after initial docetaxel-based chemotherapy in androgen independent prostate cancer. *Annals of Oncology* 2008; 19(S8):viii200.

70. Lainakis, G., Nikos, A., Gerassimos, A., Michael, C., Iraklis, M., Konstantinos, L. et al. Biweekly doxorubicin/ketoconazole as second-line treatment in docetaxel-resistant, hormone-refractory prostate cancer. *Urology* 2008; 71(6):1181-1185.

71. Nelius, T., Klatte, T., de, R.W., Haynes, A., Filleur, S. Clinical outcome of patients with docetaxel-resistant hormone-refractory prostate cancer treated with second-line cyclophosphamide-based metronomic chemotherapy. *Med Oncol* 2010; 27(2):363-367.

72. Vaishampayan, U.N., Heilbrun, L.K., Heath, E.I., Smith, D.W., Dickow, B., Baranowski, K. et al. Phase II trial of bevacizumab (B) and oral satraplatin (S) and prednisone in docetaxel pretreated metastatic castrate resistant prostate cancer (CRPC). *Journal of Clinical Oncology* 2009; 27(15 SUPPL. 1):e16028. Available from http://meeting.ascopubs.org/cgi/content/abstract/27/15S/e16028

73. Gasent Blesa, J., Alberola Candel, V., Vidal, O.J., Cerezuela Fuentes, P., Giner Marco, V. Early results of a phase II trial of second line chemotherapy with oxaliplatin (Ox) and caapecitabine (Cp) in hormone-ressitant metastatic prostate cancer. European Society for Meidcal Oncology Congress, Berlin, Germany. 2009; Abstract P-7049.

74. Gasent Blesa, J.M., Giner, M., V, Giner-Bosch, V., Cerezuela, F.P., Alberola, C., V. Phase II trial of oxaliplatin and capecitabine after progression to first-line chemotherapy in androgen-independent prostate cancer patients. *American Journal of Clinical Oncology* 2011; 34(2):155-159.

75. Buonerba, C., Federico, P., D'Aniello, C., Rescigno, P., Cavaliere, C., Puglia, L. et al. Phase II trial of cisplatin plus prednisone in docetaxel-refractory castration-resistant prostate cancer patients. *Cancer Chemotherapy and Pharmacology* 2011; 67:1455-1461.

76. Beer, T.M., Ryan, C., Alumkal, J., Ryan, C.W., Sun, J., Eilers, K.M. A phase II study of paclitaxel poliglumex in combination with transdermal estradiol for the treatment of metastatic castration-resistant prostate cancer after docetaxel chemotherapy. *Anti-Cancer Drugs* 2010; 21(4):433-438.

77. Gross, M., Prendergrass, K., Leitner, S., Leichman, G., Pugliese, L., Silberman, S. TPI 287, a third-generation taxane, is active and well tolerated as 2nd line therapy after failure of docetaxel in hormone refractory prostate cancer (HRPC). ASCO General Meeting, Chicago, IL, USA. 2008; Abstract 16130.

78. Tombal, B., Oudard, S., Ozguroglu, M., Hansen, S., Kocak, I., Gravis, G. et al. Clinical benefit of cabazitaxel plus prednisone in the TROPIC trial in men with metastatic castration resistant prostate cancer (mCRPC) who progressed after docetaxel-based treatment. *European Urology, Supplements* 2011; 10(2):335-336.

79. Sartor, A.O., Oudard, S., Ozguroglu, M., Hansen, S., Machiels, J.H., Shen, L. et al. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: final results of a multinational phase III trial (TROPIC). *American Society of Clinical Oncology* 2010; 9.

80. de Bono, J.S., Oudard, S., Ozguroglu, M., Hansen, S., Machiels, J.H., Shen, L. et al. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: final results of a multinational phase III trial (TROPIC). *Journal of Clinical Oncology* 2010; 28(15 Suppl):abstract number 4508.

