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Patient Preference Between Cabazitaxel and Docetaxel for First-line Chemotherapy in Metastatic Castration-resistant Prostate Cancer: The CABADOC Trial

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Abstract

Background: The taxanes docetaxel and cabazitaxel prolong overall survival for men with metastatic castration-resistant prostate cancer (mCRPC), with cabazitaxel approved in the postdocetaxel setting only. Recent data suggest they have similar efficacy but a different safety profile in the first-line mCRPC setting.

Objective: To assess patient preference between docetaxel and cabazitaxel among men who received one or more doses of each taxane and did not experience progression after the first taxane.

Design, setting, and participants: Chemotherapy-naïve patients with mCRPC were randomized 1:1 to receive docetaxel (75 mg/m^2 every 3 wk × 4 cycles) followed by cabazitaxel (25 mg/m^2 every 3 wk × 4 cycles) or the reverse sequence. Randomization was stratified by prior abiraterone or enzalutamide use.

Outcome measurements and statistical analysis: The primary endpoint was patient preference, assessed via a dedicated questionnaire after the second taxane. Secondary endpoints included reasons for patient preference, prostate-specific antigen response, radiological progression-free survival, and overall survival. This clinical trial is registered at ClinicalTrials.gov as NCT02044354.

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Results and limitations: Of 195 men randomized, 152 met the prespecified modified intent-to-treat criteria for analysis. Overall, 66 patients (43%) preferred cabazitaxel, 40 (27%) preferred docetaxel, and 46 (30%) had no preference ($p = 0.004$, adjusted for treatment period effect). More patients preferred treatment period 1 (43%, 95% confidence interval [CI] 36–52%) versus period 2 (27%, 95% CI 20–34%). Patient preference for cabazitaxel was mainly related to less fatigue (72%), better quality of life (64%), and other adverse events (hair loss, pain, nail disorders, edema). Adverse events were consistent with the known safety profile of each drug.
Conclusions: A significantly higher proportion of chemotherapy-naïve men with mCRPC who received both taxanes preferred cabazitaxel over docetaxel. Less fatigue and better quality of life were the two main reasons driving patient choice.
Patient summary: Men with metastatic castration-resistant prostate cancer preferred cabazitaxel over docetaxel for chemotherapy, mainly because of less fatigue and better quality of life.

1. Introduction

Docetaxel was the first treatment that improved overall survival (OS) for men with metastatic castration-resistant prostate cancer (mCRPC) [1]. Cabazitaxel is a second-generation taxane that retains activity in some tumors resistant to docetaxel and novel hormonal therapies [2–4]. In the FIRSTANA study, cabazitaxel, given at either 25 mg/m^2 (C25) or 20 mg/m^2 (C20), showed no superiority versus docetaxel for OS as first-line treatment [5]. However, cabazitaxel demonstrated a different safety profile from docetaxel, favoring C20. Peripheral edema, alopecia, nail disorders, and peripheral neuropathy were more common with docetaxel, while febrile neutropenia, diarrhea, and hematuria were more prevalent with C25. C20 showed less toxicity and a longer time to deterioration of physical wellbeing in comparison to docetaxel. In the PROSELICA study, OS with C20 was noninferior to OS with C25, and grade 3–4 adverse events (AEs) were less frequent with C20 [6]. The CARD trial recently showed that C25 given with prophylactic granulocyte colony stimulating factor (G-CSF) improves OS versus abiraterone or enzalutamide in mCRPC patients previously treated with docetaxel and who progressed within 12 mo with the alternative androgen-receptor axis inhibitor [7].

These results provide the first evidence of a survival benefit with a taxane in third-line treatment and provide important information on treatment sequencing.

Patient-reported outcomes (PROs) and patient preference studies, as complementary ways of capturing patient experience data, have increased in significance in recent years for evidence-based medicine. Randomized clinical trials are usually designed to evaluate the efficacy and toxicity of therapies, but may not always be suitable for assessing patient opinion [8]. The PISCES trial was the first study to evaluate patient preference [9]. The success of this innovative trial led us to design the CABADOC trial. The aim of our study was to evaluate patient preference between docetaxel and cabazitaxel and to better characterize the differences between these two taxanes.

