Chapter 4

CAST: A retrospective analysis of cabazitaxel and abiraterone acetate sequential treatment in patients with metastatic castrate-resistant prostate cancer previously treated with docetaxel

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Abstract

Background: Cabazitaxel and abiraterone have both received approval for treating metastatic castrate-resistant prostate cancer (mCRPC) patients after first-line docetaxel therapy. In the CAST-study, the clinical outcome of docetaxel-treated mCRPC patients treated sequentially with both cabazitaxel and abiraterone was evaluated, to study whether treatment sequence could influence clinical outcome.

Methods: Data were collected retrospectively from mCRPC patients at twelve hospitals across the Netherlands who initiated cabazitaxel and/or abiraterone before December 2012. Primary outcome measure was overall survival (OS); secondary measures were progression-free survival (PFS), biochemical PFS, and best clinical and PSA response. Hospital admission data during treatment were collected, as well as toxicities resulting in treatment discontinuation or patient death.

Results: Sixty-three and 69 patients received Cab→Abi (cabazitaxel prior to abiraterone) and Abi→Cab (abiraterone prior to cabazitaxel) before July 10th, 2013, respectively. Median OS was 19.1 months and 17.0 months in Cab→Abi and Abi→Cab treated patients, respectively (p=0.369). Median PFS and biochemical PFS were significantly extended in Cab→Abi treated patients: 8.1 versus 6.5 (p=0.050) and 9.5 versus 7.7 months (p=0.024), respectively. Although partial responses to cabazitaxel occurred in both groups, Abi→Cab treated patients had a significantly decreased antitumor response from cabazitaxel than Cab→Abi treated patients (median PFS 5.0 versus 2.6 months, p<0.001). Minor differences in toxicities were observed based on therapy sequence; generally, toxicity from cabazitaxel could be severe, while abiraterone toxicity was milder.

Conclusions: This retrospective analysis indicates that primary progression on cabazitaxel or abiraterone did not preclude a response to the other agent in mCRPC patients. However, tumor response of both agents, particularly cabazitaxel, was lower when administered as higher-line therapy in the selected study population.

Introduction

Metastatic castrate-resistant prostate cancer (mCRPC) is the second deadliest cancer in men in the Western world.[1, 2] Recently, novel therapeutic agents have emerged for the systemic treatment of these patients. Two such therapies are cabazitaxel and abiraterone acetate, which received United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA) approval between 2010 and 2011 for use in mCRPC patients following disease progression during or after docetaxel. Although abiraterone also received FDA and EMA approval for use in docetaxel-naive mCRPC patients, it has not been registered for this indication in the Netherlands.

Abiraterone acetate (Zytiga®, Johnson&Johnson) selectively inhibits the enzyme cytochrome P450 c17 (CYP17), thereby blocking testosterone biosynthesis.[3] In a double-blind phase III registration study (COU-AA-301), patients treated with abiraterone plus prednisone had an increased median overall survival (OS) (15.8 versus 11.2 months), median radiologic progression-free survival (PFS) (5.6 versus 3.6 months), and median biochemical PFS (8.5 versus 6.6 months) as compared to patients treated with placebo plus prednisone.[4, 5] Mineralocorticoid-related adverse events (fluid retention, hypokalemia, hypertension) and urinary tract infections were more frequently reported in the abiraterone-treated group than in patients receiving placebo.

Cabazitaxel (Jevtana®, Sanofi-Aventis) is a second generation taxane which exerts its antitumor activity by targeting microtubule dynamics.[6] In preclinical studies, cabazitaxel was capable of inhibiting cancer cell lines with acquired resistance against docetaxel.[7, 8] In a phase III registration study (TROPIC), patients treated with cabazitaxel plus prednisone had an increased median OS (15.1 versus 12.7 months), median PFS (2.8 versus 1.4 months) and median biochemical (6.4 versus 3.1 months) as compared to patients treated with mitoxantrone plus prednisone.[9] Grade ≥3 hematological adverse events such as (febrile) neutropenia occurred more frequently in cabazitaxel-treated patients. Frequently reported grade ≥3 non-hematological adverse events included diarrhea, fatigue and asthenia.

Aforementioned registration studies were conducted parallel to each other; both agents resulted in a significant survival benefit. Direct comparison of cabazitaxel with abiraterone based on these studies is not possible. Therefore, both agents are approved in the post-docetaxel setting, but regulatory agencies such as the EMA and US FDA have made no mention of treatment sequence. [10-12] However, therapy sequence may influence clinical outcome[13-17]: resistance to one therapy may result in resistance to another therapy by similar mechanisms of action, or progression of mCRPC may result in decreased sensitivity to therapy. No clinical study has studied cabazitaxel and abiraterone treatment sequence. For this reason the CAST-study was conducted. In this retrospective study, the clinical

outcome is reported of (subgroups of) Dutch mCRPC patients treated with both cabazitaxel and abiraterone after receiving docetaxel as first-line therapy, evaluating antitumor activity and safety of both agents.

Patients and Methods

Patients

Twelve Dutch hospitals participated in this study, comprising the Netherlands Cancer Institute, five university hospitals and six regional hospitals across the nation. Eligible patients had confirmed mCRPC, for which they had received docetaxel at least once; all patients were medically or surgically castrated. Patients who had received abiraterone and/or cabazitaxel prior to docetaxel were excluded. All other mCRPC patients receiving cabazitaxel and/or abiraterone, as registered in electronic patient files, were included, including patients who received other treatments for their mCRPC before cabazitaxel and/or abiraterone therapy.

Study design and ethics

This study was a retrospective, multicenter, observational study. All patients had been informed before initiation of mCRPC treatment that data could be used anonymously for research purposes and were able to object at any time without consequences. Oral informed consent was acquired from patients who were still under treatment; data from other patients were collected if patients had not objected to data collection for research purposes. This is in accordance with the Dutch code of conduct for medical research and is in compliance with all Dutch and international laws regarding research with human data. Medical ethics committee approval was obtained before data collection.

Treatment

Standard treatment consisted of 1000 mg oral abiraterone acetate daily plus 10 mg oral prednisone daily or intravenous cabazitaxel 20 or 25 mg/m^2 every 21 days plus 10 mg oral prednisone daily. However, physicians were allowed to deviate from this protocol, for dose reductions, to initiate treatment at a lower dose, or to delay treatment. Discontinuation of treatment was based on disease progression, adverse events, patient's or physician's decision, and/or death. This decision was made entirely by the physician and patient; participation in the CAST-study did not influence this decision.

