Published in final edited form as:

Lancet Oncol. 2019 October ; 20(10): 1432–1443. doi:10.1016/S1470-2045(19)30408-5.

Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: a randomised, open-label, phase 1–2 trial

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Summary

Background—Taxane–platinum combinations have shown promising activity in metastatic castration-resistant prostate cancers in single-group clinical studies but not in randomised trials. Distinct biological subsets of the disease might derive the greatest benefit from the addition of platinum. We aimed to determine whether adding carboplatin to cabazitaxel would improve the outcomes of men with metastatic castration-resistant prostate cancer.

Methods—We did a phase 1–2, open label, randomised study at two centres in men with progressive metastatic castration-resistant prostate cancer. In phase 1, patients received intravenous cabazitaxel 20–25 mg/m^2 and intravenous carboplatin area under the curve (AUC) 3–4 mg/mL per min every 21 days. The maximum tolerated dose was defined as the highest dose cohort studied in which one of six or fewer patients experienced a dose-limiting toxicity. In phase 2, patients were

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Contributors

PGC, CJL, and AMA participated in the design of the protocol. PGC was protocol principal investigator; NR, ES, and NN contributed the ctDNA analyses; LX and XW provided statistical design and analysis; EL-N-T and PT did pathological analyses; PGC, EIH, AZ, S-MT, SKS, JW, EE, CJL, and AMA were recruiting investigators; and TCT contributed expertise for the interpretation of the correlative data. AMA integrated clinical and correlative data and wrote the first draft of the report with input from PGC. All authors reviewed and approved the final report.

Declaration of interests

EIH reports personal fees from Bayer, Dendreon, Sanofi, Seattle Genetics, and Agensys, outside the submitted work. AZ reports personal fees from McKesson Specialty Health, Janssen-Cilag, Incyte, and Pfizer, outside the submitted work. EE reports grants, personal fees, research funding, and consulting fees from Janssen, Sanofi and Astellas, and Bayer and Tolmar, outside the submitted work. All other authors declare no competing interests.

Data sharing

There are no plans to share individual participant data but specific queries can be made to the corresponding author.

randomly assigned (1:1) centrally by a computerised algorithm to intravenous cabazitaxel 25 mg/m^2 with or without intravenous carboplatin AUC 4 mg/mL per min. All patients received growth factor support and oral prednisone 10 mg daily. The primary endpoints were the maximum tolerated dose of the combination in phase 1 and investigator-assessed progression-free survival in phase 2. This trial is registered at ClinicalTrials.gov, number .

Findings—Between Aug 17, 2012, and May 11, 2015, nine patients completed phase 1 as planned, and 160 were randomly assigned to cabazitaxel (n=79) or cabazitaxel plus carboplatin (n=81) in phase 2. During phase I, grade 3 adverse events were anaemia (n=2), fatigue (n=1), thrombocytopenia (n=1), hypomagnesaemia (n=1), diarrhoea (n=1), hypokalaemia (n=1), anorexia (n=1), and dehydration (n=1), and no grade 4 adverse events occurred. No dose-limiting toxicities were observed, therefore, a maximum tolerated dose of cabazitaxel of 25 mg/m^2 and carboplatin of AUC 4 mg/mL per min was selected for phase 2. At a median follow-up of 31·0 months (IQR 20·5–37·1), the combination improved the median progression-free survival from 4·5 months (95% CI 3·5–5·7) to 7·3 months (95% CI 5·5–8·2; hazard ratio 0·69, 95% CI 0·50–0·95, p=0·018). In the phase 2 study, the most common grade 3–5 adverse events were fatigue (7 [9%] of 79 in the cabazitaxel group *vs* 16 [20%] of 81 in the combination group), anaemia (3 [4%] *vs* 19 [23%]), neutropenia (3 [4%] *vs* 13 [16%]), and thrombocytopenia (1 [1%] *vs* 11 [14%]). There were no treatment-related deaths.

Interpretation—Carboplatin added to cabazitaxel showed improved clinical efficacy compared with cabazitaxel alone for men with metastatic castration-resistant prostate cancer. Although adverse events were more common with the combination, the treatment was safe and generally well tolerated. Our data suggest that taxane–platinum combinations have a clinically beneficial role in advanced prostate cancer and a randomised phase 3 study is planned.

Introduction

Men with advanced prostate cancer are typically treated with therapies that inhibit androgen signalling. Although many have prolonged responses, about 20% do not, and their survival is substantially shortened.[1–3] Despite the development of novel CYP-17 inhibitors and anti-androgens, such as abiraterone and enzalutamide, resistance to androgen signalling inhibition invariably emerges, and few non-androgen targeting therapies are approved for the treatment of men with androgen-indifferent prostate cancers. To overcome this challenge and find biomarkers that identify the androgen-indifferent subset, we and others have studied the small-cell or neuroendocrine prostate carcinomas, a morphological variant of the disease associated with an aggressive course, atypical clinical manifestations, resistance to androgen signalling inhibitors, sensitivity to platinum-based chemotherapy, and unique molecular features.[4–6] We screened for this entity by taking tumour biopsies from men whose prostate cancers showed virulent, atypical clinical features, but most did not show small-cell carcinoma morphology. We then codified these features into seven criteria, labelled them initially as anaplastic and later as aggressive variant prostate cancer clinicopathological criteria (AVPC-C), and used them to select patients for a single-group phase 2 trial, in which we showed that the presence of at least one of the seven AVPC-C was associated with a high proportion of patients responding to carboplatin and docetaxel, irrespective of morphology.[7] Molecular profiling of that trial's participants' tumour tissues revealed that the aggressive

variant prostate cancers were characterised by a signature composed of combined defects in at least two of the three tumour suppressors TP53, RB1, and PTEN.[8] The biological significance of this aggressive variant prostate cancer molecular signature (AVPC-MS) is supported by its association with lineage plasticity and androgen indifference in preclinical models.[9–11] On the basis of these studies, we proposed that the aggressive variant prostate cancers are a distinct group of prostate cancers with unique therapeutic vulnerabilities, including sensitivity to platinum-based chemotherapies.

Multiple phase 1 and 2 studies have shown the efficacy of taxane–platinum combinations in patients with castration-resistant prostate cancer.[12,13] However, a phase 3 randomised study of the oral platinum satraplatin versus placebo showed no difference in overall survival.[14] Given our observation that a large proportion of patients with aggressive variant prostate cancer achieved a response to the combination of carboplatin and docetaxel, we postulated that an enrichment design based on predictive markers could facilitate the development of platinum-based chemotherapy in advanced prostate cancer. To explore this idea further, we did a randomised clinical trial to test the hypothesis that carboplatin improves the efficacy of cabazitaxel in men with advanced prostate cancer. We had the additional intention of evaluating the effect of aggressive variant prostate cancer features on response and outcome. At the time of this trial's design, the definition of the AVPC-MS was in progress,[8] so patients were stratified for the presence or absence of AVPC-C and the effect of the aggressive variant prostate cancer phenotype on response included as a secondary outcome.