2. Patients and methods

2.1. Patients

Chemotherapy-naïve men with progressive mCRPC, Eastern Cooperative Oncology Group performance status of 0–2, and adequate hematologic, renal, and hepatic function were eligible for the study. Prior treatment with enzalutamide or abiraterone (but not both) was allowed (study protocol in the Supplementary material). The study protocol was approved by the local ethics committee and the study was conducted in accordance with the Declaration of Helsinki on Good Clinical Practice. All patients signed written informed consent before inclusion. The study was sponsored by Institut Gustave Roussy. Sanofi provided the study drugs and partial funding for the study. The study was registered in ClinicalTrial.gov as NCT02044354.

2.2. Study design and endpoints

CABADOC was an open-label, crossover, multicenter phase 3b study. Eligible patients were randomized at a ratio of 1:1 using TENALEA software after an informed consent form had been signed and all eligibility criteria had been checked. TENALEA is software that ensures the unpredictability of the treatment sequence allocated, after randomization was stratified by prior use of either abiraterone or enzalutamide versus no use of these drugs. Randomization was receipt of either docetaxel (75 mg/m^2 every 3 wk $\times$ 4 cycles, period 1) followed by cabazitaxel (25 mg/m^2 every 3 wk $\times$ 4 cycles, period 2) in the DO-CA arm, or the reverse sequence in the CA-DO arm. All men also received continuous treatment with prednisone 10 mg daily. Primary prophylaxis with G-CSF was recommended for patients with high-risk clinical features according to the American Society of Clinical Oncology and European Society for Medical Oncology guidelines [10,11]. The second taxane was started 3 wk after the last dose of the first taxane. Patients who discontinued the first taxane because of unacceptable toxicity crossed over to the second taxane. Patients with progressive disease during period 1 discontinued the trial. Tumor assessment was performed at the end of each period. The patient preference questionnaire was administered at the end of period 2 (Supplementary material). Further treatment with either docetaxel or cabazitaxel (as per patient preference) could be administered according to physician judgment, depending on tumor assessment and laboratory results.

The primary endpoint was the patient preference between docetaxel and cabazitaxel or the absence of a preference, assessed via a dedicated questionnaire at the end of period 2 (Supplementary material). Secondary endpoints included specific reasons for patient preference, prostate-specific antigen (PSA) response $\geq$50% with each taxane, AEs, radiological

progression-free survival (rPFS), and OS. For the PSA response, a waterfall plot describing all changes from baseline was provided in accordance with Prostate Cancer Working Group 2 (PCWG2) criteria. rPFS was defined according to the PCWG2 criteria [12]. OS was defined as the time elapsed from randomization to death from any cause. The incremental cost-utility ratio of cabazitaxel compared to docetaxel and quality of life (Functional Assessment of Chronic Illness Therapy–Fatigue [FACIT-F] and Functional Assessment of Cancer Therapy–Prostate [FACT-P]) were also assessed and will be described in a separate report.

2.3. Statistical analysis

The null hypothesis was a lack of difference in the proportion of patients preferring cabazitaxel or docetaxel. Similarly to the PISCES trial, the alternative hypothesis was a difference of more than 20% in the proportion of patients preferring cabazitaxel or docetaxel [9]. The initial assumption was that 50% of patients would prefer cabazitaxel, 30% would prefer docetaxel, and 20% would have no preference. The sample size was amended in 2016, because 22% of patients did not express any preference. Taking into account that 49% of men would prefer cabazitaxel and 29% would prefer docetaxel, the sample size was increased to maintain a difference of 20%. Considering only patients who expressed a preference, in a unpaired design it was estimated that 62.8% (49/78) of patients would prefer cabazitaxel compared to a null hypothesis of 50% (no difference in proportion of patients preferring cabazitaxel to docetaxel). With a power of 80% and bilateral α of 0.05, the estimated sample size was 125 patients expressing a preference, using a two-sided binomial test. Assuming that 22% of patients would have no preference, 160 patients needed to be evaluated. Further assuming that approximately 22% of patients would be excluded from the trial for disease progression after the first treatment period, a sample size of 195 patients (97 per arm) was required.