Medication to reduce or prevent side effects was allowed during cabazitaxel or abiraterone therapy, as well as additional symptomatic treatment against mCRPC, such as radiotherapy or denosumab. Although cabazitaxel and abiraterone are mentioned as second- and third-line therapies in this study, patients were allowed to receive alternative mCRPC therapies in between docetaxel, cabazitaxel and abiraterone. All such treatment decisions were made independent of participation in this study. Hence treatment regimens represented an

average clinical setting in the Netherlands.

Outcome measures

The primary outcome measure for patients who received both cabazitaxel and abiraterone was OS, defined as the number of days between start of second-line therapy (cabazitaxel or abiraterone) and death or censoring, regardless of therapies afterwards. Secondary outcome measures were PFS, biochemical PFS, and best clinical and prostate-specific antigen (PSA) response.

To determine PSA progression and response, guidelines from the Prostate Cancer Clinical Trials Working Group (PCWG) 2 were followed.[18] Hence, PSA progression was defined as an increase of ≥25% and ≥2 ng/ml over nadir PSA concentration. In general, PSA serum levels were measured in patients every three to four weeks. For determining the nadir PSA level, potential PSA flares were taken into account (patients with a continuous PSA rise from baseline within 12 weeks, not confirmed with imaging). Biochemical PFS was calculated from therapy start until PSA progression. Patients whose tumors responded to another systemic treatment before PSA progression, patients with PSA progression after more than three months between the last PSA assessment, and patients who died before PSA progression, were considered lost-to-follow-up.

PFS was calculated from therapy start until progression or censoring. Progression was established when PSA progression, radiological progression (CT/MRI/X-ray/bone scans), symptomatic progression (pain or other clinical symptoms) and/or death had occurred, following PCWG2 criteria. One form of progression sufficed to consider the patient's disease to be progressive, except for symptomatic progression. Symptomatic progression without radiological or PSA progression was not considered disease progression as this could be the subjective opinion of a patient unrelated to mCRPC progression, unless symptoms resulted in therapy adjustments (e.g. increased analgesic use or discontinuation of treatment). Radiological imaging was performed at the physician's discretion, and reviewed locally. 'Total (biochemical) PFS' is the sum of the separate (biochemical) PFS for cabazitaxel and abiraterone.

A patient's best response was defined as progressive disease (PD) when serum PSA levels were continuously increased compared to baseline for at least 12 weeks since treatment initiation (to exclude patients with PSA flares), and/or an increase in lesion size in radiologic imaging methods within three months of initiation of therapy. A partial response (PR) was defined as a PSA decrease of ≥50% compared to baseline in at least two separate PSA measurements three weeks apart or a decrease in lesion size (when no new lesions had occurred and no other lesions had increased in size). All patients who did not fit the criteria for PR or PD were considered to have stable disease as the best response. If results were in contrast with each other, it was considered stable disease, except when physicians reported an increased tumor lesion size: in that case the disease was always considered progressive.

Adherence to this protocol was similar to PCWG2 recommendations.[18]

For safety data, adverse events had been collected inconsistently between physicians and hospitals. Therefore, collection of adverse event data according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) was not possible. Instead, all hospital admissions between treatment initiation and 30 days after the last administration of cabazitaxel or abiraterone were registered. These were registered consistently in all hospitals. Adverse events, regardless of severity, resulting in discontinuation of treatment or patient death were recorded separately.

Statistical analyses

Microsoft Excel was used to calculate the mean, median, interquartile range (IQR), range and standard deviation (SD) for patient characteristics, treatment characteristics, best response and adverse events. SPSS (version 20) was used for the Kaplan-Meier analyses of treatment duration, follow-up, OS and (biochemical) PFS. If patient death had not occurred or its date was unknown, OS data were censored at the last date the patient was known to be alive. If no disease and/or PSA progression had occurred, (biochemical) PFS data were censored at the last date the disease state of the mCRPC patient was assessed. Log-rank tests were used to compare durations (OS etc.) between patient groups. For comparison of other parameters between patient groups, student's t-tests were conducted. Cox regression analyses were performed to calculate hazard ratios (HRs).

Results

Patients

Between January 15th, 2009 and November 30th, 2012, 326 patients initiated abiraterone and/or cabazitaxel treatment at one of the twelve participating Dutch centers. The database was closed on July 10th, 2013. At this time, 44.5% and 15.0% of patients had only received abiraterone or cabazitaxel treatment, respectively. Sixty-three patients (19.3%) had received cabazitaxel followed by abiraterone (Cab→Abi), and 69 patients (21.2%) had received abiraterone followed by cabazitaxel (Abi→Cab). These percentages were similar when evaluating patients who had passed away before database cutoff (data not shown).

Baseline characteristics of Cab→Abi and Abi→Cab treated patients

Baseline patient and tumor characteristics of Cab→Abi and Abi→Cab treated patients at the start of second-line therapy are listed in Table 1. Patients treated with Cab→Abi were younger (65.6 vs. 69.8 years; $p<0.001$) and had a higher median PSA level at baseline (291 vs 130 ng/ml; $p=0.022$). Prior treatment between groups was similar, except for the percentage of patients having undergone surgical castrations (11.1% (Cab→Abi) vs. 1.4%

(Abi→Cab); p=0.020). While patients had received a similar median number of docetaxel cycles (10 vs. 9; p=0.552), patients receiving Abi→Cab had discontinued docetaxel more frequently due to toxicity (36.2% vs. 12.7%; p=0.002), whereas a higher percentage of Cab→Abi treated patients had completed all planned cycles (usually ten) (52.4% vs. 33.3%; p=0.027). Although not reaching statistically significance, patients in the Cab→Abi group had in general a shorter duration from diagnosis to second-line mCRPC therapy, but a longer duration between mCRPC diagnosis and second-line mCRPC therapy, and docetaxel and second-line mCRPC therapy. Other baseline characteristics were similar between groups.

Treatment characteristics of Cab→Abi and Abi→Cab treated patients

Treatment characteristics from second-line mCRPC therapy onwards are listed in Table 2. Of note, second-line therapy was considered cabazitaxel or abiraterone, third-line therapy the other agent, regardless of therapies between docetaxel, cabazitaxel and abiraterone. While there was no difference in second-line therapy duration (mean 159.9 versus 152.9 days; p=0.955), patients treated with Cab→Abi received significantly longer third-line therapy (mean 138.8 versus 100.8 days; p=0.021). Indeed, patients receiving cabazitaxel in the third-line (Abi→Cab) received significantly less cabazitaxel cycles (median 4 versus 7 cycles; p<0.001). Abiraterone was primarily discontinued due to disease progression; toxicity played a role in about one-third of patients discontinuing cabazitaxel, both in the second- and third-line.