81. Oudard, S., Joulain, F., de Geer, A., Sartor, A.O. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC)previously treated with docetaxel: estimating mean overall survival (OS) for health economics analyses from a phase III trial (TROPIC). Poster presentation at ASCO-GU 2011, Orlando, Florida. 2011.

82. Sartor, A.O., Oudard, S., Ozguroglu, M., Hansen, S., Machiels, J.H., Shen, L. et al. Survival benefit from first docetaxel treatment for cabazitaxel plus prednisone compared with mitoxantrone plus prednisone in patients with metastatic castration-resistant prostate cancner (mCRPC) enrolled in the TROPIC trial. *Journal of Clinical Oncology* 2011; 29(Suppl):Abstract 4525.

83. de Bono, J.S., Oudard, S., Ozguroglu, M., Hansen, S., Machiels, J.H., Shen, L. et al. A subgroup analysis of the TROPIC trial exploring reason for discontinuation of prior docetaxel and survival outcome of cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC). *Journal of Clinical Oncology* 2011; 29(Suppl):Abstract 4526.

84. Ozguroglu, M., Oudard, S., Sartor, A.O., Hansen, S., Machiels, J.H., Shen, L. et al. Impact of G-CSF prophylaxis on the occurrence of neutropenia in patients with metastatic castration-resistant prostate cancer (mCRPC) receiving cabazitaxel. *Journal of Clinical Oncology* 2011; 29(Suppl):Abstract e15131.

85. Regional Drug and Therapeutics Centre. Evaluation report. The use of cabazitaxel for the treatment of metastatic hormone-refractory prostate cancer. *Internet* 2011; Available from http://www.nyrdtc.nhs.uk/docs/eva/RDTC_Cabazitaxel_ER.pdf (accessed July 2011).

86. Crawford, E.D., Petrylak, D. Castration-resistant prostate cancer: descriptive yet pejorative? *American Society of Clinical Oncology* 2011; 28(23):e408.

87. Collins, R., Fenwick, E., Trowman, R., Perard, R., Norman, G., Light, K. et al. A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer. *Health Technology Assessment (Winchester, England)* 2001; 11(2):iii-iiv.

88. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. 2008; available from http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf

89. Sullivan, P.W., Mulani, P.M., Fishman, M., Sleep, D., Sullivan, P.W., Mulani, P.M. et al. Quality of life findings from a multicenter, multinational, observational study of patients with metastatic hormone-refractory prostate cancer. *Quality of Life Research* 2007; 16(4):571-575.

90. Sandblom, G., Carlsson, P., Sennfalt, K., Veronhorst, E. A population-based study of pain and quality of life during the year before death in men with prostate cancer. *Br J Cancer* 2004; 90:1163-1168.

91. NHS reference costs 2009-2010. 2011; available from http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459

92. Kind, P., Hardman, G., Macran, S. UK Population Norms for EQ-5D. 2011;

93. National Institute for Health and Clinical Excellence. Appraising life-extending, end of life treatments. 2009; available from http://www.nice.org.uk/media/E4A/79/SupplementaryAdviceTACEoL.pdf

94. McGowan, J., Sampson, M., Lefebvre, C. An evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS EBC). *Evidence Based Library and Information Practice* 2010; 5(1).

## Cabazitaxel for the treatment of hormone refractory, metastatic prostate cancer.

## Errata to the ERG report

A small number of typographically errors were identified in two tables of the ERG report. These did not affect the ICER, but were related to the values for incremental costs and QALYs.

These tables (Table 31, p77 of the ERG report and Table 38, page 94 of the ERG report) are corrected in this errata.

