

# Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial



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## Summary

**Background** Cabazitaxel is a novel tubulin-binding taxane drug with antitumour activity in docetaxel-resistant cancers. We aimed to compare the efficacy and safety of cabazitaxel plus prednisone with those of mitoxantrone plus prednisone in men with metastatic castration-resistant prostate cancer with progressive disease after docetaxel-based treatment.

**Methods** We undertook an open-label randomised phase 3 trial in men with metastatic castration-resistant prostate cancer who had received previous hormone therapy, but whose disease had progressed during or after treatment with a docetaxel-containing regimen. Participants were treated with 10 mg oral prednisone daily, and were randomly assigned to receive either 12 mg/m<sup>2</sup> mitoxantrone intravenously over 15–30 min or 25 mg/m<sup>2</sup> cabazitaxel intravenously over 1 h every 3 weeks. The random allocation schedule was computer-generated; patients and treating physicians were not masked to treatment allocation, but the study team was masked to the data analysis. The primary endpoint was overall survival. Secondary endpoints included progression-free survival and safety. Analysis was by intention to treat. This study is registered at ClinicalTrials.gov, NCT00417079.

**Findings** 755 men were allocated to treatment groups (377 mitoxantrone, 378 cabazitaxel) and were included in the intention-to-treat analysis. At the cutoff for the final analysis (Sept 25, 2009), median survival was 15·1 months (95% CI 14·1–16·3) in the cabazitaxel group and 12·7 months (11·6–13·7) in the mitoxantrone group. The hazard ratio for death of men treated with cabazitaxel compared with those taking mitoxantrone was 0·70 (95% CI 0·59–0·83,  $p < 0·0001$ ). Median progression-free survival was 2·8 months (95% CI 2·4–3·0) in the cabazitaxel group and 1·4 months (1·4–1·7) in the mitoxantrone group (HR 0·74, 0·64–0·86,  $p < 0·0001$ ). The most common clinically significant grade 3 or higher adverse events were neutropenia (cabazitaxel, 303 [82%] patients vs mitoxantrone, 215 [58%]) and diarrhoea (23 [6%] vs one [ $< 1\%$ ]). 28 (8%) patients in the cabazitaxel group and five (1%) in the mitoxantrone group had febrile neutropenia.

**Interpretation** Treatment with cabazitaxel plus prednisone has important clinical antitumour activity, improving overall survival in patients with metastatic castration-resistant prostate cancer whose disease has progressed during or after docetaxel-based therapy.

**Funding** Sanofi-Aventis.

## Introduction

Prostate cancer is the second most common cause of cancer death in men in the USA<sup>1</sup> and the third most common cause of death in developed countries.<sup>2</sup> For patients with metastatic prostate cancer, androgen deprivation therapy improves symptoms, but patients invariably develop progressive disease.<sup>3</sup> On the basis of an improvement in survival compared with mitoxantrone plus prednisone in patients with metastatic castration-resistant prostate cancer,<sup>4,6</sup> docetaxel in combination with prednisone is standard first-line chemotherapy in this setting. No treatment has been approved by the US Food and Drug Administration, however, for patients whose disease progresses after docetaxel treatment. Mitoxantrone is often administered because of its favourable effects on quality-of-life outcomes.<sup>7,8</sup> However,

Cabazitaxel (XRP6258; TXD258; RPR116258A) is a tubulin-binding taxane drug as potent as docetaxel in cell lines.<sup>9</sup> Additionally, the drug has antitumour activity in models resistant to paclitaxel and docetaxel.<sup>10,11</sup> Phase 1 and 2 clinical studies have shown that neutropenia is the primary dose-limiting toxicity, and the recommended phase 2 doses were 20 and 25 mg/m<sup>2</sup>, with antitumour activity in solid tumours including docetaxel-refractory metastatic castration-resistant prostate cancer.<sup>12,13</sup> We undertook a randomised, multicentre, multinational, phase 3 trial (EFC6193; TROPIC) with the aim of assessing whether cabazitaxel plus prednisone improves overall survival compared with mitoxantrone plus prednisone in men with metastatic castration-resistant prostate cancer who had progressed after docetaxel-

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This online publication has been corrected. The corrected version first appeared at thelancet.com on February 25, 2011