Efficacy of Cab→Abi and Abi→Cab therapy

Median time to follow-up was 23.7 months and 21.8 months in Cab→Abi and Abi→Cab treated patients, respectively (p=0.068). Median OS was slightly greater in Cab→Abi treated patients: 19.1 months versus 17.0 months; however, this difference did not reach statistical significance (p=0.369) (Fig. 1A). When stratifying all patients based on second-line therapy, including patients that received cabazitaxel (n=112) or abiraterone (n=214) only, mCRPC patients that received abiraterone after docetaxel had a slightly greater median OS (13.2 versus 12.5 months); this difference was not statistically significant either (p=0.386). Median total PFS and total biochemical PFS were 8.1 versus 6.5 months (p=0.050) and 9.5 versus 7.7 months (p=0.024) in Cab→Abi versus Abi→Cab treated patients, respectively (Fig. 1B-C). Assessing (biochemical) PFS during second and third-line therapy separately, it was observed that (biochemical) PFS differed between Cab→Abi and Abi→Cab treated patients during second-line therapy, but were similar in the third-line (Table 3). When assessing best clinical and PSA responses, it was noted that during third-line therapy fewer patients had PRs, while an increased percentage of patients had PD. This was particularly evident when comparing cabazitaxel responses between second- and third-line therapy. Patients receiving cabazitaxel in the third-line also had a significantly shorter treatment duration than in the second-line (data not shown). Waterfall plots depicting maximum change in PSA from

Table 1. Baseline patient and tumor characteristics of patients treated with both cabazitaxel and abiraterone

	Cab→Abi (n=63)		Abi→Cab (n=69)		p-value
Age					
Median [years (range)]	65.6	(44-79)	69.8	(52-88)	**<0.001**
Gleason score					
Unknown	7	(11.1%)	8	(11.6%)	
Median (range)	8	(6-10)	8	(6-10)	0.080
Gleason ≥8	37	(66.1%)	34	(55.7%)	
Metastatic disease					
Number of metastatic lesions					
1	11	(17.5%)	8	(11.6%)	0.928
2	35	(55.6%)	43	(62.3%)	
≥3	17	(27.0%)	18	(26.1%)	
Prior treatment					
Radical prostatectomy	11	(17.5%)	5	(7.2%)	0.073
TUR-P	12	(19.0%)	11	(15.9%)	0.642
Surgical castration	7	(11.1%)	1	(1.4%)	**0.020**
Androgen-deprivation therapy	62	(98.4%)	69	(100%)	0.297
Lymph node dissection	13	(20.6%)	14	(20.3%)	0.961
Radiotherapy:					
- prostate	26	(41.3%)	27	(39.1%)	0.804
- metastases	32	(50.8%)	24	(34.8%)	0.064
Samarium-153/strontium-89	3	(4.8%)	3	(4.3%)	0.910
Ipilimumab/placebo	4	(6.3%)	6	(8.7%)	0.614
Enzalutamide/placebo	1	(1.6%)	1	(1.4%)	0.949
Docetaxel:					
# cycles [median (range)]	10	(3-20)	9	(2-33)	0.552
Reason to stop:					
- End of treatment	33	(52.4%)	23	(33.3%)	**0.027**
- Progressive disease	22	(34.9%)	23	(33.3%)	0.849
- Patient's decision	2	(3.2%)	1	(1.4%)	0.510
- Physician's decision	5	(7.9%)	7	(10.1%)	0.662
- Toxicity	8	(12.7%)	25	(36.2%)	**0.002**
- Unknown	0	(0.0%)	1	(1.4%)	0.341
- Other	0	(0.0%)	2	(2.9%)	0.176
Docetaxel rechallenge	9	(14.3%)	12	(17.4%)	0.413
Other	9	(14.3%)	15	(21.7%)	0.401
Time in months [median (IQR)] between:					
PCa diagnosis and 2nd line therapy	49.7	(27.6-73.1)	61.1	(29.3-89.1)	0.195
mCRPC diagnosis and 2nd line therapy	17.8	(12.0-24.2)	16.5	(10.1-29.0)	0.427
last docetaxel and 2nd line therapy	5.6	(3.0-9.3)	3.7	(1.8-6.9)	0.051
Serum PSA concentration (ng/ml) at start second-line therapy					
Median (IQR)	291	(98-635)	130	(50-293)	**0.022**
<20 ng/ml	2	(3.2%)	9	(13.0%)	
ECOG performance status at start second-line therapy					
0-1	53	(84.1%)	58	(84.1%)	0.302
2	9	(14.3%)	11	(15.9%)	
3	1	(1.6%)	0	(0.0%)	

Data are number of patients (%) if not specified otherwise. Abi, abiraterone; Cab, cabazitaxel; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; mCRPC, metastatic castrate-resistant prostate cancer; PCa, prostate cancer; PSA, prostate-specific antigen; SD, standard deviation; TUR-P, transurethral resection of the prostate

Table 2. Treatment characteristics of patients treated with both cabazitaxel and abiraterone