Methods

Study design and participants

We did a randomised, open-label, phase 1–2 study at the University of Texas MD Anderson Cancer Center (Houston, TX, USA) and Karmanos Cancer Institute (Detroit, MI, USA). Men with histological evidence of prostate adenocarcinoma, small-cell prostate carcinoma, or both, who had metastatic disease, and were at least 18 years of age were eligible. All were required to have castration-resistant disease progression as per Prostate Cancer Working Group 2 criteria[15] (except for those with small-cell prostate carcinoma), an Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2, and adequate organ function (absolute neutrophil count ≥1500 per mL, platelets ≥100 000 per mL, total bilirubin greater than or equal to the upper limit of normal [ULN], alanine or aspartate transferase ≤1·5 times the ULN, and a creatinine clearance ≥30 mL/min using the Cockroft-Gault equation). Permitted exceptions were absolute neutrophil count of 500 per mL or more and platelets of 50 000 per mL or more if due to bone marrow infiltration by a tumour, isolated hyperbilirubinemia if due to Gilbert's syndrome, and total bilirubin, aspartate transferase, or alanine transferase four times or less than the ULN if due to liver metastases or acute tumour-associated illness. There was no limit to previous hormonal therapies. However, previous treatment with cabazitaxel, carboplatin, or two or more previous chemotherapies was not allowed. Exclusion criteria also included radiotherapy within 14 days, major surgery or samarium-153 within 28 days, and strontium-89 within 12 weeks of registration. Men with imminent complications from bone metastases, uncontrolled intercurrent illnesses, an active second malignancy, or other serious medical or psychiatric

illness that could, in the investigator's opinion, interfere with the patient's ability to provide informed consent or with the completion of treatment according to the protocol were not eligible. All patients provided written, informed consent, and the study protocol was approved by the institutional review board at all participating institutions. The trial was done in accordance with the Declaration of Helsinki Good Clinical Practice guidelines.

Randomisation and masking

For phase 2, patients were randomly assigned (1:1) to cabazitaxel or cabazitaxel plus carboplatin. Randomisation was stratified by factors including ECOG performance status (0 *vs* 1 and 2), previous receipt of docetaxel (yes *vs* no), response to docetaxel (responder *vs* non-responder) among those who received it, and the presence of at least one AVPC-C (yes *vs* no). Patients were considered docetaxel responders if they had received more than 225 mg/m^2 of docetaxel and showed a decrease in prostate-specific antigen (PSA) concentration more than 50% from baseline maintained for more than 6 weeks or a partial or complete response in measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients were considered to meet AVPC-C if they had at least one of the seven following clinicopathological features: (1) histological evidence of small-cell prostate carcinoma, (2) exclusively visceral metastases, (3) predominantly lytic bone metastases, (4) bulky (>5 cm) lymphadenopathy or primary tumour with Gleason score of 8 or more at diagnosis, (5) low PSA (<10 ng/mL) plus high volume (≥20) bone metastases at initial presentation, before start of androgen deprivation therapy, or at symptomatic progression in the castrate setting, (6) elevated (two times or more the institutional ULN) lactate dehydrogenase or carcinoembryonic antigen, and (7) short interval response (<6 months) to androgen deprivation therapy. Patients were enrolled and randomly assigned centrally by the designated clinical study coordinator using a computerised algorithm through the Clinical Trial Conduct website, which was developed and maintained by the Department of Biostatistics at the University of Texas MD Anderson Cancer Center. In this open-label study, patients, investigators, and the study team were not masked to study treatment.

Procedures

For phase 1, a 3 + 3 design was used with escalating doses of intravenous cabazitaxel plus carboplatin as follows: cohort 1 received cabazitaxel 20 mg/m^2 plus carboplatin area under the curve (AUC) 3 mg/mL per min, cohort 2 received cabazitaxel 20 mg/m^2 plus carboplatin AUC 4, and cohort 3 received cabazitaxel 25 mg/m^2 plus carboplatin AUC 4. The maximum tolerated dose was defined as the highest dose cohort in which one of six patients or fewer had a dose-limiting toxicity. For phase 2, patients were randomly assigned to cabazitaxel 25 mg/m^2 or cabazitaxel 25 mg/m^2 plus carboplatin AUC 4 intravenously every 21 days. All patients received growth factor support and oral prednisone 5 mg twice daily. Treatment continued for up to ten cycles until progression or unacceptable toxicity developed or the patient decided to withdraw. The cabazitaxel dose could be reduced once, from 25 mg/m^2 to 20 mg/m^2, and the carboplatin dose twice for toxicity, from AUC 4 to AUC 3, and from AUC 3 to AUC 2. Once reduced, doses could not be re-escalated. All patients were followed up every 3 weeks with assessments of PSA, bone-specific alkaline phosphatase, and urine N-telopeptides, as well as complete blood counts and metabolic panels for adverse event monitoring according to the grading system in National Cancer Institute Common

Terminology Criteria for Adverse Events version 4.0. Tumour assessments with CT or MRI and bone scans were done at baseline and after every two cycles.

Baseline transiliac bone marrow biopsies were requested on all study patients with pelvic bone disease. Additionally, we assembled formalin-fixed, paraffin-embedded tumour tissue blocks stored in the MD Anderson Department of Pathology from study participants who had provided institutional review board-approved written consent for the banking and use of samples in research. Haematoxylin and eosin stained slides were reviewed to evaluate tumour content. Samples that contained sufficient tumour were cut in 4 μm sections and stained with antibodies against RB1 (Ab-5, MilliporeSigma, Burlington, MA, USA), PTEN (clone 6H2.1, Biocare Medical, Pacheco, CA, USA), androgen receptor N-terminus (AR441, Carpinteria, CA, USA), androgen receptor C-terminus (SP242, Abcam, Cambridge, UK), p53 (D0-7, Dako, Glostrup, Denmark), and Ki67 (M724001-2, Dako, Glostrup, Denmark) with use of an Autostainer Plus (Dako North America, Inc, Carpinteria, CA, USA). The percentage of positive cells (or labelling index) was calculated as the number of positively stained epithelial cells divided by the total number of epithelial cells, at 200 × magnification. Samples were considered negative for RB1, PTEN, androgen receptor N-terminus, and androgen receptor C-terminus if labelling index was 10% or less, and positive for TP53 if labelling index was 10% or more as before.[8] Samples with aberrant results for at least two of the three tumour suppressors met AVPC-MS criteria by immunohistochemistry.