The modified intent-to-treat (mITT) population was used to evaluate patient preference (primary endpoint) as well as factors influencing their preference. The mITT population was predefined as all patients who received at least one cycle of study drug in each period and who did not experience cancer progression after the first taxane. We excluded men with cancer progression during the first period, because their condition would have possibly influenced their choice. The safety population included all patients exposed to at least one dose of docetaxel or cabazitaxel. PSA response, PFS, and OS were analyzed in the ITT population (without the screen failure patient).

Primary endpoint was the percentage of patients preferring a given treatment and its 95% confidence interval (CI) in the mITT population without any missing data in the preference questionnaire. The percentage of patients preferring cabazitaxel over docetaxel was compared using an unpaired Fisher test, excluding patients without a preference. The period effect was tested by comparing the percentage of patients preferring the first treatment period over the second one using an unpaired Fisher test. Prescott's test was used as a complementary preplanned analysis of the primary endpoint to take into account any period effect and patients having no preference on the questionnaire [13]. Quantitative data were compared using the Student t test. Qualitative data were compared with a χ^2 test (or Fisher's exact test if appropriate). Survival data were estimated using the Kaplan-Meier method and comparison of the groups was performed using the log-rank test.

3. Results

3.1. Patient characteristics

From June 2014 to October 2016, 195 patients were screened in 17 centers (Table 1). Patient enrolment and allocation are described in the CONSORT diagram in Fig. 1. Overall, two patients did not receive any treatment; one patient was a screen failure and the other had rapid deterioration in his performance status after inclusion. Twenty-eight patients were excluded because they did not receive the second taxane (eight patients in the DO-CA arm vs 20 patients in the CA-DO arm; $p = 0.02$). In the DO-CA arm, reasons for not receiving the second taxane were cancer progression or death ($n = 4$), AEs ($n = 3$), and an unrelated coronary syndrome ($n = 1$). In the CA-DO arm, reasons for not receiving the second taxane were cancer progression or death ($n = 10$), AEs ($n = 8$), patient refusal ($n = 1$), and hospitalization ($n = 1$). The baseline characteristics of men who did not receive the second taxane were not different from those of the mITT population. Thirteen patients did not complete the preference questionnaire despite having received one or more doses of each taxane (DO-CA arm, $n = 8$; CA-DO arm, $n = 5$). Overall, 43 of the 195 patients were excluded, leaving 152 patients evaluable for the primary endpoint (DO-CA arm, $n = 79$; CA-DO arm, $n = 73$).

Table 1 – Baseline patient characteristics

Parameter	DO-CA arm (n = 97)	CA-DO arm (n = 98)	p value *
Median age, yr (interquartile range)	70 (66–75)	70 (65–76)	0.9
Type of progression before randomization, n (%)			
• Clinical	42 (44))	42 (43)	>0.9
• Radiological	87 (91))	91 (93)	0.08
• Biological	82 (85)	85 (87)	0.8
Eastern Cooperative Oncology Group performance status, n (%)			0.1
• 0	58 (60)	46 (47)	
• 1	31 (32)	47 (48)	
• 2	8 (8)	5 (5)	
Gleason score, n (%)			0.03
• <7	11 (12)	7 (7)	
• 7	38 (40)	42 (44)	
• 7	18 (19)	33 (34)	
• 9	26 (28)	13 (14)	
• Missing	1 (1)	1 (1)	
Presence of metastases at inclusion, n (%)			0.8
• Yes	41 (43)	44 (45)	
• Missing	1 (1.1)	0	
Prior treatment with abiraterone or enzalutamide, n (%)	38 (39)	38 (39)	0.6

CA = cabazitaxel; DO = docetaxel.
* p values were calculated using the Student test for continuous variables and a χ^2 or Fisher's exact test for categorical variables.