	Cab→Abi (n=63)		Abi→Cab (n=69)		p-value
Second-line treatment					
Mean treatment duration (days) (SD)	159.9	(70.9)	152.9	(89.1)	0.955
Patients with dose reduction (%)	23	(36.5%)	0	(0.0%)	
Median cumulative dose (range)	150	(60-515)	129	(25-392)	
Patients with additional therapy during treatment:					
- Radiotherapy	7	(11.1%)	8	(11.6%)	
- TUR-P/surgery	1	(1.6%)	1	(1.4%)	
Reason to discontinue:					
- End of treatment	13	(20.6%)	0	(0.0%)	
- Progressive disease	37	(58.7%)	67	(97.1%)	
- Toxicity	20	(31.7%)	4	(5.8%)	
- Other	15	(23.8%)	7	(10.1%)	
Patients without other therapy between Cab and Abi (%)	48	(76.2%)	51	(73.9%)	0.765
Patients with systemic therapy between Cab and Abi (%)	1	(1.6%)	10	(14.5%)	**0.007**
Enzalutamide/placebo (AFFIRM participants)	0	(0.0%)	5	(7.2%)	**0.029**
Docetaxel rechallenge	1	(1.6%)	6	(8.7%)	0.069
Ipilimumab	0	(0.0%)	1	(1.4%)	0.341
Mitoxantrone	0	(0.0%)	1	(1.4%)	0.341
Third-line treatment					
Mean treatment duration (days) (SD)	138.8	(97.3)	100.8	(59.8)	**0.021**
Patients with dose reduction	3	(4.8%)	11	(15.9%)	
Median cumulative dose (range)	109	(69-187)	100	(19-250)	
Patients with additional therapy during treatment:					
- Radiotherapy	19	(30.2%)	4	(5.8%)	
- TUR-P/surgery	0	(0.0%)	0	(0.0%)	
Reason to discontinue:					
- 3rd line therapy still ongoing	3	(4.8%)	8	(11.6%)	
- End of treatment	0	(0.0%)	5	(7.2%)	
- Progressive disease	52	(82.5%)	42	(60.9%)	
- Toxicity	5	(7.9%)	23	(33.3%)	
- Death	3	(4.8%)	3	(4.3%)	
- Other	10	(15.9%)	8	(11.6%)	
Number of Cab cycles					
Mean (SD)	7.3	(3.2)	4.6	(2.7)	**<0.001**
Median (range)	7	(3-21)	4	(1-10)	
Patients who initiated therapy at 20 mg/m ^{2}	6	(9.5%)	9	(13.0%)	0.528
Patients who completed ≥10 cycles	18	(28.6%)	6	(8.7%)	
Treatment duration of Cab and Abi combined (days)					
Mean (SD)	298.7	(133.8)	253.8	(114.1)	0.172
Median (IQR)	275	(215-344)	238	(160-322)	
Treatment after Cab and Abi					
Patients who had discontinued third-line therapy	60		61		
Patients with treatment after Cab and Abi	29	(48.3%)	34	(55.7%)	0.712
Enzalutamide/placebo	8	(13.3%)	13	(21.3%)	0.340
Radiotherapy	15	(25.0%)	20	(32.8%)	0.505
Samarium-153	3	(5.0%)	2	(3.3%)	0.579
Mitoxantrone	5	(8.3%)	6	(9.8%)	0.876
Cabozantinib/placebo	8	(13.3%)	4	(6.6%)	0.171
Cab rechallenge	3	(5.0%)	4	(6.6%)	0.793
Abi rechallenge	1	(1.7%)	4	(6.6%)	0.209
Other	9	(15.0%)	6	(9.8%)	0.405

Cumulative dose: Cab, mg/m^2; Abi, g. Abi, abiraterone; Cab, cabazitaxel; IQR, interquartile range; SD, standard deviation; TUR-P, transurethral resection of the prostate

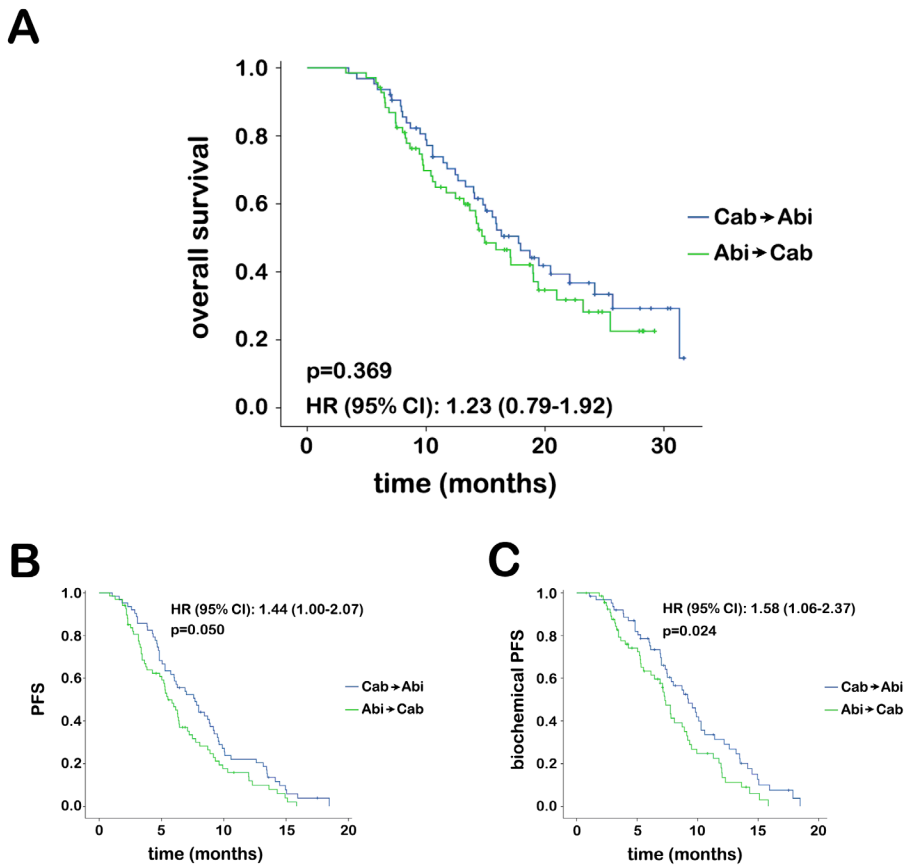


Figure 1. Overall survival (OS) (A), progression-free survival (PFS) (B) and biochemical PFS (C) in metastatic castrate-resistant prostate cancer (mCRPC) patients treated with both cabazitaxel and abiraterone.
CI, confidence interval; HR, hazard ratio.

Table 3. Efficacy of Cab->Abi and Abi->Cab treatment

	Cab→Abi (n=63)	Abi→Cab (n=69)	p-value
Second-line treatment			
PFS			
Mean [months (95% CI)]	5.3 (4.5-6.1)	3.2 (2.7-3.8)	**<0.001**
Median [months (IQR)]	5.0 (2.1-7.8)	2.7 (1.4-4.6)	
Biochemical PFS			
Mean [months (95% CI)]	6.0 (5.1-6.9)	3.4 (2.9-4.0)	**<0.001**
Median [months (IQR)]	6.2 (3.0-8.4)	2.8 (1.5-5.0)	
Best clinical response			
Progressive disease (%)	8 (12.7%)	19 (27.5%)	
Partial response (%)	29 (46.0%)	18 (26.1%)	
Best PSA response			
Progressive (%)	5 (7.9%)	21 (30.4%)	
Partial response (%)	32 (50.8%)	16 (23.2%)	