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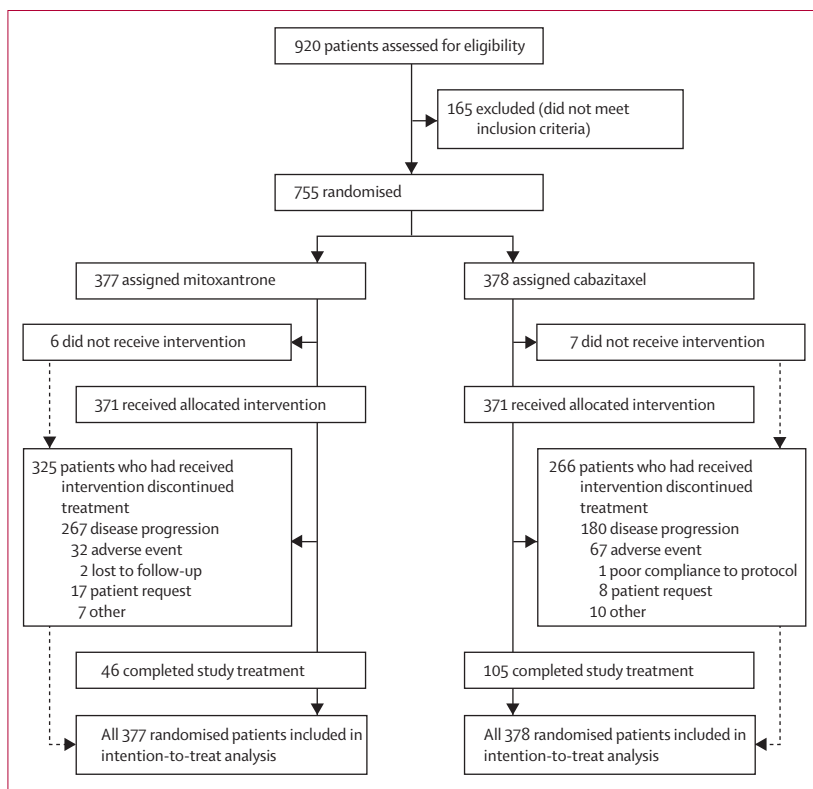


Figure 1: Trial profile

Methods

Patients

This randomised open-label phase 3 study was undertaken at 146 centres in 26 countries. Patients had pathologically proven prostate cancer with documented disease progression during or after completion of docetaxel treatment. Eligible patients were aged at least 18 years, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients who had previous mitoxantrone therapy, radiotherapy to 40% or more of the bone marrow, or cancer therapy (other than luteinising-hormone-releasing hormone [LHRH] analogues) within 4 weeks before enrolment were excluded. Patients with measurable disease were required to have documented disease progression by Response Evaluation Criteria in Solid Tumors (RECIST)<sup>14</sup> with at least one visceral or soft-tissue metastatic lesion. Patients with non-measurable disease were required to have rising serum prostate-specific antigen (PSA) concentrations (at least two consecutive increases relative to a reference value measured at least a week apart) or the appearance of at least one new demonstrable radiographic lesion.

Additional inclusion criteria were: previous and ongoing castration by orchiectomy or LHRH agonists, or both; antiandrogen withdrawal followed by progression had to have taken place at least 4 weeks (6 weeks for