3.2. Primary endpoint: patient preference

Among the 152 evaluable patients, 66 (43%, 95% CI 36–52%) preferred cabazitaxel, 40 (27%, 95% CI 20–34%) preferred docetaxel, and 46 (30%, 95% CI 23–38%) expressed no preference between the two taxanes (Table 2). Of the 106 patients who expressed a preference, a significantly higher proportion preferred cabazitaxel (62%, 95% CI 53–71%) than docetaxel (38%, 95% CI 29–50%; $p = 0.008$).

There was a period effect: 66 patients (43%, 95% CI 36–52%) preferred period 1 and 40 (27%, 95% CI 20–34%)

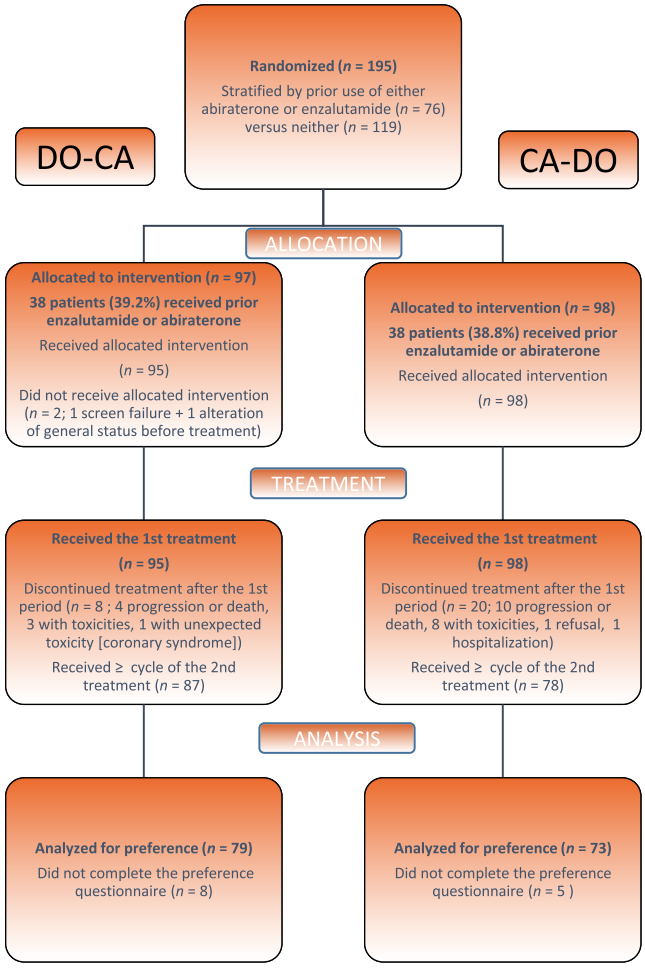


Fig. 1 – Consolidated Standards of Reporting Trials (CONSORT) diagram. DO = docetaxel; CA = cabazitaxel.

Table 2 – Patient preferences

Preference	Received docetaxel first (*n* = 79)	Received cabazitaxel first (*n* = 73)
Preferred docetaxel, *n* (%)	28 (36)	12 (16)
Preferred cabazitaxel, *n* (%)	28 (36)	38 (52)
Did not have any preference, *n* (%)	23 (28)	23 (32)

preferred period 2. In the DO-CA arm, 28 patients (35.5%) preferred docetaxel, 28 (35.5%) preferred cabazitaxel, and 23 (29%) had no preference. In the CA-DO arm, 38 patients (52%) preferred cabazitaxel, 12 (16.5%) preferred docetaxel, and 23 (31.5%) had no preference. After adjusting for the period effect and patients without a preference using the Prescott test, more men preferred cabazitaxel in the mITT population ($p = 0.004$). During the first period, the number of dropouts due to AEs, progression, or death was numerically higher with cabazitaxel compared to docetaxel (19 vs 7). An exploratory analysis including these 26 patients was performed: 66/178 men (37%, 95% CI 30–44) preferred cabazitaxel, while 40 (22%, 95% CI 16–28%) preferred docetaxel ($p = 0.004$). A total of 72 patients (41%, 95% CI 33–47%) did not express a preference or did not receive the second taxane.