**Table 31: Deterministic results using the alternative subgroups**

| | **Total Costs (£)** | **Total QALYs** | **Δ Cost (£)** | **Δ QALY** | **Cost per QALY (£)** |
|---|---|---|---|---|---|
| Base case | | | | | |
| Mitoxantrone | 13,047 | 0.849 | | | |
| Cabazitaxel | 35,372 | 1.147 | 22,325 | 0.298 | 74,938 |
| | | | | | |
| Subgroup 1 : The entire TROPIC population | | | | | |
| Mitoxantrone | 12,724 | 0.880 | | | |
| Cabazitaxel | 34,093 | 1.133 | 21,368 | 0.244 | 87,684 |
| | | | | | |
| Subgroup 2 : European patients within TROPIC | | | | | |
| Mitoxantrone | 12,736 | 0.875 | | | |
| Cabazitaxel | 34,703 | 1.174 | 21,966 | 0.260 | 84,540 |
| | | | | | |
| Subgroup 3 : Patients within TROPIC who received $\geq 225 mg/m^2$ of first-line docetaxel and with ECOG 0 or 1 | | | | | |
| Mitoxantrone | 13,085 | 0.916 | | | |
| Cabazitaxel | 34,493 | 1.190 | 21,408 | 0.259 | 82,538 |

**Table 38: Sensitivity analyses undertaken by the ERG**

| Sensitivity analyses | ΔCost (£) | ΔQALY | Cost per QALY (£) |
|---|---|---|---|
| | | | |
| None (ERG base case) | 22,233 | 0.248 | 89,476 |
| Using Subgroup 1 (entire TROPIC population) | 22,283 | 0.239 | 93,177 |
| Upper 95% of SD from the EAP at cycle 2 ([redacted]) | 22,233 | 0.298 | 74,620 |
| Lower 95% of SD from the EAP at cycle 2 ([redacted]) | 22,233 | 0.199 | 111,719 |
| Utility difference between SD and PD estimated from Sandblom[90] | 22,233 | 0.245 | 90,865 |

**Author**

**Matt Stevenson, ScHARR**

**23rd August 2011**

Addendum to the STA report on Cabazitaxel.

During the process of developing the lead team slides, the authors of the STA report were asked to provide additional data to allow a more detailed investigation of: the numbers of people in each health state; the breakdown of incremental QALYs and the breakdown of incremental costs.

These were provided and are replicated within this addendum. (Figures 1 to 3) The values contained within these figures have been taken directly from the manufacturer's model with the amendments required to represent the ERG base case model. These amendments are listed on page 89 of the ERG report.

Figure 1.