|  | Mitoxantrone (n=377) | Cabazitaxel (n=378) |
|--|----------------------|---------------------|
| <b>Age</b>   |                      |                     |
| Median (years)   | 67 (61–72)           | 68 (62–73)          |
| ≥75 years  | 70 (19%)             | 69 (18%)            |
| <b>Ethnic origin</b>   |                      |                     |
| White  | 314 (83%)            | 317 (84%)           |
| Asian  | 32 (8%)              | 26 (7%)             |
| Black  | 20 (5%)              | 20 (5%)             |
| Other  | 11 (3%)              | 15 (4%)             |
| ECOG performance status 0 or 1                                       | 344 (91%)            | 350 (93%)           |
| <b>Extent of disease</b>   |                      |                     |
| Metastatic   | 356 (94%)            | 364 (96%)           |
| Bone metastases  | 328 (87%)            | 303 (80%)           |
| Visceral metastases  | 94 (25%)             | 94 (25%)            |
| Locoregional recurrence  | 20 (5%)              | 14 (4%)             |
| Unknown  | 1 (<1%)              | 0                   |
| Median serum PSA concentration (µg/L)*                               | 127.5 (44.0–419.0)   | 143.9 (51.1–416.0)  |
| Serum PSA concentration ≥20 µg/L                                     | 325 (86%)            | 329 (87%)           |
| Measurable disease   | 204 (54%)            | 201 (53%)           |
| Pain at baseline†  | 168 (45%)            | 174 (46%)           |
| <b>Previous therapy</b>  |                      |                     |
| Hormonal‡  | 375 (99%)            | 375 (99%)           |
| <b>Number of chemotherapy regimens</b>                               |                      |                     |
| 1  | 268 (71%)            | 260 (69%)           |
| 2  | 79 (21%)             | 94 (25%)            |
| >2   | 30 (8%)              | 24 (6%)             |
| Radiation  | 222 (59%)            | 232 (61%)           |
| Surgery  | 205 (54%)            | 198 (52%)           |
| Biological agent   | 36 (10%)             | 26 (7%)             |
| <b>Number of previous docetaxel regimens</b>                         |                      |                     |
| 1  | 327 (87%)            | 316 (84%)           |
| 2  | 43 (11%)             | 53 (14%)            |
| >2   | 7 (2%)               | 9 (2%)              |
| Total previous docetaxel dose (mg/m <sup>2</sup> )                   | 529.2 (380.9–787.2)  | 576.6 (408.4–761.2) |
| <b>Disease progression relative to docetaxel administration</b>      |                      |                     |
| During treatment   | 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%)              |
| Median time from last docetaxel dose to disease progression (months) | 0.7 (0.0–2.9)        | 0.8 (0.0–3.1)       |

Data are number of patients (%) or median (IQR). \*Serum PSA concentrations were available for 370 mitoxantrone and 371 cabazitaxel patients. †Pain was assessed with the McGill-Melzack present pain intensity scale<sup>15</sup> and analgesic score was derived from analgesic consumption (morphine equivalents). ‡Two patients in the cabazitaxel group did not receive previous orchiectomy or hormone therapy. ECOG=Eastern Cooperative Oncology Group. PSA=prostate-specific antigen.

**Table 1: Baseline characteristics and treatment history of patients in the intention-to-treat population**

hepatic, renal, and cardiac function; and a left-ventricular ejection fraction of more than 50% assessed by multi-

|   | Mitoxantrone<br>(n=377) | Cabazitaxel<br>(n=378) |
|---|-------------------------|------------------------|
| Patients receiving study treatment                        | 371 (98%)               | 371 (98%)              |
| Patients completing planned ten cycles of study treatment | 46 (12%)                | 105 (28%)              |
| Discontinuation of study treatment                        | 325 (86%)               | 266 (70%)              |
| Reasons for discontinuation of study treatment            |                         |                        |
| Disease progression                                       | 267 (71%)               | 180 (48%)              |
| Adverse event   | 32 (8%)                 | 67 (18%)               |
| Non-compliance with protocol                              | 0                       | 1 (<1%)                |
| Lost to follow-up   | 2 (1%)                  | 0                      |
| Patient request   | 17 (5%)                 | 8 (2%)                 |
| Other   | 7 (2%)                  | 10 (3%)                |
| Median number of treatment cycles*                        | 4 (2–7)                 | 6 (3–10)               |
| Median relative dose intensity (%)*                       | 97.3%<br>(92.0–99.3)    | 96.1%<br>(90.1–98.9)   |
| Treatment delays, number of cycles†                       |                         |                        |
| ≤9 days   | 110 (6%)                | 157 (7%)               |
| >9 days   | 28 (2%)                 | 51 (2%)                |
| Dose reductions, number of cycles‡                        | 88 (5%)                 | 221 (10%)              |

Data are number of patients or cycles (%) or median (IQR). \* Assessed in patients who received study treatment. † Percentages are of total number of treatment cycles (1736 for mitoxantrone and 2251 for cabazitaxel).