3.3. *Secondary endpoints*

The main factors influencing patient preference were less fatigue, better quality of life, less hair loss, less pain, less change in food taste, less nail deterioration, less nausea/vomiting, and less edema (Fig. 2). In both groups, fatigue had the most influence on preference choice. PSA response ≥50% was evaluated in 96 patients in the DO-CA arm and 98 in the CA-DO arm (Supplementary Fig. 1). For patients treated with cabazitaxel, the PSA response was 60.2% (95% CI 50–70%) in period 1 and 43.8% (95% CI 33–54%) in period 2. For patients treated with docetaxel, the PSA response was 50% (95% CI 40–60%) in period 1 (Supplementary Fig. 1A) and 37.8% (95% CI 28–47%) in period 2 (Supplementary Fig. 1C). PSA responses according to previous treatment with novel hormonal agents are reported in Supplementary Fig. 1B,C,E,F. Median PFS (all periods combined) was 10.3 mo in the DO-CA arm and 9.4 mo in the CA-DO arm (Fig. 3A). Median OS was 20.5 mo in the DO-CA arm and 18.9 mo in the CA-DO arm (Fig. 3B).

3.4. *Safety*

The median number of taxane cycles received was four in each period, regardless of treatment arm. During period 1, 95% and 89% of patients received four cycles in the DO-CA and CA-DO arms, respectively ($p = 0.13$). During period 2, 80% and 65% of patients received four cycles in the DO-CA and CA-DO arms, respectively ($p = 0.02$). During period 1, the most common AEs of any grade with docetaxel versus cabazitaxel were fatigue (45% vs 49%), anemia (47% vs 44%), alopecia (31% vs 9%), diarrhea (26% vs 15%), and nausea (18% vs 27%); similar findings were observed during period 2 with the exception of peripheral neuropathy, which was more prevalent with docetaxel (28.2% vs 18.4%; Supplementary Tables 1 and 2). During period 1, grade ≥3 AEs were more common with cabazitaxel versus docetaxel (52.0% vs 24.2%). During period 2, grade ≥3 AEs were reported by 32.1% and 25.3% of patients treated with docetaxel and cabazitaxel, respectively. Grade 5 AEs were reported for five patients treated with cabazitaxel, exclusively during period 1 (febrile neutropenia, $n = 2$; sepsis, $n = 2$; clinical deterioration, $n = 1$), mainly after cycle 1 or 2 ($n = 4$). Three of these AEs were related to cabazitaxel ($n = 3/152$, 1.97%). Grade 5 AEs were reported for two patients treated with docetaxel (one sudden death of unknown origin after cycle 3 in period 1; one death related to surgical procedure after cycle 7 in period 2). Febrile neutropenia was reported for 11 patients (docetaxel, $n = 1$; cabazitaxel, $n = 10$), exclusively during period 1. Of these, five patients had received prophylactic G-CSF.