Third-line treatment					
PFS					
Mean [months (95% CI)]	2.9	(2.2-3.6)	3.2	(2.5-3.8)	0.451
Median [months (IQR)]	2.4	(0.9-3.5)	2.6	(1.3-4.5)	
Biochemical PFS					
Mean [months (95% CI)]	3.6	(2.7-4.5)	4.0	(3.3-4.7)	0.389
Median [months (IQR)]	2.7	(1.4-4.7)	4.1	(1.4-5.1)	
Best clinical response		(n=62)		(n=68)	
Progressive disease (%)	24	(38.7%)	21	(30.9%)	
Partial response (%)	10	(16.1%)	18	(26.5%)	
Best PSA response		(n=61)		(n=66)	
Progressive (%)	17	(27.9%)	14	(21.2%)	
Partial response (%)	11	(18.0%)	21	(31.8%)	

Patients with stable disease as the best response, are not reported in the table. CI, confidence interval; IQR, interquartile range; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen

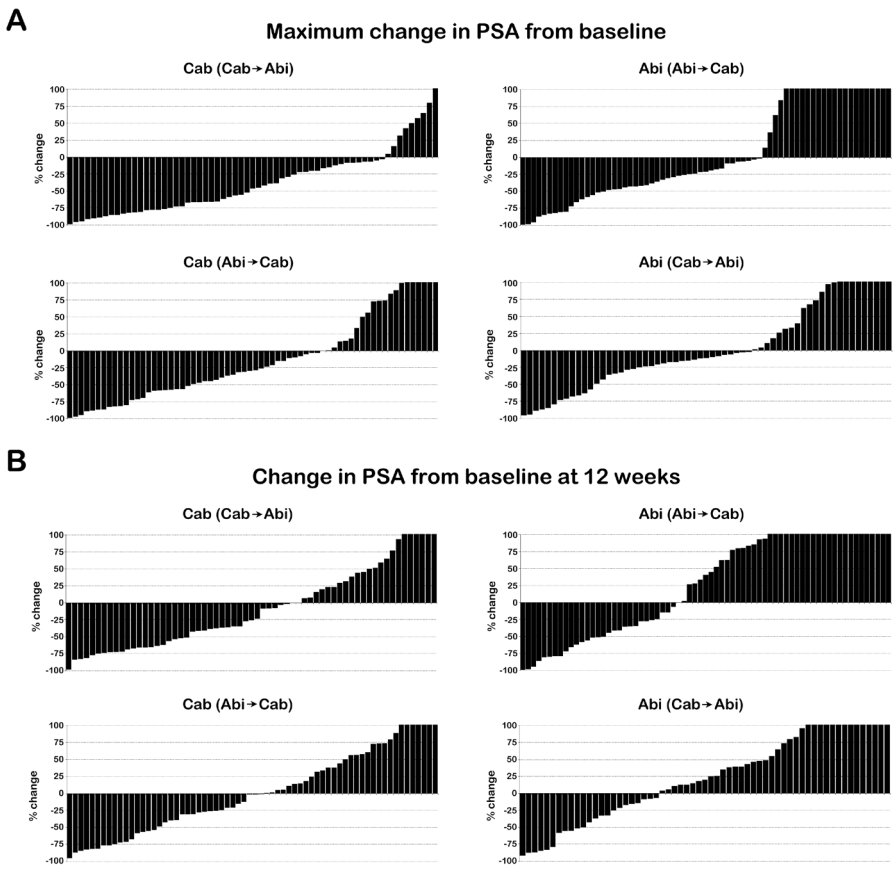


Figure 2. Waterfall plots depicting maximum prostate-specific antigen (PSA) changes from baseline (A) and change in PSA from baseline at 12 weeks (B) in mCRPC patients treated with cabazitaxel and abiraterone.
Abi, abiraterone; Cab, cabazitaxel.

baseline and change in PSA from baseline at 12 weeks are displayed in Figure. 2. Cab→Abi treated patients had more frequently continuously rising PSA levels during cabazitaxel than Abi→Cab treated patients (Fig. 2A). This difference did not occur in abiraterone-treated patients; however, when assessing change in PSA from baseline at 12 weeks, patients receiving abiraterone after docetaxel had a slightly worse PSA outcome (Fig. 2B).

Subsequent performed subgroup analyses did not indicate that a subpopulation had a significantly improved OS when treated with one of the treatment sequences (Fig. 3A). However, a trend towards favorable median OS in Cab→Abi treated patients was observed in all subpopulations (HR>1; p>0.05 though), except for patients treated with less than 10 cycles and patients who discontinued docetaxel due to PD (HR 0.90 and 0.76, respectively). Similar results were found when performing subgroup analyses for PFS (Fig. 3B). Patients aged below 65, patients with a Gleason 8-10, patients who received ≥10 docetaxel cycles and patients who had not received enzalutamide before abiraterone had a significantly better PFS when treated with Cab→Abi (HR 2.64, 1.64, 1.85 en 1.44, respectively, p≤0.05).

Safety of Cab→Abi and Abi→Cab therapy

In total, about 60% of patients needed hospitalizations during cabazitaxel or abiraterone treatment (Table 4). In the second-line, 15.9% of cabazitaxel-treated patients required ≥2 hospitalizations, while only 7.2% of abiraterone patients required at least two hospitalizations (Abi→Cab group). No difference in hospitalizations was evident in the third-line. The primary adverse event causing hospitalization during cabazitaxel was febrile neutropenia (9.5% in Cab→Abi treated patients; 14.5% in Abi→Cab treated patients). Intriguingly, patients in the Abi→Cab group required more hospitalizations due to pain during both treatments (31.9% vs. 17.5% of Cab→Abi patients), while patients treated with Cab→Abi required more hospitalizations due to urinary tract infections (15.9% vs. 8.7%) and urinary obstruction during both treatments (7.9% vs. 1.4%).

Discontinuation of treatment due to toxicity occurred primarily during cabazitaxel therapy, with 21 patients (16.9%) having discontinued entirely because of toxicities (Table 4). For both therapies, main reasons to discontinue treatment were fatigue, malaise, nausea and vomiting. In cabazitaxel-treated patients, polyneuropathy was another frequently occurring toxicity resulting in treatment discontinuation.

Fifteen patients (11.4%) died within 30 days of the last administration of abiraterone or cabazitaxel (Table 5). Two-thirds of these patients were treated with Cab→Abi. The greater number of deaths in this patient group most likely reflects the general trend of physicians to continue abiraterone treatment longer as compared to cabazitaxel, e.g. when patients have a lower ECOG performance status. Three patients (60.0%) in the Abi→Cab group died due to toxicities; two of these had febrile neutropenia, the third had a non-neutropenic infection.