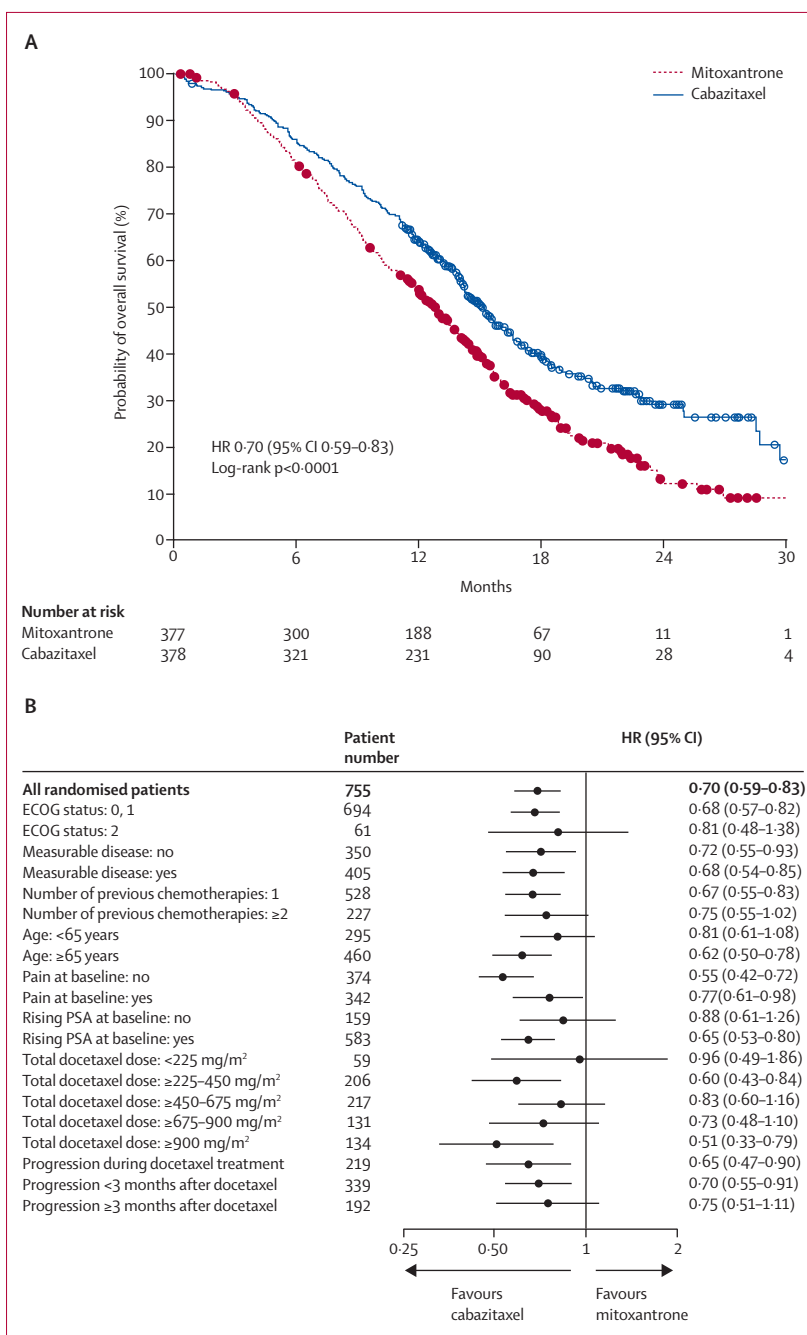
**Table 2: Treatment received and reasons for discontinuation in the intention-to-treat population\***

Concomitant use of bisphosphonates was allowed if the dose had been stable for 12 weeks before enrolment. Patients receiving LHRH agonists were mandated to continue this treatment during the study. Additional exclusion criteria were active grade 2 or higher peripheral neuropathy or stomatitis, other serious illness (including secondary cancer), or a history of hypersensitivity to polysorbate 80-containing drugs or prednisone.

On the basis of emerging guidelines recommending the delivery of 12 weeks of treatment before adjustment of therapy for metastatic castration-resistant prostate cancer, 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/m<sup>2</sup>. The study was undertaken in accordance with principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and with local ethics committee approval. Written informed consent was obtained from all participants.