4. Discussion

To the best of our knowledge, this is the first study reporting patient preference between two taxanes (docetaxel and cabazitaxel) among men with mCRPC, and the first study assessing patient preference between systemic treatments

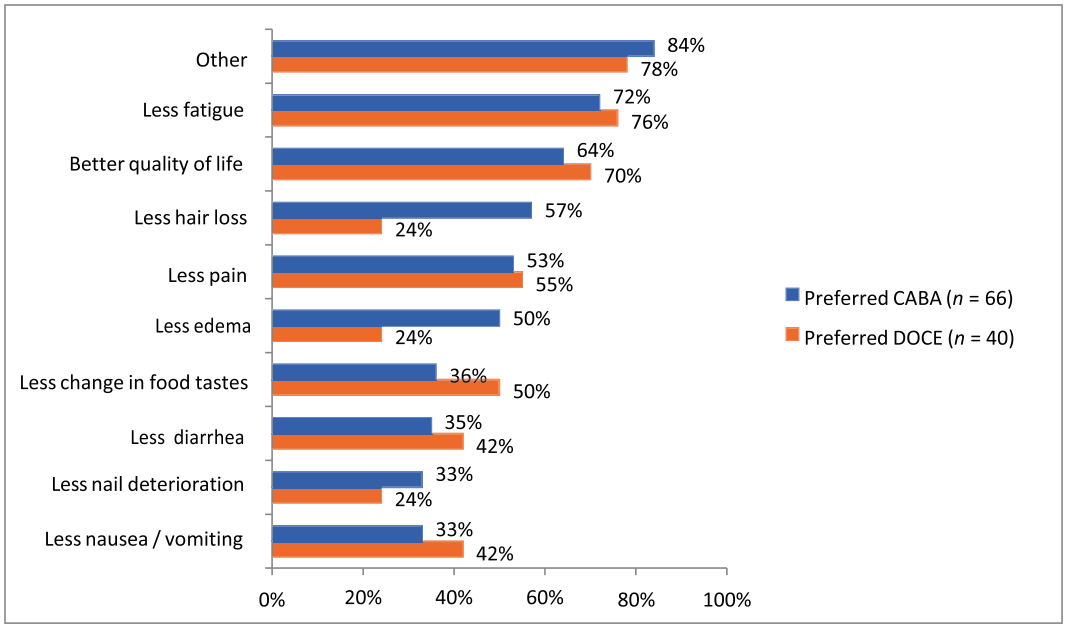
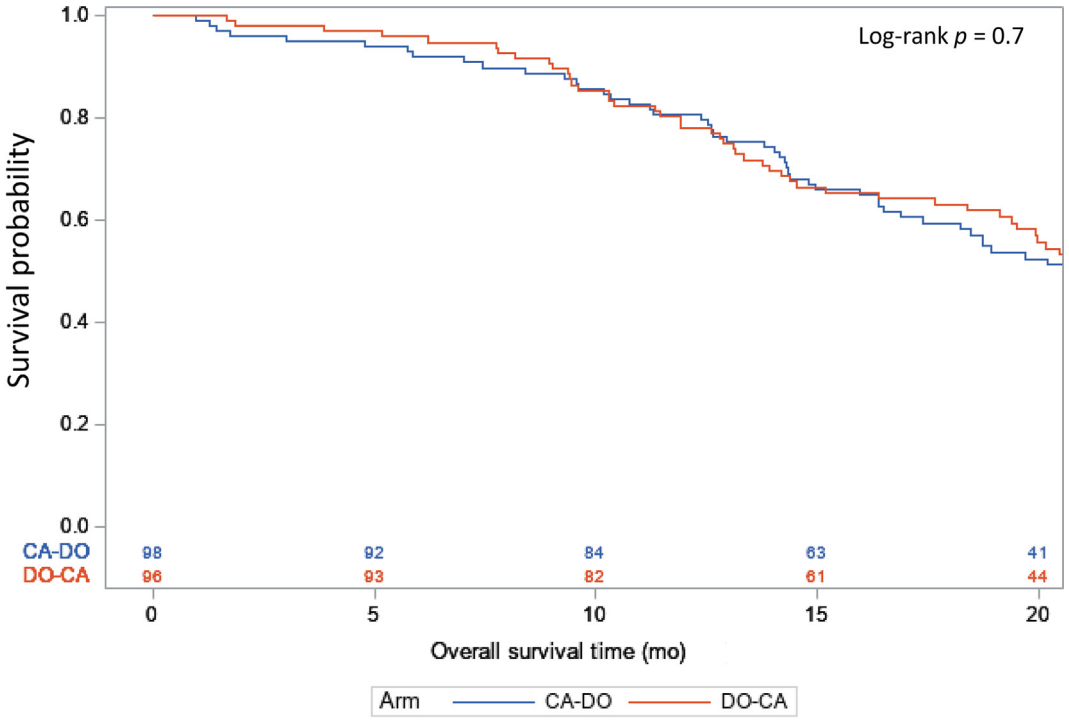


