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Sequencing of Taxanes and New Androgen-targeted Therapies in Metastatic Castration-resistant Prostate Cancer: Results of the International Multicentre Retrospective CATS Database

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Abstract

Background: The optimal sequence of life-extending therapies in metastatic castration-resistant prostate cancer (mCRPC) is unknown.
Objective: To evaluate outcomes among mCRPC patients treated with docetaxel (DOC), cabazitaxel (CABA), and a novel androgen receptor–targeted agent (ART; abiraterone acetate or enzalutamide) according to three different sequences.
Design, setting, and participants: Data from 669 consecutive mCRPC patients were retrospectively collected between November 2012 and October 2016.
Outcome measurements and statistical analysis: The primary endpoint was the prostate-specific antigen (PSA) response (decrease $\geq$50% from baseline) to each therapy. Secondary endpoints included best clinical benefit, time to PSA progression, radiological progression-free survival (rPFS), overall survival (OS), and toxicity.

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Castration-resistant prostate cancer
Cabazitaxel
Docetaxel
Enzalutamide
Sequence

Results and limitations: A total of 158 patients received DOC → CABA → ART (group 1), 456 received DOC → ART → CABA (group 2), and 55 received ART → DOC → CABA (group 3). At baseline, PSA progression only and Gleason <8 were more common in group 3. PSA response on DOC was lower in group 3 than in other groups ($p = 0.02$) and PSA response on CABA was higher in the second than in the third line ($p = 0.001$). In Group 3, rPFS on ART (6.6 mo) and DOC (9.2 mo) was also shorter than in the other groups. OS calculated from the first life-extending therapy reached 34.8, 35.8, and 28.9 mo in groups 1, 2 and 3, respectively ($p = 0.007$). Toxicity was comparable between the arms. The main limitations of the trial are its retrospective design and the low number of patients in group 3.

Conclusions: In this retrospective trial, sequencing of DOC, CABA, and one ART, was associated with median OS of up to 35.8 mo. CABA seemed to retain its activity regardless of treatment sequence. DOC activity after ART appeared to be reduced, but the data are insufficient to conclude that cross-resistance occurs.

Patient summary: The order of drugs administered to patients with metastatic castration-resistant prostate cancer could impact their efficacy, with cabazitaxel appearing to retain its activity whatever the therapeutic sequence.

1. Introduction

A major step forward in the treatment of metastatic castration-resistant prostate cancer (mCRPC) was achieved in 2004 when two landmark randomised controlled trials showed for the first time that docetaxel (DOC) with daily prednisone improves overall survival (OS) [1,2], making it a standard of care. Subsequently, since 2010 it has been demonstrated that five new agents have an OS benefit: the radiopharmaceutical radium-223 [3], the autologous cellular immunotherapy sipuleucel-T [4] (only licensed in the USA), cabazitaxel (CABA), a new taxane active in patients experiencing progression during or after DOC [5], and two novel androgen receptor–targeted (ART) agents, abiraterone acetate (AA) and enzalutamide (ENZA). An OS benefit was initially observed for AA and ENZA in the post-DOC setting [6,7] and subsequently in the pre-DOC setting, with median OS reaching approximately 35 mo [8,9].

All these phase 3 studies were conducted in parallel in different populations and with different comparators, and the optimal sequence of these life-extending therapies is unknown. The aim of the CATS retrospective registry was to determine which sequence of DOC, CABA, and ART is associated with better outcomes among patients with mCRPC.

2. Patients and methods

2.1. Data collection

Data were retrospectively collected for consecutive patients with mCRPC treated with three life-extending therapies (DOC, one ART [AA or ENZA], and CABA), regardless of the order, between November 2012 and October 2016 in 34 centres in eight countries. All patients satisfying the following inclusion criteria were enrolled: (1) histologically proven prostate cancer; (2) metastatic disease that had progressed despite castrate levels of testosterone; and (3) minimum follow-up of 3 mo after the third life-extending therapy if the patient was still alive. As AA and ENZA target the same pathway [10–13] they were analysed together. Previous treatment with DOC, AA, or ENZA in hormone-sensitive disease was not allowed. Patients were classified into three groups: group 1 received DOC → CABA → ART; group 2 received DOC → ART → CABA; and group 3 received ART → DOC → CABA (Fig. 1).