Discussion

In recent years, cabazitaxel, abiraterone, enzalutamide, sipuleucel-T and radium-223 have been introduced to the clinic for mCRPC treatment. This rapidly expanding variety of available therapies has significantly improved survival of mCRPC patients.[19] However, many questions remain how these therapies should be deployed in clinic to maximize clinical benefit.

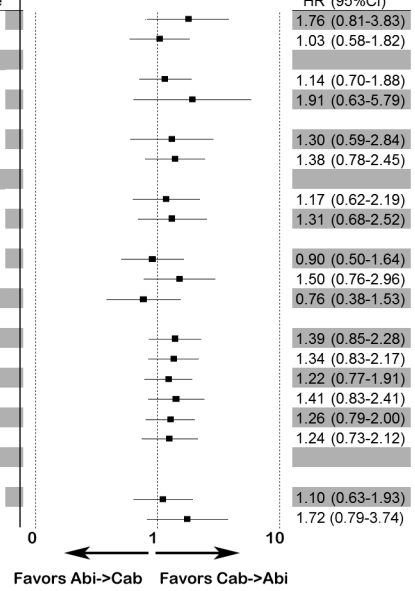
Treatment with one agent may influence the efficacy of another therapy. Recent studies have suggested decreased antitumor effects of mCRPC therapies when administered later in the disease. In a retrospective analysis of a small group of abiraterone pretreated mCRPC patients, docetaxel seemed to have lower antitumor efficacy than normally observed.[13] No responses to docetaxel were evident in abiraterone-refractory patients. In other retrospective analyses, abiraterone had limited antitumor activity in patients treated with docetaxel and enzalutamide, although some patients still benefited from abiraterone therapy.[16, 17] Similar modest antitumor activity was reported when enzalutamide was administered to mCRPC patients after docetaxel and abiraterone.[14, 15, 20] A recent preclinical study has suggested that cross-resistance may occur between taxanes and abiraterone.[21]

Despite suggestions of cross-resistance, multiple recent retrospective studies reported antitumor activity from cabazitaxel in mCRPC patients after docetaxel and abiraterone or enzalutamide, with partial responses occurring in 14% to 30% of patients.[22-24] In line with these study results, we observed a similar percentage of mCRPC patients who responded to cabazitaxel therapy after docetaxel and abiraterone, confirming that progression on these agents does not prelude a response to cabazitaxel. Similarly, we observed partial responses with abiraterone in mCRPC patients who had received docetaxel and cabazitaxel prior to abiraterone. Hence, these results suggest that additional clinical benefit may be accomplished by treating patients sequentially with all three agents.

However, when comparing PFS and biochemical PFS of cabazitaxel in Cab→Abi and Abi→Cab treated patients, a significantly decreased PFS and biochemical PFS was observed in patients who had received cabazitaxel after abiraterone. Of note, when only selecting patients who discontinued second-line therapy due to PD, a similar decreased antitumor efficacy of particularly cabazitaxel as third-line therapy was observed (data not shown). Although PFS and biochemical PFS did not differ significantly in abiraterone treated patients based on prior therapy with or without cabazitaxel, the PSA response after twelve weeks of abiraterone treatment was slightly better in Abi→Cab treated patients as judged by the waterfall plots. Further research is needed to assess whether this observed decreased antitumor efficacy in higher-line therapy is due to cross-resistance or other factors, such as tumor mutations, differences in the patient populations, or a decreased tolerability of advanced mCRPC patients to aggressive therapies. Mechanisms for therapy resistance need to be unraveled

A

	Cab→Abi # patients	Median	p-value	Abi→Cab # patients	Median	p-value	HR (95%CI)
age <65 years	29	16.3	0.550	17	17.1	0.465	1.76 (0.81-3.83)
age ≥65 years	34	17.9		52	14.2		1.03 (0.58-1.82)
ECOG 0-1	53	17.8	0.738	58	15.9	0.130	1.14 (0.70-1.88)
ECOG 2-3	10	10.0		11	14.2		1.91 (0.63-5.79)
Gleason <8	19	19.5	0.379	27	17.1	0.198	1.30 (0.59-2.84)
Gleason 8-10	37	14.8		34	12.5		1.38 (0.78-2.45)
PSA <250 ng/ml	29	15.7	0.776	45	14.7	0.672	1.17 (0.62-2.19)
PSA ≥250 ng/ml	34	17.9		24	17.1		1.31 (0.68-2.52)
Docetaxel <10 cycles	28	12.5	0.009	41	14.2	0.262	0.90 (0.50-1.64)
Docetaxel ≥10 cycles	35	22.1		28	17.1		1.50 (0.76-2.96)
Docetaxel discontinued due to PD	22	10.5		23	13.2		0.76 (0.38-1.53)
no systemic therapy other than docetaxel before or between cabazitaxel and abiraterone	54	17.8		52	14.2		1.39 (0.85-2.28)
no systemic therapy other than docetaxel before cabazitaxel and abiraterone	55	17.9		60	14.4		1.34 (0.83-2.17)
no enzalutamide before cabazitaxel and abiraterone	62	17.8		68	14.9		1.22 (0.77-1.91)
no treatment between cabazitaxel and abiraterone	48	19.5		51	14.4		1.41 (0.83-2.41)
no systemic therapy between cabazitaxel and abiraterone	62	16.3		59	14.2		1.26 (0.79-2.00)
no radiotherapy during cabazitaxel or abiraterone	40	18.7		57	15.9		1.24 (0.73-2.12)
Time between PCa diagnosis and second-line therapy							
<5 years	40	14.0	0.001	33	14.2	0.051	1.10 (0.63-1.93)
≥5 years	23	25.7		36	17.1		1.72 (0.79-3.74)