Fig. 2 – Common factors influencing patient preference. DOCE = docetaxel; CABA = cabazitaxel.

in advanced prostate cancer. The primary endpoint was met. Among 106 out of 152 men who expressed a preference between the two taxanes, 62% preferred cabazitaxel over docetaxel. When taking into account in the analysis patients who did not receive the second taxane because of AEs, progression, or death, the proportion of patients who preferred cabazitaxel was smaller (37%), but it remained significantly higher than the proportion of patients who preferred docetaxel (22%). In recent decades, the number of clinical trials that include PROs has progressively grown [14]. Patient preference differs from PROs, since it reflects an eventual choice made when presented with different options, representing a subjective evaluation by the patient after considering different parameters, such as treatment activity, drug characteristics, toxicity profile, and other individual factors [15]. We believe that such information can help clinicians to better discuss treatment plans with patients and can therefore improve clinical outcomes, possibly also by improving adherence [16].

The main reason for preferring cabazitaxel over docetaxel was less fatigue (72%). Interestingly, there was no difference in the clinicians' assessment of fatigue between the two drugs (Supplementary Tables 1 and 2). More patients treated with cabazitaxel in period 1 experienced grade 3 AEs in comparison to treatment with docetaxel. Nevertheless, a greater number of men in the CA-DO arm preferred cabazitaxel. This demonstrates a gap between patient and physician evaluations, but it could also be indicative of the relative importance that patients attribute to the different side effects (an obvious preference observed from our results is a desire to avoid fatigue). Without doubt, treatment remains a subjective experience for which patients and physicians may have different perceptions. Cabazitaxel was also associated with better quality of life, less hair loss, less pain, less change in food taste, less nail deterioration, less nausea/vomiting, and less edema. Docetaxel and cabazitaxel have a different toxicity profile. Since cabazitaxel is not superior to docetaxel in first-line mCRPC, it might be considered for men with contraindications to docetaxel, such as those with preexisting grade 2 peripheral neuropathy or glucocorticoid intolerance, even as first-line chemotherapy. Together with the FIRSTANA, PROSELICA, TROPIC, and CARD studies, the CABADOC trial supports the activity and the manageable safety profile of cabazitaxel in men with mCRPC [4–7]. The incidence of febrile neutropenia with C25 was 8%, 12%, and 9% in TROPIC, FIRSTANA, and PROSELICA, respectively, but primary G-CSF prophylaxis was not allowed in cycle 1 and was left to physician judgment for subsequent cycles. In our study, primary G-CSF prophylaxis was also not mandatory and febrile neutropenia was observed in ten men receiving cabazitaxel, including two treatment-related deaths for men not receiving prophylactic G- CSF. In the CARD trial, G-CSF prophylaxis was mandatory in all cycles including cycle 1 and the incidence of febrile neutropenia with C25 was 3.2%, approximately half of the rate in our trial (7.1%) [7]. Prophylactic G-CSF, including in cycle 1, is thus recommended for mCRPC patients treated with cabazitaxel. One limitation is the open-label study design. Since investigators were not involved in the treatment preference decision and patients were not previously exposed to these drugs, we considered that blinding of the study was unnecessary. Furthermore, the high doses of steroids needed for docetaxel premedication would have unmasked the treatment, or this would have required a double placebo. Another limitation is that docetaxel was compared to cabazitaxel dosed at C25 only, since this is the recommended starting dose in Europe. It is possible that the lower dose of cabazitaxel (C20) that was noninferior to C25 in PROSELICA might have further improved the tolerability of cabazitaxel and thus the perceived difference between the taxanes [6]. An important finding is that more patients who received cabazitaxel did