Baseline plasma samples were also requested from all study participants. Details of DNA extraction and analysis from plasma and matched normal white blood cells are described in the appendix (p 3). To meet AVPC-MS criteria in circulating tumour DNA (ctDNA), samples had to have genomic alterations (exonic nonsynonymous missense or stop-gain mutations, frameshift or non-frameshift indels [insertions or deletions], or copy number losses) in at least two of *TP53*, *RB1*, and *PTEN*. We also examined genomic alterations in *BRCA2*, because previous publications have linked it to carboplatin responsiveness in prostate cancer.[16,17]

Outcomes

The primary endpoint of the phase 1 part of the study was to determine the maximum tolerated dose of cabazitaxel and carboplatin. The primary endpoint in the phase 2 part of the study was investigator-assessed progression-free survival, a composite endpoint defined as the time from chemotherapy initiation to disease progression, defined as the time from study entry to first occurrence of any of the following: (1) progression of measurable disease by RECIST criteria, (2) two or more new areas by bone scan attributable to prostate cancer (rather than fiare) or new or increasing size of lytic lesions by CT scan or MRI, (3) need for palliative radiotherapy involving more than one site, (4) surgery or kyphoplasty to any neoplastic bone lesion, (5) cancer-associated clinical deterioration as determined by the treating physician, and (6) receipt of any additional prostate cancer-specific therapy as prescribed by the treating physician. Secondary endpoints were the evaluation of PSA response (defined as ≥50% decline from baseline); association of changes in bone-specific alkaline phosphatase and urine n-telopeptides with response; overall survival (defined as time interval between the time of study entry and date of death); safety and toxicity; effect of

the anaplastic or aggressive variant prostate cancer phenotype on response to therapy; and the collection and archiving of serum, plasma, and urine samples from study patients for later hypothesis-generating associations.

Statistical analysis

We sought to test the hypothesis that cabazitaxel plus carboplatin provides a 50% improvement in median progression-free survival, from 2·8 months to 4·2 months.[18] An accrual rate of three patients per month was assumed. A two-sided group sequential procedure was designed, using statistical software East version 5.2, with overall type I error 0·1 and power 0·8 to detect the alternative median progression-free survival of 4·2 months.[19] On the basis of this design, the sample size required to achieve the necessary number of events was calculated at 80 per group. Interim tests after 78 events included both outer bounds for superiority (Z score cutoff to reject the null hypothesis ±2·538) and inner bounds for futility (Z score cutoff to accept the null hypothesis ±0·246). The trial was originally designed for patients previously treated with docetaxel (Aug 23, 2011), but was amended to permit inclusion of chemotherapynaive patients (Dec 4, 2012). We kept the assumption of a relative improvement in median progression-free survival by 50% in patients receiving the combination and stratified patients by receipt of and response to previous chemotherapy. The alpha-spending function corresponds to the O'Brien-Fleming boundaries. The final data analysis was performed after 150 events had been observed. Final data cutoff was on Oct 30, 2017. A standardised log-rank statistic was used for the analyses of primary and secondary clinical endpoints based on the intention-to-treat population, which included all randomly assigned participants analysed according to the group they were originally allocated to, regardless of what treatment they received, as long as they received at least one cycle of chemotherapy. Patients were considered evaluable for activity and safety if they received one cycle of chemotherapy, for PSA response if their baseline concentration of PSA was 5 ng/mL or more, and for bone marker responses if their baseline values were above the institutional ULN. Post-hoc analyses were the evaluation of the median overall survival of patients who did not receive a platinum-containing regimen at progression and the evaluation of differences in partial responses of measurable disease by RECIST version 1.1 between the groups. We also did post-hoc analyses to evaluate the effect of the AVPC-MS determined by immunohistochemistry and ctDNA sequencing and the effect of *BRCA2* mutations, determined by ctDNA, on progression-free and overall survival. The χ^2 test was used to compare response parameters between the groups. Fisher's exact test and Wilcoxon rank sum test were applied to evaluate the association between molecular markers, and log-rank test and univariate Cox models were applied to evaluate the association of progression-free survival and overall survival with covariates, including the interaction between treatment and the AVPC-MS signatures in post-hoc analyses. An independent data monitoring committee reviewed safety and activity data. Statistical analyses were done using SAS (version 9.4) and Splus (version 8.2) Figures were generated in GraphPad Prism (version 8.0).

This trial is registered at ClinicalTrials.gov, number .

Role of the funding source

This study was an investigator-initiated trial approved and funded by Sanofi Genzyme. The protocol and manuscript were reviewed by Sanofi Genzyme, but the funders had no role in data collection, analysis, or interpretation. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 17, 2012, and May 11, 2015, 170 patients were registered and 169 patients were treated (figure 1). During phase 1, nine patients were treated; three per dosing cohort. All nine patients reported at least one adverse event, with fatigue, anaemia, nausea, and diarrhoea being the most common (appendix p 4). Grade 3 adverse events were anaemia (n=2), fatigue (n=1), thrombocytopenia (n=1), hypomagnesaemia (n=1), diarrhoea (n=1), hypokalaemia (n=1), anorexia (n=1), and dehydration (n=1), and no grade 4 adverse events occurred. No dose-limiting toxicities were observed, therefore, a maximum tolerated dose of cabazitaxel of 25 mg/m^2 and carboplatin of AUC 4 was selected for phase 2. An additional 160 patients (ten of whom were from Karmanos Cancer Institute) were treated in the phase 2 study (79 of whom were randomly assigned to cabazitaxel and 81 to cabazitaxel plus carboplatin). Two patients assigned to cabazitaxel erroneously received the combination. Baseline characteristics for both groups are shown in table 1.

At a median follow-up of 31·0 months (IQR 20·5–37·1), 74 (94%) of 79 patients in the cabazitaxel group and 77 (95%) of 81 in the combination group had progressed or died. Median progression-free survival was 4·5 months (95% CI 3·5–5·7) in the cabazitaxel group versus 7·3 months (5·5–8·2) in the combination group (hazard ratio [HR] 0·69, 95% CI 0·50–0·95, p=0·018) in the intention-to-treat population (figure 2A). Prespecified subgroup analyses showed that the combination favoured patients with ECOG performance status 0 (HR 0·36, 95% CI 0·19–0·7, p=0·0027) and no previous docetaxel exposure (HR 0·62, 0·42–0·90, p=0·014) as well as those meeting AVPC-C criteria (HR 0·58, 0·37–0·89, p=0·013), but tests for interaction were not significant in the intention-to-treat population (appendix p 6).