Data on disease history, patient characteristics at initiation of each life-extending therapy, treatment outcomes, and grade ≥3 toxicities were retrospectively collected using a centralised electronic case report form. All prostate-specific antigen (PSA) measurements were captured (usually every 3–4 wk). A standard radiological evaluation (bone scan, computed tomography scan) was performed at the physician's discretion (usually every 8–12 wk) or when disease progression was suspected from clinical evaluation or PSA results.

2.2. Endpoints

The primary endpoint was PSA response, defined as a ≥50% decrease in PSA levels from baseline. Secondary endpoints included best clinical benefit according to physician judgment (improved, stable, nonresponder) on the basis of Eastern Cooperative Oncology Group (ECOG) performance status, cancer-related pain or symptoms, and analgesic consumption; time to PSA progression (TPP) according to Prostate Cancer Working Group 2 (PCWG2) criteria [14]; radiological progression-free survival (rPFS) collected from radiologist and consultation reports, and defined as the time from therapy initiation to radiological progression as per PCWG2 criteria [14] or death; OS calculated from initiation of first, second, and third life-extending therapy to death for each sequence; and grade ≥3 toxicities. Prognostic factors were also analysed.

2.3. Statistical analyses

Statistical analyses were descriptive and p values were exploratory. On the basis of published PSA responses to DOC [1,15], CABA [5], and ART [6,8,9,16], it was estimated that a minimum of 120 patients per group would be needed in each arm to achieve relative precision ranging from 17.9% to 31.0%. OS, TPP, and rPFS were estimated using the Kaplan-Meier

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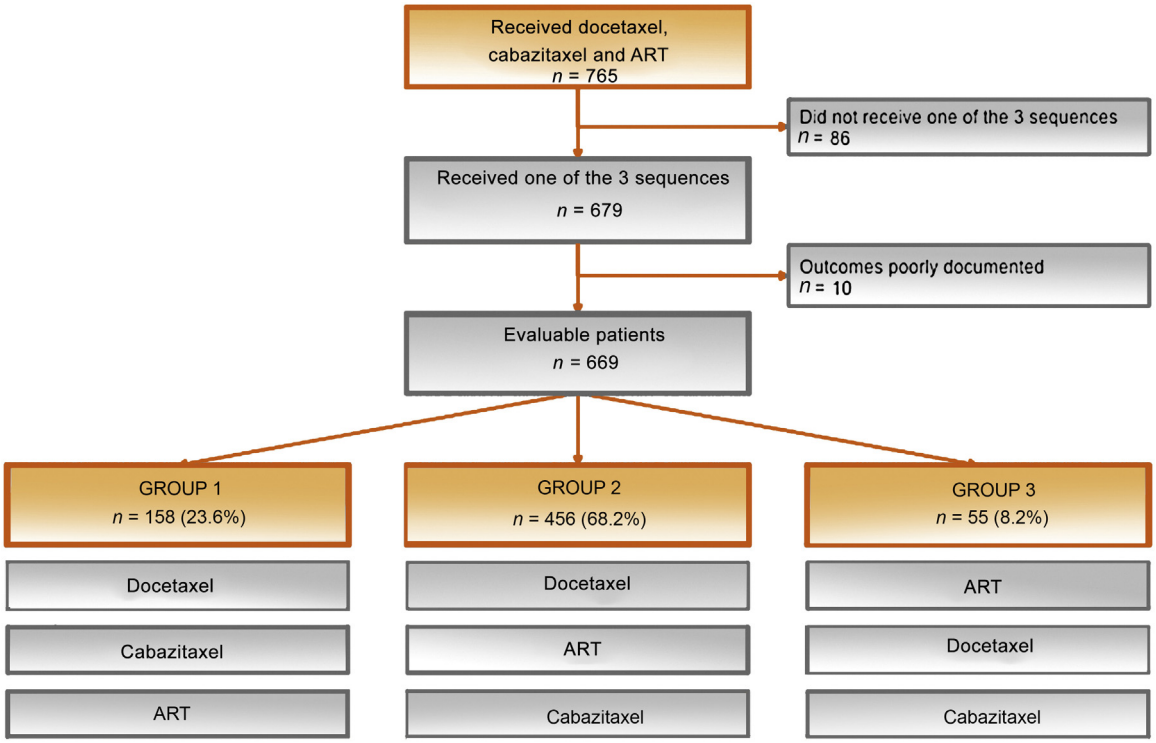