### Procedures

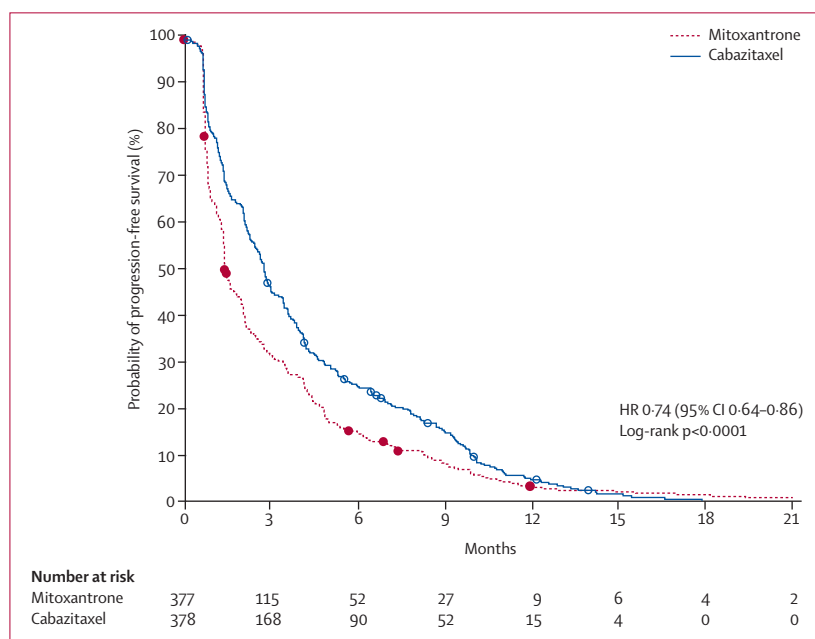
All patients received oral prednisone 10 mg daily (or similar doses of prednisolone where prednisone was unavailable). Patients were centrally randomly assigned to receive cabazitaxel 25 mg/m<sup>2</sup> intravenously over 1 h or mitoxantrone 12 mg/m<sup>2</sup> intravenously over 15–30 min on day 1 of each 21-day cycle, and were stratified for disease measurability (measurable vs non-measurable) and ECOG performance status (0–1 vs 2). A contract



**Figure 2: Overall survival**

(A) Kaplan-Meier estimates of the probability of survival in patients in all patients randomly assigned to treatment with cabazitaxel plus prednisone or mitoxantrone plus prednisone. The points on the curves show censored observations. (B) Intention-to-treat analysis of overall survival in subgroups of patients defined by baseline characteristics. Hazard ratios (HRs) lower than 1 favour the cabazitaxel group and greater than 1 favour the mitoxantrone group.

patients using an interactive voice response system and for the computer-generated random allocation schedule, but had no other involvement in the trial. A dynamic allocation method was used to avoid treatment



**Figure 3: Progression-free survival**

Kaplan-Meier estimates of the probability of progression-free survival in all patients randomly assigned to treatment with cabazitaxel plus prednisone or mitoxantrone plus prednisone. The points on the curves show censored observations. Progression-free survival was established from the date of randomisation to whichever event occurred first—prostate-specific antigen progression, radiological progression, symptomatic progression, or death. HR=hazard ratio.

treating physicians were not masked to treatment allocation, but the study team was masked to the data analysis. Premedication, consisting of single intravenous doses of an antihistamine, corticosteroid (dexamethasone 8 mg or equivalent), and histamine H<sub>2</sub>-antagonist (except cimetidine), was administered 30 min or more before cabazitaxel. Antiemetic prophylaxis was given at physicians' discretion.

Treatment was continued for a maximum of ten cycles to minimise risk of mitoxantrone-induced cardiac toxicity, while allowing for comparable exposure to the study treatment and a similar schedule of evaluation. Patients were followed up until the cutoff date for analysis or until death (whichever occurred first). Treatment delays of up to 2 weeks were allowed, with one dose reduction (cabazitaxel 20 mg/m<sup>2</sup> or mitoxantrone 10 mg/m<sup>2</sup>) per patient. Prophylactic granulocyte colony-stimulating factor was not allowed during the first cycle, but was allowed (at physicians' discretion) after first occurrence of either neutropenia lasting 7 days or more or neutropenia complicated by fever or infection.