B

	Cab→Abi # patients	Cab→Abi Median	p-value	Abi→Cab # patients	Abi→Cab Median	p-value	HR (95%CI)
age <65 years	29	8.8	0.189	17	5.3	0.215	2.64 (1.33-5.22)
age ≥65 years	34	6.0		52	5.8		1.12 (0.71-1.77)
ECOG 0-1	53	7.8	0.176	58	6.1	0.271	1.46 (0.98-2.18)
ECOG 2-3	10	4.8		11	3.7		1.24 (0.49-3.10)
Gleason <8	19	6.2	0.635	27	6.1	0.567	1.28 (0.69-2.37)
Gleason 8-10	37	7.6		34	4.9		1.64 (1.00-2.69)
PSA <250 ng/ml	29	5.7	0.611	45	5.3	0.866	1.3 (0.79-2.14)
PSA ≥250 ng/ml	34	8.4		24	6.4		1.6 (0.91-2.79)
Docetaxel <10 cycles	28	4.8	<0.001	41	5.3	0.286	0.93 (0.56-1.54)
Docetaxel ≥10 cycles	35	9.2		28	6.1		1.85 (1.09-3.14)
Docetaxel discontinued due to PD	22	4.7		23	6.1		0.72 (0.38-1.34)
no systemic therapy other than docetaxel before or between cabazitaxel and abiraterone	54	7.0		52	5.6		1.40 (0.93-2.11)
no systemic therapy other than docetaxel before cabazitaxel and abiraterone	55	7.7		60	5.9		1.47 (0.99-2.18)
no enzalutamide before cabazitaxel and abiraterone	62	7.7		68	5.9		1.44 (1.00-2.08)
no treatment between cabazitaxel and abiraterone	48	8.0		51	6.1		1.43 (0.94-2.19)
no systemic therapy between cabazitaxel and abiraterone	62	7.6		59	6.0		1.38 (0.95-2.01)
no radiotherapy during cabazitaxel or abiraterone	40	7.7		57	6.1		1.21 (0.79-1.86)
Time between PCa diagnosis and second-line therapy							
<5 years	40	6.0	0.066	33	6.0	0.459	1.37 (0.85-2.21)
≥5 years	23	8.9		36	5.9		1.79 (1.00-3.18)

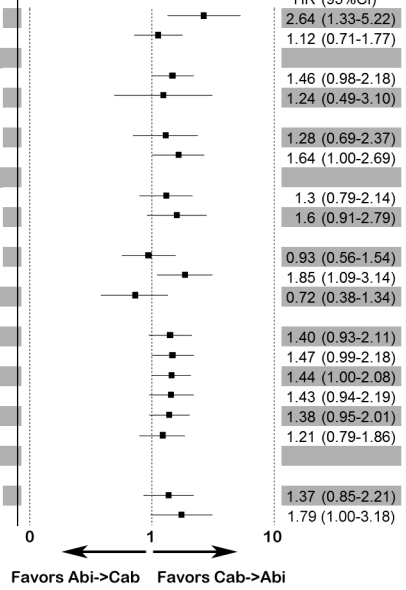


Figure 3. Analysis of overall survival (A) and progression-free survival (B) in subgroups of patients defined by baseline characteristics.
Hazard ratios (HRs) higher than 1 favor the Cab→Abi group, lower than 1 favor the Abi→Cab group. #, number; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status; PCa, prostate cancer; PD, progressive disease.

Table 4. Severe adverse events during cabazitaxel and abiraterone treatment

	Cab→Abi (n=63)						Abi→Cab (n=69)					
	During cab		During abi		Total		During abi		During cab		Total	
Patients with ≥1 hospitalization	21	(33.3%)	28	(44.4%)	37	(58.7%)	19	(27.5%)	35	(50.7%)	42	(60.9%)
Patients with ≥2 hospitalizations	10	(15.9%)	11	(17.5%)	20	(31.7%)	5	(7.2%)	10	(14.5%)	21	(30.4%)
Duration of hospitalizations (days) [median (IQR)]	5	(2-8)	5	(2-9)	5	(2-8)	5	(2-7)	5	(4-9)	5	(3-9)
Adverse events causing hospitalization												
Anemia	1	(1.6%)	3	(4.8%)	4	(6.3%)	0	(0.0%)	3	(4.3%)	3	(4.3%)
Thrombocytopenia	1	(1.6%)	2	(3.2%)	3	(4.8%)	0	(0.0%)	1	(1.4%)	1	(1.4%)
Neutropenia	2	(3.2%)	0	(0.0%)	2	(3.2%)	0	(0.0%)	1	(1.4%)	1	(1.4%)
Febrile neutropenia	6	(9.5%)	3	(4.8%)	7	(11.1%)	0	(0.0%)	10	(14.5%)	10	(14.5%)
Pain	5	(7.9%)	6	(9.5%)	11	(17.5%)	11	(15.9%)	12	(17.4%)	22	(31.9%)
Urinary tract infection	5	(7.9%)	6	(9.5%)	10	(15.9%)	2	(2.9%)	5	(7.2%)	6	(8.7%)
Urinary obstruction	2	(3.2%)	3	(4.8%)	5	(7.9%)	0	(0.0%)	1	(1.4%)	1	(1.4%)
Hematuria	3	(4.8%)	1	(1.6%)	4	(6.3%)	1	(1.4%)	5	(7.2%)	6	(8.7%)
Renal function abnormalities	4	(6.3%)	2	(3.2%)	5	(7.9%)	2	(2.9%)	2	(2.9%)	4	(5.8%)
Pyrexia (not neutropenic)	3	(4.8%)	3	(4.8%)	6	(9.5%)	2	(2.9%)	5	(7.2%)	6	(8.7%)
Diarrhea	3	(4.8%)	1	(1.6%)	4	(6.3%)	0	(0.0%)	4	(5.8%)	4	(5.8%)
Nausea	3	(4.8%)	3	(4.8%)	4	(6.3%)	4	(5.8%)	4	(5.8%)	8	(11.6%)
Vomiting	4	(6.3%)	2	(3.2%)	6	(9.5%)	4	(5.8%)	4	(5.8%)	8	(11.6%)
Constipation	1	(1.6%)	2	(3.2%)	3	(4.8%)	1	(1.4%)	1	(1.4%)	2	(2.9%)
Dyspnoe	1	(1.6%)	2	(3.2%)	3	(4.8%)	3	(4.3%)	3	(4.3%)	5	(7.2%)
Pneumonia	2	(3.2%)	4	(6.3%)	6	(9.5%)	2	(2.9%)	2	(2.9%)	4	(5.8%)
Infection of the GI tract	0	(0.0%)	1	(1.6%)	1	(1.6%)	1	(1.4%)	2	(2.9%)	3	(4.3%)
Sepsis e.c.i.	1	(1.6%)	1	(1.6%)	2	(3.2%)	1	(1.4%)	3	(4.3%)	4	(5.8%)
Liver function test abnormalities	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(4.3%)	3	(4.3%)
Hypokalemia	0	(0.0%)	1	(1.6%)	1	(1.6%)	0	(0.0%)	2	(2.9%)	2	(2.9%)
Edema	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.4%)	1	(1.4%)
Allergic response	1	(1.6%)	0	(0.0%)	1	(1.6%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Spinal cord compression	4	(6.3%)	4	(6.3%)	7	(11.1%)	1	(1.4%)	4	(5.8%)	5	(7.2%)
Pathological fracture	0	(0.0%)	2	(3.2%)	2	(3.2%)	0	(0.0%)	1	(1.4%)	1	(1.4%)
Hypotension	1	(1.6%)	0	(0.0%)	1	(1.6%)	0	(0.0%)	2	(2.9%)	2	(2.9%)
Vertigo	0	(0.0%)	1	(1.6%)	1	(1.6%)	3	(4.3%)	1	(1.4%)	4	(5.8%)
Other	4	(6.3%)	12	(19.0%)	16	(25.4%)	11	(15.9%)	12	(17.4%)	20	(29.0%)
Discontinuation due to toxicity												
# patients that discontinued therapy	63		60				69		61			
- toxicity sole reason to discontinue	9	(14.3%)	2	(3.3%)			1	(1.5%)	12	(19.7%)		
- toxicity important factor for discontinuation	11	(17.5%)	3	(5.0%)			3	(4.3%)	10	(16.4%)		
- adverse events resulting in discontinuation:												
- febrile neutropenia	1	(1.6%)	0	(0.0%)			0	(0.0%)	2	(3.3%)		
- other hematological toxicity	1	(1.6%)	1	(1.7%)			0	(0.0%)	2	(3.3%)		
- fatigue	8	(12.7%)	1	(1.7%)			2	(2.9%)	9	(14.8%)		
- nausea/vomiting/malaise	5	(7.9%)	1	(1.7%)			1	(1.4%)	6	(9.8%)		
- diarrhea	2	(3.2%)	0	(0.0%)			0	(0.0%)	3	(4.9%)		
- polyneuropathy	5	(7.9%)	0	(0.0%)			0	(0.0%)	4	(6.6%)		
- liver function abnormality	2	(3.2%)	1	(1.7%)			0	(0.0%)	2	(3.3%)		
- other non-hematological toxicity	6	(9.5%)	3	(5.0%)			1	(1.4%)	11	(18.0%)		