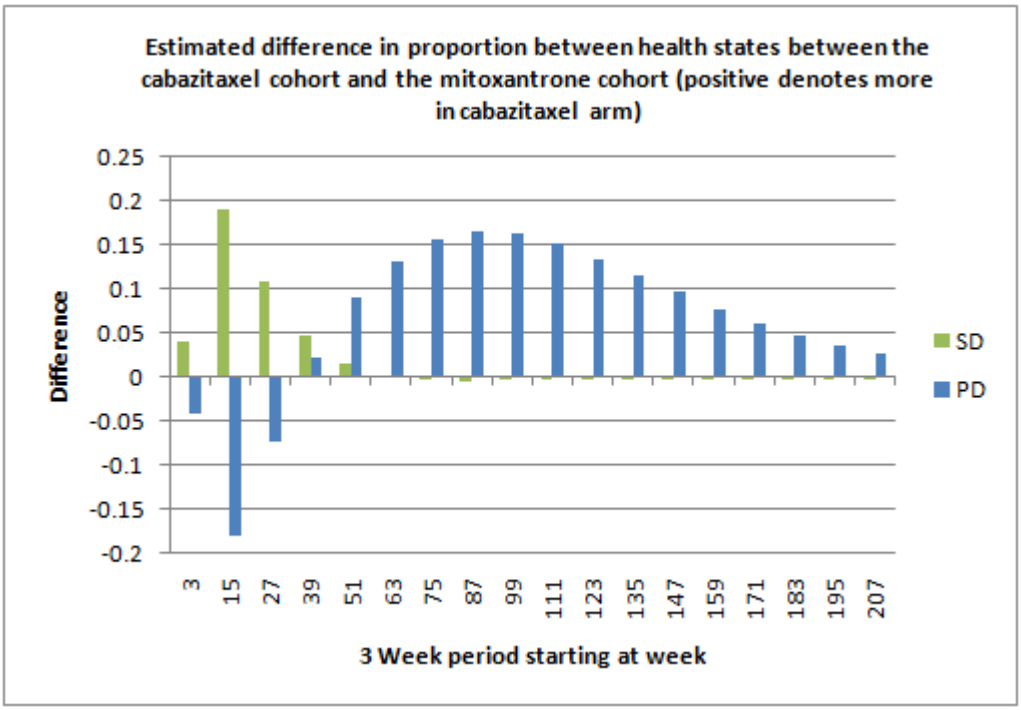


Figure 2

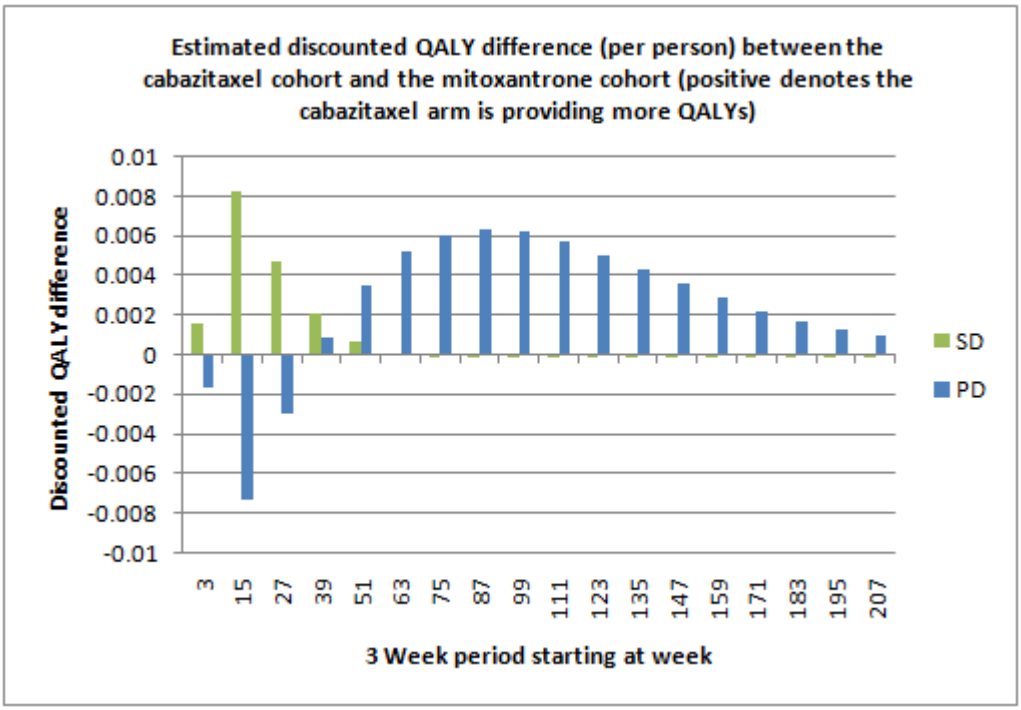
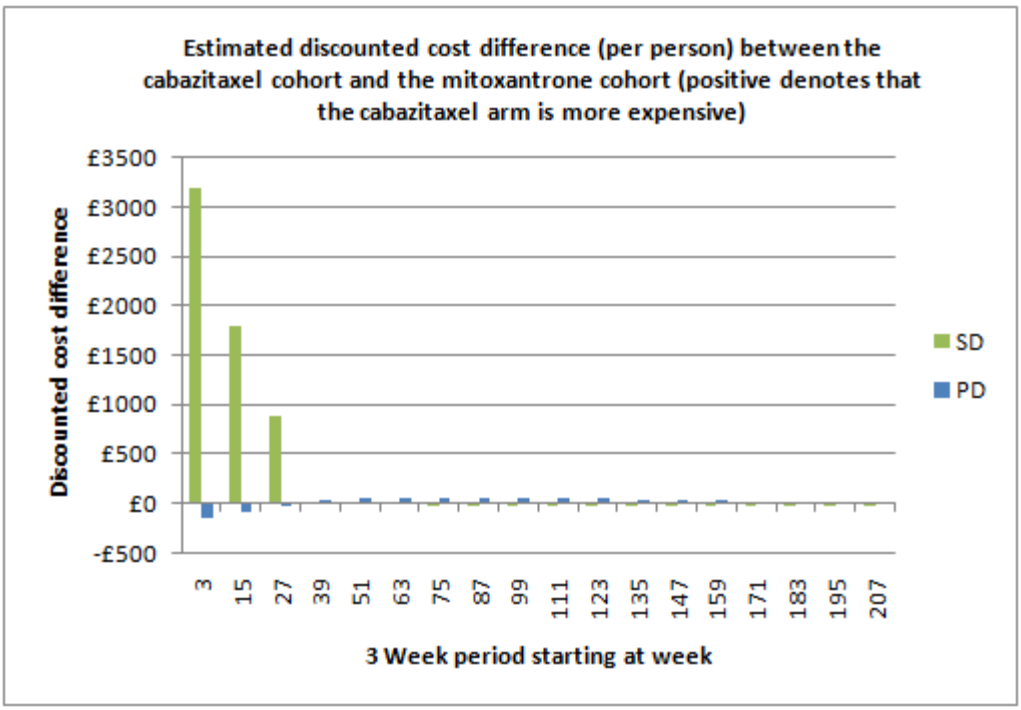