Fig. 1 – Selection of patients for inclusion in the study. Data for patients treated with docetaxel, cabazitaxel, and one next-generation androgen receptor–targeted therapy (ART; abiraterone acetate or enzalutamide) between November 2012 and October 2016 were retrospectively collected.

method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using a Cox proportional hazards model. Variables examined as potential factors influencing OS were patient age at sequence initiation, Gleason score and TNM staging at diagnosis, prior therapy with curative intent, duration of response to first androgen deprivation therapy (ADT), number of ADT lines before first life-extending therapy, sequence of therapies, and the following parameters at sequence initiation: type of progression (PSA progression only, radiological progression, clinical progression), metastatic sites, ECOG performance status, pain, and PSA levels. The neutrophil/lymphocyte ratio, haemoglobin, and alkaline phosphatase were not analysed because of missing data. Multivariate analysis was performed using stepwise logistic regression. Statistical analyses were carried out using SAS v.9.2 (SAS Institute, Cary, NC, USA).

Confidentiality approval was obtained from the Commission Nationale de l'Informatique et des Libertés (CNIL) and the study was approved by the relevant ethics committees. All patients included were informed of this noninterventional study and withdrawal of consent for the use of their data was permitted.

3. Results

3.1. Patient characteristics

A total of 765 patients with mCRPC treated in 34 centres in eight countries between November 2012 and October 2016 were retrospectively identified. Among these, 669 evaluable patients were included in the final analysis (Fig. 1). At diagnosis, the median age was 67 yr, 51.4% of patients had metastatic disease, and 53.2% had Gleason score 8–10. Five patients received radium-223 (all in group 2; 4 after CABA, 1 before CABA) but no patient received sipuleucel-T. At sequence initiation, Gleason score 8–10 was more common in group 1 (63.5%) than in groups 2 and 3 (50% for both; $p = 0.003$), whereas patients in group 3 mostly had PSA-only progression ($p = 0.01$), lower median PSA at sequence initiation ($p = 0.03$), and a higher number of prior ADT lines ($p = 0.002$). Other variables were well balanced between the groups (Table 1), as was the use of bone-modifying agents (data not shown). Median follow-up from first life-extending therapy was 33.7 mo (95% CI 35.5–42.9) in group 1, 31.5 mo (95% CI 34.5–38.1) in group 2, and 27.9 mo (95% CI 25.4–32.6) in Group 3 ($p = 0.013$).

3.2. PSA response according to treatment sequence

The PSA response rate (Fig. 2) to DOC was greater in groups 1 (59.8%) and 2 (64.3%) than in group 3 (44.0%; $p = 0.021$). The PSA response to CABA was significantly greater in the second-line (56.1% in group 1) than in the third-line setting (37.5% and 30.2% in groups 2 and 3, respectively; $p = 0.001$). The PSA response to ART did not differ significantly among groups 1, 2, and 3 (33.7%, 40.2%, and 52.2%; $p = 0.11$).

3.3. Secondary endpoints

Median rPFS (Table 2) with DOC was significantly shorter in group 3 (9.2 mo) than in groups 1 and 2 (17.0 and 15.0 mo; $p = 0.001$). Conversely, median rPFS with CABA did not differ

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Table 1 – Disease history, clinical characteristics, and treatment modalities for 669 patients with metastatic castration-resistant prostate cancer subsequently treated with three life-extending therapies[a]