At data cutoff (Oct 30, 2017), 132 patients had died: 63 (80%) in the cabazitaxel group and 69 (85%) in the combination group. Median overall survival was 17·3 months (95% CI 13·8–21·9) with cabazitaxel versus 18·5 months (16·7–21·9) with the combination (HR 0·89, 95% CI 0·63–1·25, p=0·50; figure 2B). In post-hoc analyses, we estimated the median overall survival of patients that did not receive a platinum-containing regimen at progression (74 [51%] of 144 had follow-up treatment data available). In this subset, the median overall survival was 12·6 months (95% CI 7·8–24·3) in the cabazitaxel group versus 18·9 months (14·6–28·6) in the combination group (HR 0·68, 95% CI 0·38–1·22, p=0·15; appendix p 7).

Of the individuals with evaluable PSA concentrations, 27 (40·9%, 95% CI 30·2–51·8) of 66 patients in the cabazitaxel group versus 42 (61·7%, 51·4–72·6) of 68 patients in the combination group had a decline of greater than 50% (odds ratio [OR] 2·53, 95% CI 1·25–5·10; p=0·016). Of those with evaluable bone-specific alkaline phosphatase, ten (29·4%, 95% CI 19–39) of 34 patients in the cabazitaxel group versus 31 (62·0%, 51·4–72·6) of 50 patients in the combination group had a decline of greater than 50% (OR 3·92, 95% CI 1·54–

9·95; p=0·0033). Declines in urine n-telopeptides did not differ between the groups (11 [55·0%, 95% CI 33·2%–76·8%] of 20 patients in the cabazitaxel group *vs* 15 [62·5%, 43·1%–81·9%] of 24 patients in the combination group; OR 1·36, 95% CI 0·41–4·56; p=0·61). Although not prespecified as a secondary analysis, we explored differences in partial responses of measurable disease by RECIST as a post-hoc analysis. Partial responses (ie, ≥30% decrease in the sum of diameters of target lesions compared with baseline) were also less common in the cabazitaxel group (ten [22·7%, 11·2–28·8] of 44 patients) than in the combination group (24 [57·1%, 39·1–69] of 42 patients; OR 4·53 [1·78–11·52]; p=0·0011; appendix p 8).

Adverse events occurring in 10% or more of patients are listed in table 2. The most common grade 3–5 adverse events were fatigue (7 [9%] of 79 in the cabazitaxel group, 16 [20%] of 81 in the combination group), anaemia (3 [4%] in the cabazitaxel group, 19 [23%] in the combination group), neutropenia (3 [4%] in the cabazitaxel group, 13 [16%] in the combination group), and thrombocytopenia (1 [1%] in the cabazitaxel group, 11 [14%] in the combination group). Additional grade 3 events in the cabazitaxel group not shown in table 2 were upper gastro intestinal bleed (one [1%] of 79 patients), cystitis (one [1%]), atrial fibrillation (one [1%]), anaphylaxis (one [1%]), confusion (one [1%]), and hyponatremia (one [1%]). Additional grade 3 events not listed in table 2 in the combination group included upper gastrointestinal bleed (one [1%] of 81 patients), cystitis (one [1%]), colitis (one [1%]), bowel obstruction (one [1%]), hypophosphatemia (one [1%]), and hyponatremia (one [1%]). Additional grade 4 events were hyponatremia (one [1%]) in the cabazitaxel group and upper gastrointestinal bleed (one [1%]) in the combination group. Serious adverse events were reported for 17 (22%) patients in the cabazitaxel group and 32 (40%) patients in the combination group. The most common serious adverse events were dehydration (one [1%] *vs* six [7%]), pain (three [4%] *vs* one [1%]), neutropenia (0 *vs* two [1%]), and neutropenic fever (0 *vs* two [1%]). Dose reductions and treatment delays are shown in table 3. Adverse events leading to treatment discontinuation occurred in eight (10%) patients treated in the cabazitaxel group and ten (12%) in the combination group. The most frequent adverse events leading to treatment discontinuation were fatigue (three [4%] in the cabazitaxel group) and haematuria and cystitis (two [3%] in the cabazitaxel group and three [4%] in the combination group), toxicities previously associated with cabazitaxel use[18,20] that resolved upon treatment cessation. All deaths occurred more than 30 days after the last dose of chemotherapy (including one patient who died of a lethal pulmonary embolus 31 days after his last dose of cabazitaxel) and were not considered to be treatment-related.

We did post-hoc analyses to evaluate the effect of the aggressive variant prostate cancer phenotype on outcomes in the as-treated population that included the phase 1 patients. We reviewed 133 paraffin-embedded tissue samples obtained from 96 (57%) of the 169 participants within 1 year of registration, including the bone marrow biopsies requested from patients at baseline for this purpose. Of these, 72 samples (from 62 patients) contained sufficient tumour for immunohistochemistry. 72 solid tumour samples from 62 (37%) of the 169 participants (160 from phase 2 and nine from phase 1) were stained for TP53, RB1, and PTEN. Samples were also stained for androgen receptor N-terminus and C-terminus and Ki67 to explore associations between the AVPC-MS and androgen receptor expression and

proliferation (appendix p 9). Staining was considered positive for TP53 in 21 (34%) of 62 evaluable samples and negative for RB1 in 23 (34%) of 68, for PTEN in 48 (68%) of 71, for androgen receptor N-terminus in 9 (13%) of 68, and for androgen receptor C-terminus in ten (15%) of 65 (appendix p 10). The different combinations of tumour suppressor abnormalities are provided in the appendix (p 11). 56 (90%) of 62 patients had samples considered evaluable for assessment of the AVPC-MS by immunohistochemistry (ie, results were available for all three tumour suppres sors or abnormal for the only two available). In four of eight patients who had two evaluable samples, AVPC-MS results were discordant between them (appendix p 11). We reasoned that this discrepancy was probably due to tumour heterogeneity and that the presence of the signature would dictate the phenotype, so we considered these four cases positive for AVPC-MS by immunohistochemistry (ctDNA sequencing was available for three, and all were positive for the AVPC-MS). Thus, 26 (46%) of 56 patients had tumours positive for AVPC-MS by immunohistochemistry. These men had a median progression-free survival of 1·7 months (95% CI 1·3 to NA) when treated with cabazitaxel versus 7·5 months (4·4–9·6) when treated with the combination (p=0·017) and an estimated median overall survival of 8·5 months (4·8 to NA) versus 20·2 months (13·3–37·2, p=0·0002). Men with AVPC-MS-negative tumours treated with cabazitaxel had an estimated median progression-free survival of 6·3 months (5·9–10·9) versus 6·5 months (3·9–8·4; p=0·38) for the combination and an estimated median overall survival of 21·7 months (95% CI 17·4 to NA) versus 21·5 months (9·1 to NA; p=0·702; appendix p 12). Similar numbers of combination chemotherapy cycles were administered in each group (appendix p 13). In a post-hoc exploratory analysis, the presence of the AVPC-MS in immunohistochemistry showed an inverse correlation with the labelling indices for androgen receptor N-terminus and C-terminus but no association with that for Ki67 (appendix p 13).