Pretreatment evaluations included a medical history, ECOG performance status, physical examination, laboratory screening, serum PSA concentration, CT, bone scan, electrocardiography, and assessment of left-ventricular ejection fraction. Pain and analgesic consumption were assessed at baseline. Pain was assessed with the McGill-Melzack present pain intensity (PPI) scale<sup>15</sup> and analgesic use was derived from

Physical examinations and blood tests were repeated before each infusion of study drug and at the end of treatment. Complete blood counts were taken on days 1, 8, and 15 of each treatment cycle and repeated when clinically indicated. Patients who progressed or started another anticancer therapy were followed up every 3 months; patients who withdrew before documented disease progression were followed up every 6 weeks for the first 6 months and thereafter every 3 months.

The primary endpoint of overall survival was calculated from date of randomisation to death. Secondary endpoints included a composite endpoint of progression-free survival, defined as the time between randomisation and the first date of progression as measured by PSA progression, tumour progression, pain progression, or death. Other secondary endpoints were PSA response (reduction in serum PSA concentration of ≥50% in patients with a baseline value of ≥20 µg/L); PSA progression (increase of ≥25% over nadir PSA concentration provided that the increase in the absolute PSA value was ≥5 µg/L for men with no PSA response, or ≥50% over nadir for PSA responders); objective tumour response for patients with measurable disease based on RECIST; pain response (for patients with median PPI score of ≥2 or mean analgesic score of ≥10 points at baseline, or both), which was defined as a reduction of 2 points or more from baseline median PPI score without increasing analgesic score, or decreases of more than 50% in analgesic use without an increase in pain, maintained for 3 or more weeks;<sup>15</sup> pain progression (increase in median PPI score of ≥1 point from the reference value or an increase of ≥25% in the mean analgesic score or requirement for palliative radiotherapy);<sup>15</sup> and time to tumour progression, defined as the number of months from randomisation until evidence of progressive disease (RECIST).

Adverse events, biochemistry, haematology, vital signs, and electrocardiograms were monitored throughout the study. Left-ventricular ejection fraction was monitored throughout the study in mitoxantrone-treated patients, but only if clinically indicated in those who received cabazitaxel. All adverse events were graded according to National Cancer Institute Common Terminology Criteria for adverse events (version 3.0).<sup>16</sup>

#### Statistical analysis

SAS (version 9.1.3) was used for all analyses. The study required an estimated sample size of 720 patients (360 per group) to detect a 25% reduction in the hazard ratio (HR) for death in the cabazitaxel group relative to the mitoxantrone group with 90% power, with a two-sided log-rank test at a significance level of 0.05 and on the assumption of 8 months median overall survival in the mitoxantrone group. We planned for the final analysis to take place when 511 deaths had occurred. Analysis of the primary endpoint was for the intention-to-treat population

|   | Mitoxantrone      | Cabazitaxel            | Hazard ratio (95% CI) | p value for comparison |
|---|-------------------|------------------------|-----------------------|------------------------|
| <b>Tumour response rate*</b>                      |                   |                        |                       |                        |
| Number of evaluable patients                      | 204               | 201                    | ..                    | ..                     |
| Response rate (%)                                 | 4.4% (1.6–7.2)    | 14.4% (9.6–19.3)       | ..                    | 0.0005                 |
| <b>PSA response rate†</b>                         |                   |                        |                       |                        |
| Number of evaluable patients                      | 325               | 329                    | ..                    | ..                     |
| Response rate (%)                                 | 17.8% (13.7–22.0) | 39.2% (33.9–44.5)      | ..                    | 0.0002                 |
| <b>Pain response rate‡</b>                        |                   |                        |                       |                        |
| Number of evaluable patients                      | 168               | 174                    | ..                    | ..                     |
| Response rate (%)                                 | 7.7% (3.7–11.8)   | 9.2% (4.9–13.5)        | ..                    | 0.63                   |
| <b>Progression</b>                                |                   |                        |                       |                        |
| Number of patients in intention-to-treat analysis | 377               | 378                    | ..                    | ..                     |
| Median time to tumour progression (months)        | 5.4 (2.3–10.0)    | 8.8 (3.9–12.0)         | 0.61 (0.49–0.76)      | <0.0001                |
| Median time to PSA progression (months)           | 3.1 (0.9–9.1)     | 6.4 (2.2–10.1)         | 0.75 (0.63–0.90)      | 0.001                  |
| Median time to pain progression (months)§         | Not reached       | 11.1 (2.9–not reached) | 0.91 (0.69–1.19)      | 0.52                   |