	Overall (*n* = 669)	Group 1 (*n* = 158)	Group 2 (*n* = 456)	Group 3 (*n* = 55)	*p* value
Disease history					
Gleason score	(*n* = 585)	(*n* = 137)	(*n* = 396)	(*n* = 52)	
Gleason 8–10, *n* (%)	311 (53.2)	87 (63.5)	198 (50.0)	26 (50.0)	0.003
Metastatic disease at diagnosis	(*n* = 611)	(*n* = 138)	(*n* = 419)	(*n* = 54)	
Patients, *n* (%)	314 (51.4)	82 (59.4)	204 (48.7)	28 (51.9)	0.20
Prior therapy with curative intent	(*n* = 658)	(*n* = 149)	(*n* = 454)	(*n* = 55)	
Patients, *n* (%)	328 (49.8)	71 (47.7)	235 (51.8)	22 (40.0)	0.84
Duration of response to first ADT[b]	(*n* = 645)	(*n* = 150)	(*n* = 440)	(*n* = 55)	
Median (mo)	24.4	24.0	25.2	22.9	0.076
≤12 mo, *n* (%)	150 (23.3)	43 (28.7)	93 (21.1)	14 (25.5)	0.16
Patient characteristics at SI					
Median age (yr)	67	68	66	68	0.75
ECOG performance status 2	(*n* = 467)	(*n* = 95)	(*n* = 332)	(*n* = 40)	
Patients, *n* (%)	24 (5.1)	4 (4.2)	17 (5.1)	3 (7.5)	0.80
Pain	(*n* = 616)	(*n* = 137)	(*n* = 424)	(*n* = 55)	
Patients, *n* (%)	261 (42.4)	58 (42.3)	183 (43.2)	20 (36.4)	0.65
Metastatic sites	(*n* = 648)	(*n* = 151)	(*n* = 442)	(*n* = 55)	
Bone, *n* (%)	521 (80.3)	123 (81.5)	355 (80.1)	43 (78.2)	0.88
Lymph nodes, *n* (%)	268 (41.4)	63 (41.7)	180 (40.7)	25 (45.5)	0.79
Visceral, *n* (%)	54 (8.3)	15 (9.9)	36 (8.1)	3 (5.5)	0.56
Type of progression	(*n* = 668)	(*n* = 158)	(*n* = 455)	(*n* = 54)	
PSA only, *n* (%)	203 (30.4)	46 (29.1)	135 (29.7)	22 (40.7)	0.01
Radiological, *n* (%)	408 (61.1)	93 (58.9)	286 (62.9)	29 (53.7)	
Clinical, *n* (%)[c]	159 (23.8)	44 (27.8)	108 (23.7)	7 (12.7)	
Median baseline PSA (ng/ml)	47.0	48.4	55.4	34.0	0.03
Treatment modalities by sequence					
Median prior ADT lines before SI (*n*)[d]	1.0	1.5	1.0	2.0	0.002
Median DOC cycles, *n* (range)	6 (1–28)	6 (1–16)	6.0 (1–28)	6 (2–17)	0.07
DOC initial dosage and schedule	(*n* = 567)	(*n* = 116)	(*n* = 400)	(*n* = 51)	
75 mg/m^2 every 3 wk, *n* (%)	453 (79.9)	85 (73.3)	333 (83.3)	35 (68.6)	0.006
Other schedule, *n* (%)	114 (20.1)	31 (26.7)	67 (16.7)	16 (31.4)	
Prophylactic G-CSF with DOC	(*n* = 669)	(*n* = 158)	(*n* = 456)	(*n* = 55)	
Patients, *n* (%)	126 (18.8)	19 (12.0)	87 (19.1)	20 (36.4)	0.001
Median ART duration, mo (range)	5.5(0.4–42.4)	4.8 (0.4–34.5)	5.9 (0.5–42.4)	5.0 (0.9–15.0)	0.03
Median CABA cycles, *n* (range)	6 (1–22)	7 (1–19)	6 (1–22)	4 (1–15)	0.002
CABA initial dose and schedule	(*n* = 621)	(*n* = 140)	(*n* = 432)	(*n* = 49)	
25 mg/m^2 every 3 wk, *n* (%)	409 (65.9)	101 (72.1)	283 (65.5)	25 (51.0)	0.11
20 mg/m^2 every 3 wk, *n* (%)	122 (19.6)	23 (16.4)	86 (19.9)	13 (16.5)	
Other schedule, *n* (%)	90 (14.5)	16 (11.4)	63 (14.6)	11 (22.4)	
Prophylactic G-CSF use with CABA	(*n* = 621)	(*n* = 140)	(*n* = 432)	(*n* = 49)	
Patients, *n* (%)	318 (51.2)	62 (44.3)	231 (53.5)	25 (51.0)	0.17

ADT = androgen deprivation therapy; ART = next-generation androgen receptor–targeted agent (abiraterone acetate or enzalutamide); CABA = cabazitaxel; DOC = docetaxel; ECOG = Eastern Cooperative Oncology Group; G-CSF = granulocyte colony-stimulating factor; PSA = prostate-specific antigen; SI = sequence initiation.