In post-hoc analyses, plasma obtained from 140 (83%) of the 169 phase 1 or 2 participants at baseline contained a median ctDNA concentration of 1·13 ng/mL (range 0·02–1731·15). DNA from 91 (65%) of the 140 patients was analysed for whole-genome copy number analysis. Copy number deletions were found in 36 (40%) of 91 samples for *TP53*, 47 (52%) for *RB1*, and 31 (34%) for *PTEN*. Of the 91 samples, 65 (71%) contained sufficient DNA (>2 ng) for targeted exome sequencing. We identified six indels and 14 point mutations for *TP53*, one indel and one point mutation for *RB1*, and one indel for *PTEN*. Most indels and point mutations overlapped with copy number deletions. Thus, genomic alterations were found in 40 (44%) of 91 patients for *TP53*, 47 (52%) for *RB1*, and 33 (36%) for *PTEN* (appendix p 9). 40 (44%) had genomic alterations in at least two of the three tumour suppressors, and thus were positive for AVPC-MS ctDNA. Men with AVPC-MS ctDNA-positive tumours treated with cabazitaxel had an estimated median progression-free survival of 2·2 months (95% CI 1·5–4·4) versus 5·1 months (95% CI 2·9–8·2) in the combination group (p=0·030) and an estimated median overall survival of 10·5 months (8·4–17·4) versus 11·2 months (8·2–29·9, p=0·11). Men with AVPC-MS ctDNA-negative tumours treated with cabazitaxel had an estimated median progression-free survival of 5·7 months (4·8–9·1) versus 6·0 months (4·5–8·2) for those treated with the combination (p=0·65) and an estimated median overall survival of 21·8 months (95% CI 17·3–30·8) versus 16·7 months (11·2–24·6, p=0·046; appendix p 12). In post-hoc exploratory analyses, we observed a positive correlation between the AVPC-MS ctDNA and AVPC-C, but the correlation of the

ctDNA and immunohistochemistry results was poor for all three genes, and immunohistochemistry with the AVPC-C and the AVPC-MS ctDNA were not significantly correlated (appendix pp 12–14).

We reasoned that the presence of the AVPC-MS by either assay (ctDNA and immunohistochemistry) would dictate the phenotype, and we explored the combination of both to test associations with clinical outcomes in post-hoc analyses. Men with tumours positive for AVCP-MS by either assay in the cabazitaxel group had median progression-free survival of 2·2 months (95% CI 1·7–3·0) versus 6·0 months (95% CI 4·4–8·2) in the combination group (p=0·00033) and a median overall survival of 9·9 months (95% CI 8·5–13·8) versus 17·4 months (11·2–29·5, p=0·0024). Men with AVPC-MS-negative tumours treated with cabazitaxel had a median progression-free survival of 5·9 months (5·1–7·4) versus 6·0 months (4·5–8·1) for those treated with the combination (p=0·74) and a median overall survival of 22·2 months (95% CI 20·3–31·0) versus 18·9 months (11·2–27·3; p=0·19; appendix p 12). Post hoc, we explored whether the addition of carboplatin to cabazitaxel was beneficial in the 36 (40%) men with *BRCA2* somatic alterations detected in ctDNA (12 in the cabazitaxel group and 23 in the combination group), but did not observe significant differences between the groups (appendix p 15). Two (2%) of the 91 patients with sequenced ctDNA had germline pathogenic mutations (one in *ATM* and another in *FANCG*).

Discussion

The results of our study support the hypothesis that carboplatin added to cabazitaxel improves median progression-free survival and response in men with metastatic castration-resistant prostate cancer, and they show that the combination was safe and tolerable with appropriate antiemetic and growth factor support. To our knowledge, only one previous randomised study[21] of docetaxel with or without carboplatin has been reported. In that study, patients with metastatic castration-resistant prostate cancer previously treated with docetaxel and with a progression-free interval of at least 3 months after initial docetaxel treatment, were randomly assigned to receive docetaxel 75 mg/m^2 or docetaxel 60 mg/m^2 plus carboplatin AUC 4. The trial was halted after only 75 of a planned 150 patients had been registered, and no differences in progression-free or overall survival were observed. The discrepancy with our results is probably explained by the previous docetaxel treatment and insufficient power, and possibly by the lower dose of docetaxel given with carboplatin and the use of docetaxel in lieu of cabazitaxel. Thus, to our knowledge, ours is the first randomised study to show a benefit for a taxane–platinum combination in advanced prostate cancer.

Nonetheless, the observed improvement was modest in the overall population and we sought to gather support for the hypothesis that men with aggressive variant features were the ones most likely to benefit from the combination. In a prespecified subgroup analysis based on stratification factors at randomisation, the benefit from the combination was greater in men with AVPC-C compared with those without. Furthermore, the presence of AVPC-MS assessed by immunohistochemistry or ctDNA in post-hoc analyses was associated with clinically meaningful improvements in both median progression-free and overall survival with the addition of carboplatin to cabazitaxel. No improvement in median progression-free

or overall survival was observed with the combination in men with AVPC-MS-negative tumours. The reduction in overall survival in men with AVPC-MS-negative tumours suggests that men without aggressive variant prostate cancer might be harmed by the more intense therapy. These data are consistent with the preclinical observations that the aggressive variant prostate cancers encompass a distinct subset of prostate cancers with unique therapeutic vulnerabilities, which must be accounted for in clinical and translational studies.