Figure 3



## Issue 1: Comment on the assessment of Pain

| Description of problem | Description of proposed amendment | Justification for amendment | ERG Response |
|---|---|---|---|
| Page 25, Pain. This section states that "The limitation of its use to only one of its three major components, the PPI, is not customary and requires further explanation which was not provided".<br><br>The use of only the PPI component alone was to minimise respondent burden and focus on the most relevant component of pain intensity, consistent with earlier studies in this area.<br><br>Indeed we note that use of the PPI scale alone is not unusual in prostate cancer. It has for example been used in the TAX327 trial of docetaxel, the SPARC trial of satraplatin, and the trial (Tannock 1996) which demonstrated a significant benefit of mitoxantrone on pain palliation in the first-line setting. | We propose that this sentence be removed. | We feel it would be helpful for the committee to know that the PPI component of the McGill-Melzack questionnaire has often been used alone and has precedent in prostate cancer trials. | In light of the further explanation offered the sentence has now been replaced with: 'The PPI aspect of the Short-Form McGill-Melzack pain questionnaire has precedent in previous prostate cancer trials.' |

## Issue 2: Definition of "other" chemotherapy

| Description of problem | Description of proposed amendment | Justification for amendment | ERG Response |
|---|---|---|---|
| Page 36 bullet point 2, Page 47<br><br>When discussing the broader systematic review and identification of trials of "other" chemotherapy agents that could be used to address the question of the second comparator, the report describes abiraterone as a potentially relevant agent (page 36) and notes that the manufacturer's searches also identified RCTs of a further three agents: abiraterone, cetuximab and CNTO 328 (page 47).<br><br>However, the term "chemotherapy" is usually interpreted as referring to cytotoxic agents. Abiraterone acts to inhibit hormone synthesis, while cetuximab and CNTO 328 are monoclonal antibodies, and therefore none of these agents would be classed as chemotherapy. This is the reason why we did not present a specific rationale for not comparing against these agents in the submission. | We suggest that the text on page 47 be modified so that, after stating "the manufacturer's searches also identified RCTs of a further three agents: abiraterone, cetuximab and CNTO 328", an additional sentence is included stating that none of these are chemotherapy agents according to the usual interpretation of the term in oncology. | This is a minor clarification point. The ERG and their clinical advisor(s) agreed with the approach to the second comparator that we took in our submission and therefore none of these studies are actually relevant to the decision problem. However we would like this to be clarified so that the committee understand the approach taken. | In the light of this clarification, the following sentence has been added: 'It is understood that none of these three agents are chemotherapy agents according to the usual interpretation of the term in oncology'. |