[a] Group 1: DOC CABA ART; group 2: DOC ART CABA; group 3: ART DOC CABA.

[b] Time between first ADT intake and disease progression (PSA, radiological, or clinical).

[c] Appearance of worsening of cancer-related pain or symptoms as per physician's judgment.

[d] Old-generation hormonal therapy lines.

significantly among the groups ($p = 0.317$). Median rPFS with ART was longer in groups 1 and 2 (26.9 and 11.04 mo) than in group 3 (6.6 mo).

The best clinical benefit during treatment (Table 2) was apparently poorer with ART in the third line ($p < 0.001$) but did not differ significantly between treatment sequences with DOC ($p = 0.71$) and CABA ($p = 0.60$).

The median OS from initiation of the treatment sequence was 34.8, 35.8, and 28.9 mo in groups 1, 2, and 3, respectively (Table 2 and Fig. 3). The corresponding 2-yr OS rates were 75.7%, 74.6%, and 63.1%. Since the outcome in group 3 was unexpected, a sensitivity analysis of TPP, rPFS, and OS was performed in which patients starting the first life-extending at the same time in the three groups were considered (611 patients in total). Outcomes were similar to those for the overall cohort (Supplementary Table 1).

3.4. *Safety and treatment modalities*

The most common toxicities reported with DOC and CABA were grade ≥3 neutropenia and febrile neutropenia (Supplementary Table 2). Nail disorders and neuropathy were less common with CABA than with DOC. The most common toxicities reported with ART were hypertension, hypokalaemia, and transaminase elevation. There were four deaths related to CABA (0.6%): three due to febrile neutropenia and one related to diarrhea with severe dehydration. All deaths occurred in the third-line setting,

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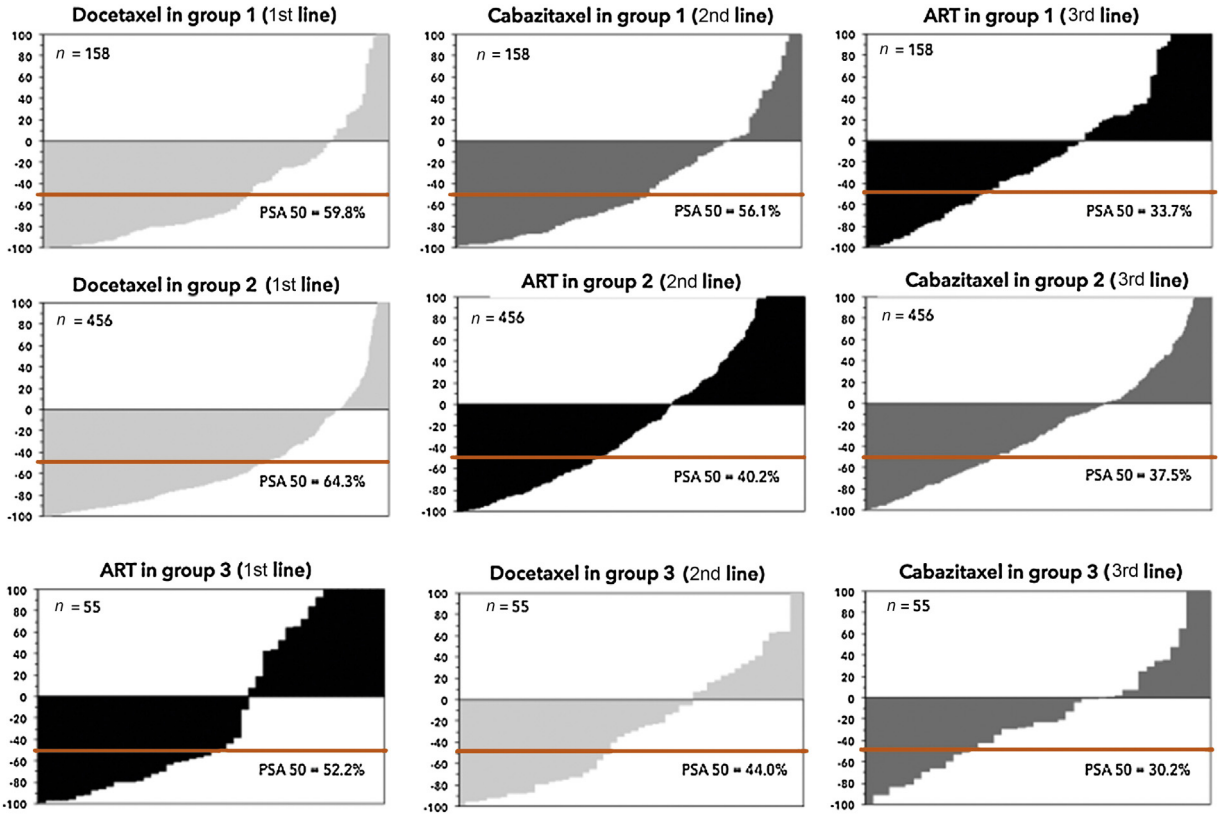