The functional importance of the AVPC-MS is reinforced by findings in preclinical models in which single deletions of any of the *p53*, *RB1*, or *PTEN* tumour suppressor genes failed to produce aggressive prostate cancers, whereas combined deletions resulted in virulent disease associated with lineage plasticity and androgen indifference.[9–11] The importance of the AVPC-MS is also supported by a study in which the ctDNA obtained from 115 patients with metastatic castration-resistant prostate cancer receiving treatment with enzalutamide or abiraterone was sequenced.[22] In our reading of the results presented for their 72-gene panel, about 40% of patients appeared to be positive for AVPC-MS in baseline ctDNA. Of these, about 60% progressed within 3 months and 90% within 6 months. These exploratory data lend support to the association of the AVPC-MS with androgen indifference and suggests potential clinical use as a biomarker of resistance to both androgen-targeting agents and platinum-based chemotherapy, although further studies are needed to validate its role.

Our study is limited by the absence of central review of response and progression, by the few participating institutions, by the relatively small numbers of solid and liquid tumour samples that were evaluable for the markers of interest, and by the fact that the samples were not consistently paired. These limitations might explain in part the imperfect correlation between expression of tumour suppressors by immunohistochemistry and their genomic alterations, although this has been previously reported,[23–25] and could also be explained by epigenetic or posttranscriptional silencing and tumour heterogeneity. Because of the relatively small number of samples, questions, such as how each tumour suppressor defect contributed to the functional and biomarker properties of the AVPC-MS or whether immunohistochemistry or next-generation sequencing is best to determine AVPC-MS status, cannot be answered here. Larger samples sizes will help in determination of the individual predictive contribution of each of the genes and in unravelling additional heterogeneity within the aggressive variant prostate cancer.

In conclusion, the addition of carboplatin added to cabazitaxel seems to be a safe and tolerable regimen for men with metastatic castration-resistant prostate cancer, and further study of this regimen is warranted. Given the association of the AVPC-MS with outcomes using two independent assays and the convergence of our observations with those of others in experimental and clinical settings, a phase 3 study of cabazitaxel with or without carboplatin in men with metastatic castration-resistant prostate cancer stratified by the presence or absence of the AVPC-MS is planned.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank patients and their family members, Sarah E Townsend (employee of the University of Texas MD Anderson Cancer Center) for editorial assistance and the agencies that supported this work: Sanofi Genzyme (drug and clinical trial costs), the University of Texas MD Anderson Prostate Cancer Moon Shot Program, the National Institutes of Health and National Cancer Institute (NCI; under award numbers P50 CA 140388 [University of Texas MD Anderson NCI Prostate Cancer SPORE Grant] and P30 CA16672 [University of Texas MD Anderson NCI Prostate Cancer Center Support Grant]), the Solon Scott III Prostate Cancer Research Fund, the Eckstein Tissue Acquisition Laboratory, the Joan Stanford Alexander Family Fund and the David H Koch Center for Applied Research of Genitourinary Cancers. NR is funded by the MD Anderson CPRIT Research Training Program (RP170067).

Funding

Sanofi Genzyme, University of Texas MD Anderson Cancer Center Prostate Cancer Moon Shot Program, and Solon Scott III Prostate Cancer Research Fund.

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Research in context

Evidence before this study

Platinum-based chemotherapy has activity in metastatic castration-resistant prostate cancer, but has not improved overall survival, in part owing to the paucity of predictive biomarkers. The aggressive variant prostate cancers share clinical and chemotherapy response profiles with androgen indifferent, platinum-sensitive small-cell prostate carcinomas and are molecularly characterised by defects in at least two of TP53, RB1, and PTEN (aggressive variant prostate cancer molecular signature; AVPC-MS). We searched PubMed and the databases of the American Society of Clinical Oncology and European Society for Medical Oncology for journal publications and meeting abstracts published between database inception and Feb 12, 2019, using the search terms “platinum” or “carboplatin” and “prostate cancer”, with or without “biomarker”. Most entries were phase 1 studies, non-randomised phase 2 studies, a pooled analysis of phase 1–2 studies, retrospective studies, and literature reviews, all of which reported responses to platinum-based chemotherapy combinations, particularly after previous docetaxel exposure. Two published studies suggested that alterations in *BRCA2* (germline or somatic) predicted response to docetaxel plus carboplatin. One abstract suggested DNA repair defects (not otherwise specified) did not correlate with response to platinum-based chemotherapy.

Added value of this study

To our knowledge, our study is the first to establish the benefit of combining a platinum agent with a taxane agent in metastatic castration-resistant prostate cancer using a randomised, prospective trial design. Improved responses in prostate-specific antigen, bone specific alkaline phosphatase, and Response Evaluation Criteria in Solid Tumours were associated with the combination of cabazitaxel plus carboplatin compared with cabazitaxel alone. More patients treated with cabazitaxel plus carboplatin experienced grade 3 and 4 toxicities than those treated with cabazitaxel alone, but adverse events leading to treatment discontinuation were similarly low between the two groups. Subgroup analyses suggested that treatment with the combination seemed to benefit patients with aggressive variant prostate cancer features, but not those without.

Implications of all the available evidence

The improvements in outcomes with cabazitaxel and carboplatin in men were clinically meaningful, particularly in men with aggressive variant prostate cancer features, and the combination was safe and tolerable. A phase 3 study of cabazitaxel with or without carboplatin in men with AVPC-MS-positive tumours is warranted to establish a therapy standard for androgen-indifferent tumours and provide a foundation for a molecular classification of prostate cancer.