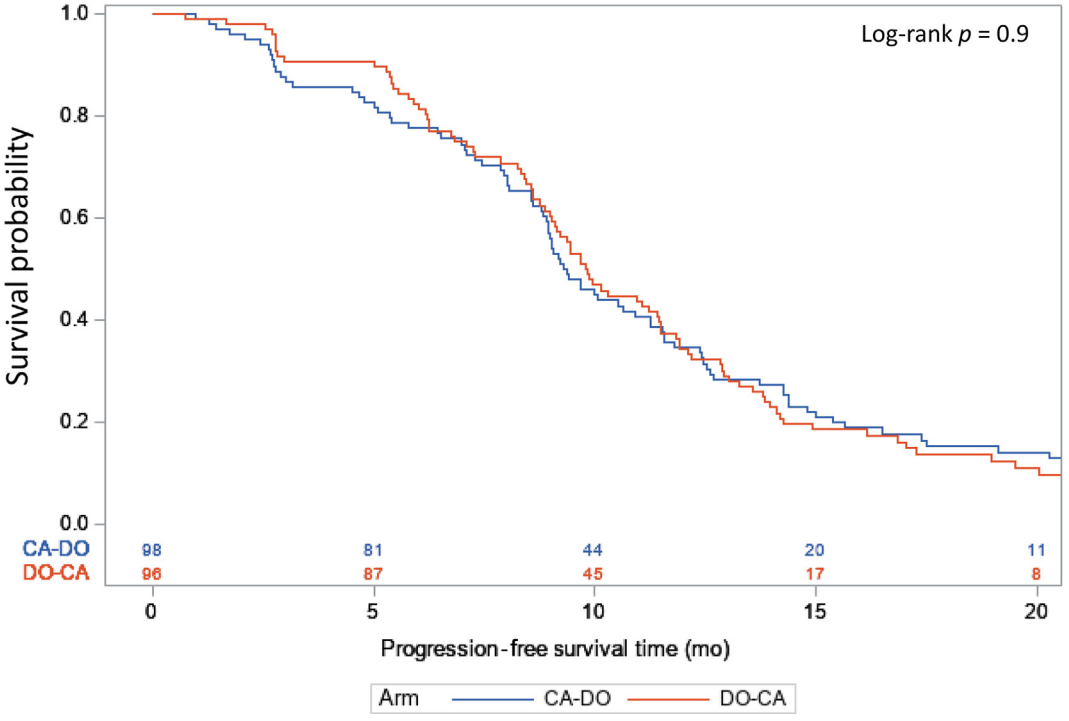


Fig. 3 – (A) Radiographic progression-free survival and (B) overall survival. DO = docetaxel; CA = cabazitaxel.

not proceed to the second taxane (20.4% vs 8.4% for the CA-DO and DO-CA arms, respectively, a total dropout rate after period 1 of 22.1%). Nevertheless, our study design assumed that approximately 22% of patients would be excluded from the trial for disease progression after the first treatment period (see Statistical analysis section), therefore allowing for retention of statistical power.

5. Conclusions

In conclusion, a significantly higher proportion of chemotherapy-naïve men with mCRPC starting taxane therapy prefer cabazitaxel over docetaxel. Fewer AEs and better quality of life were the two main reasons provided by

patients for their choice. This should be considered when managing men with mCRPC.

Author contributions: Karim Fizazi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Fizazi, Borget.
Acquisition of data: All authors.
Analysis and interpretation of data: Borget, Fizazi.
Drafting of the manuscript: Baciarello, Borget, Fizazi.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Borget.
Obtaining funding: All authors.
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Supervision: All authors.
Other: None.

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Peer Review Summary

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