Fig. 2 – prostate-specific antigen (PSA) response in patients with metastatic castration-resistant prostate cancer according to treatment sequence. Group 1: patients received DOC before CABA and then ART; group 2: patients received DOC before ART and then CABA; group 3: patients received ART before DOC and then CABA. ART = novel androgen receptor–targeted therapy (abiraterone acetate or enzalutamide); CABA = cabazitaxel; DOC = docetaxel; PSA 50 = decrease in PSA from baseline of ≥50%.

Table 2 – Best clinical benefit, duration of response, and overall survival[a]

	Overall (*n* = 669)	Group 1 (*n* = 158)	Group 2 (*n* = 456)	Group 3 (*n* = 55)	*p* value
Best clinical benefit [b]					
ART	(*n* = 522)	(*n* = 104)	(*n* = 370)	(*n* = 48)	
Improved, *n* (%)	156 (29.9)	25 (24.0)	118 (31.9)	13 (27.1)	
Stable, *n* (%)	268 (51.3)	45 (43.3)	194 (52.4)	29 (60.4)	0.001
Nonresponder, *n* (%)	98 (18.8)	34 (32.7)	58 (15.7)	6 (12.5)	
DOC	(*n* = 512)	(*n* = 101)	(*n* = 365)	(*n* = 46)	
Improved, *n* (%)	164 (32.0)	23 (22.8)	127 (34.8)	14 (30.4)	
Stable, *n* (%)	312 (60.9)	69 (68.3)	214 (58.6)	29 (63.0)	0.24
Nonresponder, *n* (%)	36 (7.0)	9 (8.9)	24 (6.6)	3 (6.5)	
CABA	(*n* = 514)	(*n* = 114)	(*n* = 359)	(*n* = 41)	
Improved, *n* (%)	176 (34.2)	48 (42.1)	118 (32.9)	10 (24.4)	
Stable, *n* (%)	261 (50.8)	49 (43.0)	185 (51.5)	27 (65.9)	0.11
Nonresponder, *n* (%)	77 (15.0)	17 (14.9)	56 (15.6)	4 (9.8)	
Median TPP, mo (95% CI)					
ART	7.4 (6.9–8.1)	9.3 (7.7–11.9)	7.3 (6.4–8.0)	5.0 (4.0–8.1)	0.001
DOC	9.2 (8.7–9.9)	11.6 (10.3–13.5)	8.6 (8.1–9.5)	6.6 (5.0–10.4)	0.065
CABA	8.7 (7.9–9.2)	8.4 (6.5–9.0)	9.1 (7.8–9.9)	8.9 (5.1–12.7)	0.013
Median rPFS, mo (95% CI)					
ART	11.5 (10.3–13.1)	26.9 (14.8–NR)	11.0 (9.5–12.9)	6.6 (5.0–10.2)	<0.001
DOC	15.0 (14.1–16.6)	17.0 (14.3–20.5)	15.0 (14.0–17.0)	9.2 (5.5–12.6)	<0.001
CABA	14.0 (12.5–16.2)	13.5 (11.5–16.3)	15.0 (13.0–16.9)	10.7 (7.3–18.3)	0.317
Median OS, mo (95% CI)					
From first LET	35.2 (34.0–37.2)	34.8 (32.4–41.5)	35.8 (33.9–38.4)	28.9 (23.3–35.9)	0.007
From second LET	22.6 (21.6–24.2)	21.0 (17.7–23.2)	23.1 (22.0–25.6)	21.4 (17.3–28.4)	0.42
From third LET	12.9 (11.5–13.8)	10.9 (9.1–14.1)	13.1 (12.1–14.7)	12.7 (7.95–16.7)	0.76