#, number; Abi, abiraterone; Cab, cabazitaxel; IQR, interquartile range

Table 5. Patient deaths within 30 days of last treatment

	Cab→Abi (n=63)	Abi→Cab (n=69)
# patients	10 (15.9%)	5 (7.2%)
reason for patient death		
- disease progression	8 (80.0%)	2 (40.0%)
- febrile neutropenia	0 (0.0%)	2 (40.0%)
- Non-neutropenic infection	0 (0.0%)	1 (20.0%)
- ileus	1 (10.0%)	0 (0.0%)
- unknown	1 (10.0%)	0 (0.0%)

#, number; Abi, abiraterone; Cab, cabazitaxel

(mutations that occur, pathways that are circumvented). Some evidence exists that taxanes play a role in the transnuclear localization of the androgen receptor, suggesting that taxanes target tumor cells in the androgen receptor pathway too.[25] Such overlapping mechanisms of action may form a basis for cross-resistance.

In the CAST-study, we did not observe a statistically significant difference in median OS between Cab→Abi and Abi→Cab treated patients. However, a trend towards improved OS in Cab→Abi treated patients was noted, except for the subgroup of patients with rapid PD during docetaxel therapy. In a similar retrospective study, a better survival was reported in a cohort of patients treated with Cab→Abi compared to Abi→Cab treated patients.[26] However, analysis of all patients that received cabazitaxel and/or abiraterone after docetaxel, including patients who received only one therapy, indicated that patients receiving abiraterone as second-line therapy tended to have a survival advantage, particularly due to a subgroup of patients with an extensive response duration (>1 year) to abiraterone. Therefore, no clear benefit of one therapy sequence over the other was observed in terms of OS. Larger patient groups may be needed to observe significant differences between therapy sequence, but currently this is the largest retrospective study comparing such treatment sequence in mCRPC patients.

When evaluating the safety data of Cab→Abi and Abi→Cab treated patients, we observed more severe toxicity during cabazitaxel treatment than during abiraterone treatment, similar to toxicity reports in their respective phase III studies.[4, 9] Although results from cabazitaxel compassionate use programs reported fewer adverse events as compared to the TROPIC study,[9, 27, 28] our results indicate that particularly febrile neutropenia can be serious and even life-threatening, contributing to patient death in 2-3% of cabazitaxel-treated patients. The potentially severe toxicity from cabazitaxel needs to be taken into account by physicians and patients when deciding treatment for their mCRPC.

This study has various limitations due to its retrospective nature. Patients' and treatments' characteristics were inevitably not completely equal between treatment groups and not all

potentially variable characteristics were collected in the clinical setting (such as baseline lactate dehydrogenase or circulating tumor cell counts). Treatment choices were not standardized but based on factors such as the physician's and patient's preference. E.g., patients who responded well to docetaxel, were most likely more interested in cabazitaxel as second-line therapy than patients who discontinued docetaxel early due to heavy toxicity. Differences in the use of tumor imaging methods were evident: while some patients received bone and/or CT scans multiple times during treatment, others had not received a CT scan at all. Serum PSA levels were consistently measured every 3 to 4 weeks, but this marker has its limitations too.[29] All such limitations occur with every retrospective study. Nevertheless, when several retrospective studies have a similar conclusion, this may be the best evidence we can get as a prospective randomized study may never be performed. Such a prospective study would need an extensive study duration and will be costly, whereas its clinical value will be limited due to the rapidly changing treatment landscape. E.g., patients had more advanced disease and had received extensive (experimental) chemotherapies in early cabazitaxel and abiraterone studies compared to mCRPC patients currently receiving these therapies. To a lesser extent the study population in our retrospective study is presumably not completely equal to the current mCRPC population, e.g. as some of these patients would receive enzalutamide these days. In the Netherlands, abiraterone is still only administered after docetaxel, while in other countries abiraterone is also administered before docetaxel.

In conclusion, this retrospective analysis of mCRPC patients treated with both cabazitaxel and abiraterone post-docetaxel found that progression on one agent did not prelude a response to the other agent, although antitumor efficacy of the agents, particularly cabazitaxel, was decreased when administered as higher-line therapy. Abi→Cab treated patients had more hospital admissions during cabazitaxel than Cab→Abi treated patients and discontinued cabazitaxel more frequently due to toxicity, while, as expected, abiraterone resulted generally in less severe toxicity as compared to cabazitaxel. These results should be used in the shared decision-making between patients and physicians, balancing the pros and cons of cabazitaxel or abiraterone after docetaxel. Further research is needed to provide more data regarding optimal treatment sequencing.

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