## Issue 3: Post-marketing studies

| Description of problem | Description of proposed amendment | Justification for amendment | ERG Response |
|---|---|---|---|
| Page 63, paragraph 2. This states that “Because of its concerns about serious toxicity in general, and renal toxicity in particular, the FDA recommended four post-marketing requirements”:<br><br>However, the first of the FDA’s requirements refers to a trial that is unrelated to safety (a trial of docetaxel versus cabazitaxel).<br><br>In addition, we would like to highlight that the expert review of renal toxicity is now available, together with results from a trial evaluating the effect of cabazitaxel on the QTc interval. These can be made available to the ERG/ committee if requested. | Amend wording to state that “Four post-marketing requirements were set up following discussions with the FDA, including 3 related to safety”. | To clarify what post-marketing requirements actually were in relation to safety.<br><br>In addition, although not a factual correction, we would like to highlight that there is evidence available on the renal safety report and the cardiac trial, which can be provided to the ERG/ committee. | The proposed amendment has not been made, for the following reason. It is clear from the FDA report that the first of the FDA's requirements does not refer to a trial that is unrelated to safety, as claimed by the manufacturer. The FDA specified as the primary endpoint of that trial "overall survival to evaluate the incidence of drug-related death as well as efficacy". It should be noted that the trial compares docetaxel and two different doses of cabazitaxel with a view not only to comparing cabazitaxel with docetaxel but also to evaluating whether a 20 mg dose of cabazitaxel would have lower toxicity and comparable efficacy compared with the 25mg dose used in the TROPIC study.<br><br>In relation to the comment relating to the expert review on renal toxicity, the following sentences have been added to the report: ‘During the fact check process, the manufacturer indicated that they had information from the renal safety report, and also from a trial evaluating the effect of cabazitaxel on the QTc interval, which has relevance for cardiac toxicity, which could be provided. However, these data were not offered within the timescale of the ERG report.’ |

## Issue 4: Adjustments to model in clarification process

| Description of problem | Description of proposed amendment | Justification for amendment | ERG Response |
|---|---|---|---|
| Page 74, 5.2.10. The list of corrections stated to impact the base case ICER includes one addressing the value for the risk ratio for neutropenia prophylaxis.<br><br>This parameter actually only affects sensitivity analyses, not the base-case ICER. | We propose including a statement in brackets to indicate that the value for the risk ratio for neutropenia prophylaxis only affects the sensitivity analyses, not the submitted base-case ICER. | This is very minor but we would like this amendment included for clarity. | Text amended to comment that the correction in the relative risk of neutropenia prophylaxis does not affect the base case. |

## Issue 5: Justification of model structure

| Description of problem | Description of proposed amendment | Justification for amendment | ERG Response |
|---|---|---|---|
| Page 96, paragraph 3. The report states that "In their response to clarification requests A2 and A9 the manufacturer reports that there were no *a priori* reasons for these choices, nor can they be justified on statistical grounds".<br><br>We do not agree this statement reflects accurately our response to clarification questions.<br><br>We stated in our clarification responses that there was no *a priori* clinical hypothesis for a difference in treatment effect by region. However, treatment practices vary between different countries, and these different practices can affect treatment outcomes. This was a pre-planned analysis included in the trial statistical plan.<br><br>We did not discuss *a priori* reasoning as to the choice of parametric curves throughout versus Kaplan-Meier. However we did include our justification of the use of the Kaplan-Meier approach, namely that this uses actual empirical TROPIC data, which offers greater validity than a fitted parametric function.<br><br>Therefore, we do not agree that these choices have not been justified. | We propose that this section be expanded to reflect our responses to clarification questions A2 and A9, and to describe separately the views of the ERG on the approaches taken. | As this is an important aspect of our submission, we believe it is important for the Committee to be clear on what our viewpoint is as the manufacturer, and what represents the views of the ERG. | The potential ambiguity of this passage has been removed. The third paragraph now begins 'As detailed in section 5.2.12 the ERG believes....<br><br>This directs the reader to the relevant section, which contains the response from the manufacturer in detail, |