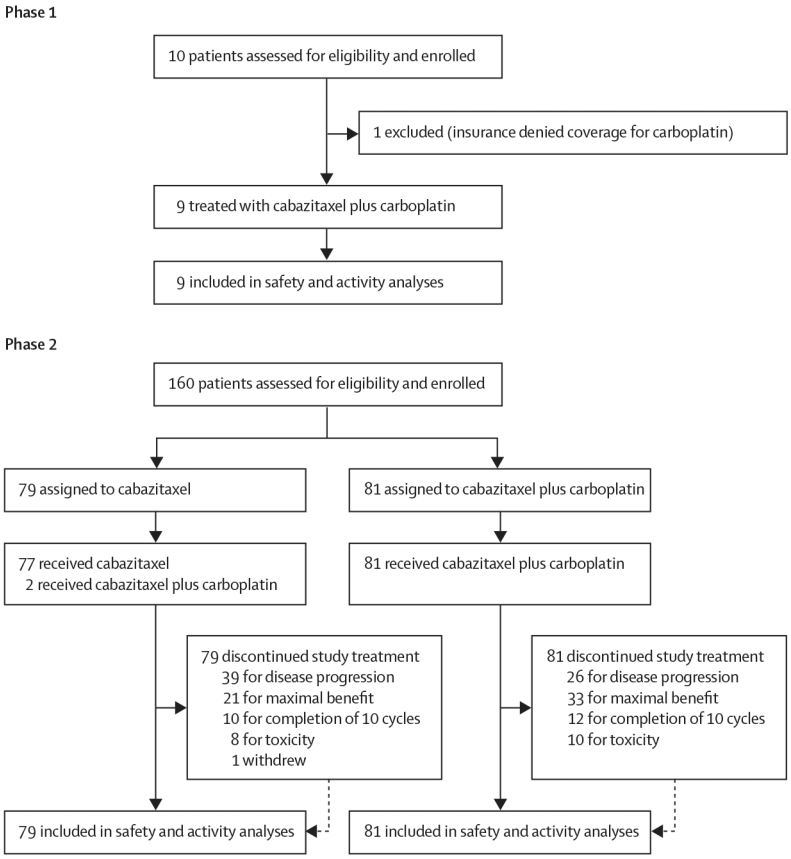

Figure 1: Trial profile

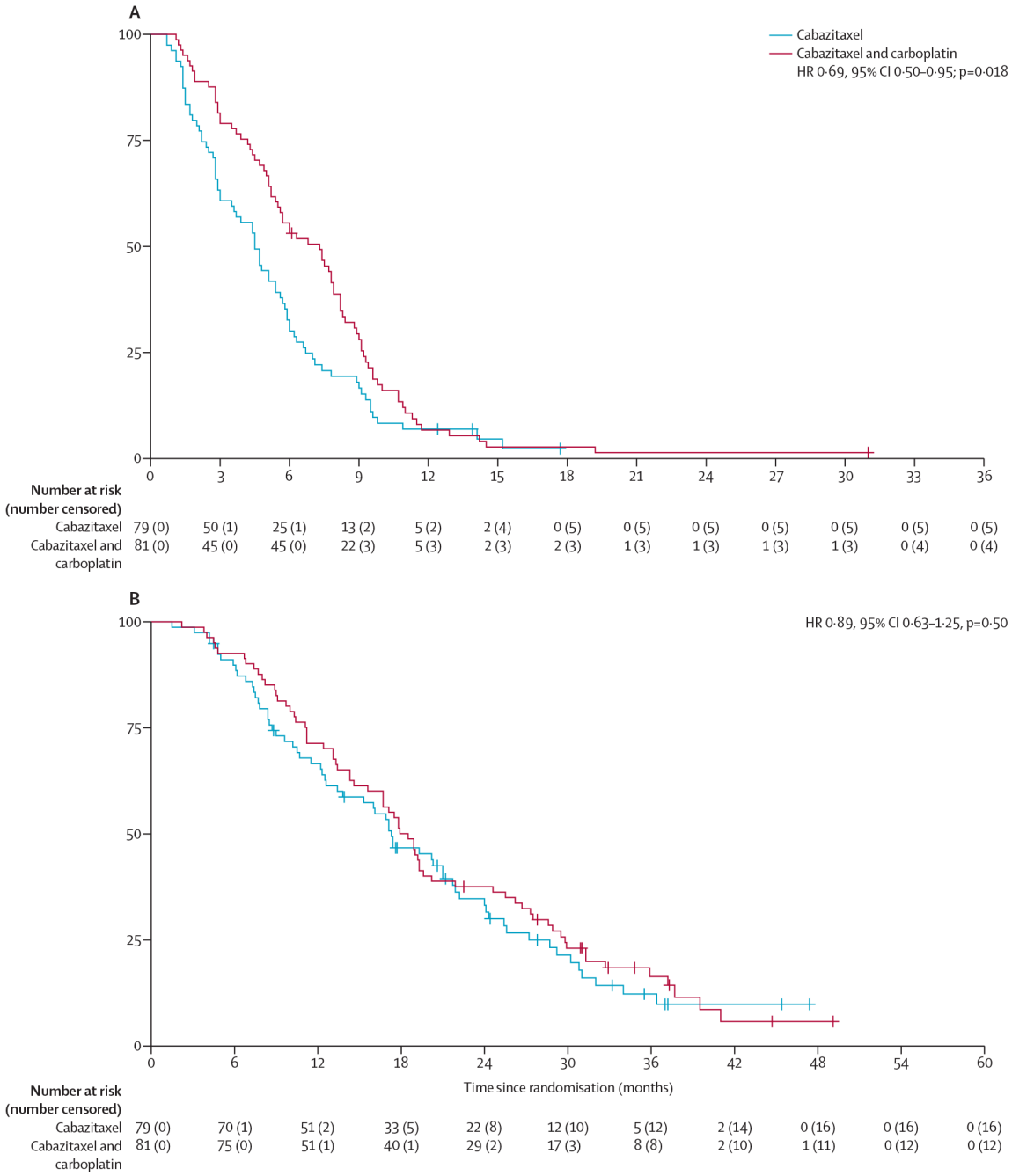

Figure 2: Kaplan-Meier survival estimates

Progression-free survival (A) and overall survival (B) in the intention-to-treat population.

Table 1:

Baseline characteristics

	Phase 1	Phase 2	
	Cabazitaxel and carboplatin group (n=9)	**Cabazitaxel group (n=79)**	**Cabazitaxel and carboplatin group (n=81)**
Age, years	72 (67–76)	66 (61–69)	68 (62–73)
Race			
White	8 (89%)	57 (72%)	64 (79%)
Black	0	16 (20%)	8 (10%)
Other	1 (11%)	6 (8%)	9 (11%)
Eastern Cooperative Oncology Group performance status			
0	0 (%)	21 (27%)	22 (27%)
1 and 2	9 (100%)	58 (73%)	59 (73%)
Aggressive variant prostate cancer clinicopathological criteria *	5 (56%)	41 (52%)	45 (56%)
Previous therapies for castration-resistant prostate cancer			
Docetaxel	9 (100%)	23 (29%)	23 (28%)
Abiraterone	6 (67%)	42 (53%)	56 (69%)
Enzalutamide	0	26 (33%)	23 (28%)
Prostate-specific antigen, ng/mL	74·7 (11·5–181·0)	23·7 (8·6–81·2)	33·8 (11·4–146·3)
Lactate dehydrogenase, IU/L	521·0 (448·5–805·0)	528·0 (416·0–751·0)	552·0 (418·3–831·8)
Bone-specific alkaline phosphatase, μg/L	16·0 (9·1–60·5)	28·0 (14·0–74·0)	32·0 (17·3–65·5)
Bone metastases			
No	1 (11%)	7 (9%)	6 (7%)
Yes	8 (89%)	72 (91%)	75 (93%)
Response Evaluation Criteria in Solid Tumors-measurable disease			
No	4 (44%)	32 (41%)	37 (46%)
Yes	5 (56%)	47 (59%)	44 (54%)
Lymph node	4 (44%)	36 (46%)	30 (37%)
Visceral	3 (33%)	18 (23%)	22 (27%)
Lymph node plus visceral	2 (22%)	5 (6%)	12 (15%)
Previous treatment to primary			
No	3 (33%)	34 (43%)	32 (40%)