DOC = docetaxel; CABA = cabazitaxel; ART = androgen receptor–targeted agent (abiraterone acetate or enzalutamide); TPP = time to PSA progression, rPFS: radiological progression-free survival; NR = not reached; PSA = prostate-specific antigen; LET = life-extending therapy; OS = overall survival.

[a] Group 1: DOC CABA ART; group 2: DOC ART CABA; group 3: ART DOC CABA.

[b] On the basis of performance status, symptom severity, and analgesic consumption.

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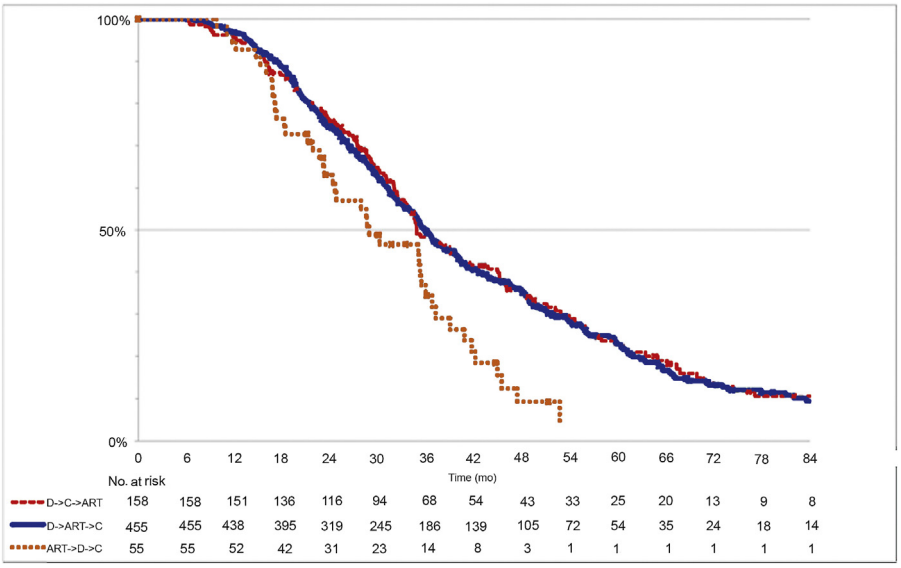

Fig. 3 – Overall survival from sequence initiation. ART = next-generation androgen receptor targeted therapy; C = cabazitaxel; D = docetaxel.

mainly during cycle 1 ($n = 3$). The initial CABA dose was 20 mg/m^2 in three cases and 25 mg/m^2 in one case, and only one patient received prophylactic granulocyte colony-stimulating factor (G-CSF).

3.5. *Multivariate analysis of factors influencing OS*

In univariate analysis, duration of response to first ADT of ≤12 mo, treatment sequence ART → DOC → CABA, baseline PSA ($\log_{10}$), presence of visceral metastases, presence of pain, and ECOG performance status ≥2 were associated with worse OS. In multivariate analysis with stepwise regression, only the presence of visceral metastases, pain, ECOG performance status ≥2 at initiation of first life-extending therapy, and treatment sequence ART → DOC → CABA remained independent predictors of worse OS (Table 3).