\*Tumour response was evaluated only for patients with measurable disease according to Response Evaluation Criteria in Solid Tumors.<sup>14</sup> †Prostate-specific antigen (PSA) response was defined as a 50% or more reduction in serum PSA concentration, established only for patients with a serum PSA concentration of 20 µg/L or more at baseline, confirmed by a repeat PSA measurement after at least 3 weeks. ‡Pain response was established only for patients with median present pain intensity (PPI) score of 2 or more or mean analgesic score (AS) of 10 points or more at baseline, or both, and was defined as a two-point or greater reduction from baseline median PPI score without an increased AS or a decrease of 50% or more in the AS without an increase in the PPI score, maintained for at least 3 weeks. §Data for 265 patients in the cabazitaxel group and 279 patients in the mitoxantrone group were censored as a result of more than two PPI or AS assessments, or both, being missed during the same week (unless a complete evaluation of ≥5 values showed pain progression).

**Table 3: Response to treatment and disease progression**

Safety analyses included patients who received at least part of one dose of study drug.

We analysed overall survival using the Kaplan-Meier method, with log-rank comparisons stratified according to disease measurability (measurable versus non-measurable) and ECOG performance status (0–1 versus 2). HRs and 95% CIs were calculated with a Cox proportional hazards model (for both primary and secondary analyses). Overall survival data were censored at the last date the patient was known to be alive or at the analysis cutoff date, whichever was earliest. Progression-free survival and progression of tumour, PSA, and pain were compared between treatments by log-rank testing.

A planned futility analysis of progression-free survival was done after 225 patients had a progression event. Additionally, an interim analysis of the primary efficacy endpoint of overall survival was planned after 307 events, but was actually done after 365 events with an adjusted significance level of 0.016, on the basis of the O'Brien-Fleming type 1 error spending function. A two-sided significance level of 0.0452 was used for the final analysis. Although the study team was masked to treatment allocation and patient outcomes throughout the trial, an independent contract statistician provided unmasked results to an independent data monitoring committee with the appropriate analyses for assessment.

This study is registered at [ClinicalTrials.gov](http://ClinicalTrials.gov), NCT00417079.

#### Role of the funding source

The chief investigators (JSB and AOS) designed the trial

sponsor, who funded the trial. The decision to submit the report for publication was made by the chief investigators, who drafted and then finalised the report with the help of a medical writer. The sponsor funded editorial assistance and reviewed the final draft before submission.

#### Results

Between Jan 2, 2007, and Oct 23, 2008, 755 patients were randomly assigned to treatment groups (378 cabazitaxel and 377 mitoxantrone; figure 1). The treatment groups were well balanced at baseline with respect to demographic and disease characteristics and previous treatments (table 1). Roughly 50% of patients had measurable soft-tissue disease and 25% had visceral (poor prognosis) disease. The median dose of docetaxel received before the study was 576.6 mg/m<sup>2</sup> (IQR 408.4–761.2) in the cabazitaxel group and 529.2 mg/m<sup>2</sup> (380.9–787.2) in the mitoxantrone group. Overall, 59 (8%) patients had received a cumulative dose of docetaxel less than 225 mg/m<sup>2</sup> and 482 (65%) received a cumulative dose of 450 mg/m<sup>2</sup> or more. About 70% of patients had progressive disease either during or within 3 months of completing docetaxel treatment, including about 30% of patients who had disease progression during docetaxel treatment (table 1). The median time from last docetaxel dose to disease progression, before trial participation, was 0.8 months (IQR 0.0–3.1) for the cabazitaxel group and 0.7 months (0.0–2.9) for the mitoxantrone group.

Patients in the cabazitaxel group were on study treatment longer—a median of six treatment cycles compared with four cycles—and were more likely to



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