	Phase 1	Phase 2	
	Cabazitaxel and carboplatin group (n=9)	**Cabazitaxel group (n=79)**	**Cabazitaxel and carboplatin group (n=81)**
Yes	6 (67%)	45 (57%)	49 (60%)
Radical prostatectomy	3	29	33
Radiotherapy	3	16	15
Cryosurgery	0	0	1
Tp53			
Immunohistochemistry	0/2 (0%)	11/22 (50%)	7/30 (23%)
ctDNA	3/6 (50%)	18/45 (40%)	19/40 (47%)
RB1			
Immunohistochemistry	2/3 (66%)	6/23 (23%)	13/32 (41%)
ctDNA	2/6 (33%)	22/45 (49%)	21/40 (52%)
PTEN			
Immunohistochemistry	3/3 (100%)	16/25 (64%)	25/33 (76%)
ctDNA	1/6 (17%)	18/45 (40%)	11/40 (27%)
Aggressive variant prostate cancer molecular signature			
Immunohistochemistry	2/3 (66%)	8/22 (36%)	16/31 (52%)
ctDNA	2/6 (33%)	21/45 (47%)	17/40 (42%)

Values are median (IQR), n (%), or n/N (%). ctDNA=circulating tumour DNA.

* The distribution of the aggressive variant prostate cancer clinicopathological criteria is shown in the appendix (p 5).

Table 2:

Adverse events in the phase 2 part of the study

	Cabazitaxel group (n=79)				Cabazitaxel and carboplatin group (n=81)			
	Grade 1–2	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Fatigue	49 (62%)	7 (9%)	0	0	51 (63%)	16 (20%)	0	0
Nausea	25 (32%)	1 (1%)	0	0	49 (60%)	5 (6%)	0	0
Diarrhoea	38 (48%)	2 (3%)	0	0	48 (59%)	4 (5%)	0	0
Constipation	12 (15%)	0	0	0	30 (37%)	2 (2%)	0	0
Dyspnea	14 (18%)	3 (4%)	0	0	27 (33%)	7 (9%)	0	0
Vomiting	14 (18%)	0	0	0	27 (33%)	1 (1%)	0	0
Alopecia	14 (18%)	0	0	0	24 (30%)	0	0	0
Paresthesia	7 (9%)	0	0	0	15 (19%)	0	0	0
Dysgeusia	8 (10%)	0	0	0	14 (17%)	0	0	0
Neuropathy	3 (4%)	1 (1%)	0	0	13 (16%)	0	0	0
Pain	6 (8%)	5 (6%)	0	0	8 (10%)	1 (1%)	0	0
Dizziness	6 (8%)	0	0	0	13 (16%)	1 (1%)	0	0
Anorexia	5 (6%)	1 (1%)	0	0	12 (15%)	2 (2%)	0	0
Weight loss	3 (4%)	0	0	0	9 (11%)	0	0	0
Oedema	11 (14%)	0	0	0	10 (12%)	0	0	0
Fever	3 (4%)	0	0	0	8 (10%)	1 (1%)	0	0
Haematuria	3 (4%)	0	0	0	6 (7%)	4 (5%)	0	0
Hypotension	1 (1%)	1 (1%)	0	0	4 (5%)	3 (4%)	0	0
Abdominal pain	2 (3%)	2 (3%)	0	0	4 (5%)	3 (4%)	0	0
Dehydration	1 (1%)	3 (4%)	0	0	3 (4%)	7 (9%)	0	0
Pneumonia	0	4 (5%)	0	0	0	3 (4%)	0	0
Thromboembolic event	0	0	0	1 (1%)	0	2 (2%)	1 (1%)	0
Febrile neutropenia	0	1 (1%)	0	0	0	3 (4%)	1 (1%)	0
Urinary tract infection	1 (1%)	1 (1%)	0	0	0	2 (2%)	2 (2%)	0
Fracture	0	0	0	0	0	2 (2%)	0	0
Hypomagnesaemia	6 (8%)	0	0	0	33 (41%)	1 (1%)	0	0
Anaemia	16 (20%)	3 (4%)	0	0	23 (28%)	18 (22%)	1 (1%)	0

	Cabazitaxel group (n=79)				Cabazitaxel and carboplatin group (n=81)			
	Grade 1–2	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Thrombocytopenia	4 (5%)	0	1 (1%)	0	18 (22%)	8 (10%)	3 (4%)	0
Hyperglycaemia	12 (15%)	2 (3%)	0	0	15 (19%)	1 (1%)	0	0
Neutropenia	3 (4%)	3 (4%)	0	0	2 (2%)	6 (7%)	7 (9%)	0
Lymphopenia	8 (10%)	1 (1%)	0	0	3 (4%)	4 (5%)	1 (1%)	0
Hypokalaemia	7 (9%)	0	0	0	10 (12%)	2 (2%)	1 (1%)	0
Elevated aspartate aminotransferase	5 (6%)	0	0	0	10 (12%)	0	0	0
Hypocalcaemia	5 (6%)	0	0	0	9 (11%)	0	0	0
Elevated creatinine	7 (9%)	1 (1%)	0	0	8 (10%)	0	0	0

Values are n (%).Grade 1–2 adverse events that occurred in 10% or more of patients in either group and grade 3–5 events that occurred in 2% or more patients in either group are shown.

Table 3:

Summary of treatment

	Cabazitaxel group (n=79)	Cabazitaxel plus carboplatin group (n=81)
Number of cycles received	5·0 (2·5–7·0)	6·0 (5·0–8·0)
Median treatment duration, months	3·8 (1·8–5·4)	4·9 (3·5–6·8)
Patients requiring reduction of cabazitaxel dose	3 (4%)	17 (21%)
Patients requiring reduction of carboplatin dose	··	3 (4%)
Patients with treatment delays	31 (39%)	53 (65%)
Reasons for treatment discontinuation		
Disease progression	39 (49%)	26 (32%)
Radiographic	25 (32%)	18 (22%)
Clinical	19 (24%)	13 (16%)
Maximal clinical benefit	21 (27%)	33 (41%)
Receipt of 10 cycles	10 (13%)	12 (15%)
Toxicity	8 (10%)	10 (12%)
Patient withdrawal	1 (1%)	0

Values are median (IQR) or n (%).