4. Discussion

This retrospective cohort is, to the best of our knowledge, the largest ever in which the sequence of life-extending

Table 3 – Factors influencing overall survival at first extending therapy initiation: univariate and multivariate analyses

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Duration of response to first ADT				
>12 mo	Reference			
≤12 mo	1.33 (1.08–1.64)	0.008		
Treatment sequence				
DOC → ART → CABA	Reference		Reference	
DOC → CABA → ART	0.96 (0.78–1.18)		1.04 (0.79–1.36)	
ART → DOC → CABA	1.62 (1.18–2.23)	0.008	1.98 (1.36–2.89)	0.002
Metastatic sites at sequence initiation				
Lymph node only	Reference		Reference	
Bone	1.5 (1.11–2.02)		1.19 (0.83–1.69)	
Visceral	2.32 (1.54–3.49)	<0.001	1.76 (1.09–2.82)	<0.001
Type of progression				
PSA only	Reference			
Radiological	1.31 (1.07–1.59)			
Clinical	1.92 (1.35–2.73)	0.002		
ECOG PS				
0–1	Reference		Reference	
≥2	3.09 (1.96–4.89)	<0.001	2.13 (1.32–3.45)	0.002
Pain				
No	Reference		Reference	
Yes	1.63 (1.35–1.96)	<0.001	1.44 (1.14–1.83)	0.003
PSA ($\log_{10}$)	1.42 (1.22–1.64)	<0.001		

ADT = androgen deprivation therapy; CABA = cabazitaxel; DOC = docetaxel; ECOG PS = Eastern Cooperative Oncology Group performance status; PSA = prostate-specific antigen; CI = confidence interval; HR = hazard ratio.

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therapies (DOC, CABA, one ART) in mCRPC patients in daily practice has been evaluated. Median OS was longer than for historical cohorts [1,2] regardless of the order of life-extending therapies (ranging from 28.9 to 35.8 mo). Moreover, these data confirm the benefit of new life-extending therapies in mCRPC demonstrated in pivotal studies [5–9]. In multivariate analysis, OS was shorter when DOC was used after ART (HR 1.98; 95% CI 1.36–2.89; $p = 0.002$). Secondary outcomes also suggested lower activity of DOC in the post-ART setting. Hence, rPFS with DOC was only 9.2 mo in group 3, compared to 17.0 and 15.0 mo in groups 1 and 2, respectively ($p < 0.001$). rPFS with ART was unexpectedly low in group 3 (median 6.6 mo), but was good with CABA whatever the sequence (median 10.6 mo). The overall incidence of grade ≥3 toxicities was similar in the three groups despite the four deaths related to CABA, which occurred in the largest subgroup (group 2).

Our results should be considered with caution considering the retrospective nonrandomised design of the study and the possible selection bias. Furthermore, the fact that eligible patients had to be treated with three life-extending therapies possibly contributed to selection of fitter patients with aggressive disease (ie, requiring the use of 2 taxanes).

Choice of PSA as a primary endpoint might also be criticised. rPFS would have been a much stronger endpoint since it is better correlated to OS than PSA response; however, it is not easy to use such a parameter as a primary endpoint in a retrospective registry, since timing and imaging modalities may vary between centres in real-life practice. Although patients were usually imaged at initiation of a life-extending therapy and at regular intervals during treatment, there is currently no clear recommendation on the optimal imaging frequency. Therefore, imaging was probably not evaluated at the same time in all patients, as is the case in randomised clinical trials.

Lastly, the small number of patients in group 3 and their short follow-up are also weaknesses of the study; this is probably related to the recent approval of ART before chemotherapy and the fact that patients had to subsequently receive DOC and CABA for inclusion in the analysis. Long responders not requiring further life-extending therapies were not included in this registry. Differences in epidemiological characteristics between the three groups were expected and consistent with expert consensus [12,17], as patients with high Gleason score were preferentially treated with chemotherapy as first life-extending therapy while asymptomatic patients with PSA-only progression received ART in the first line.

Regarding ART in the first line, our results are in contrast to data from the COU-AA-302 [9] and PREVAIL [8] studies. In those trials evaluating AA and ENZA in a pre-DOC setting, the rates of PSA response ≥50% were 62% and 78%, and the median rPFS was 11.1 and 11.2 mo, respectively. The poor PSA response (52%) and poor rPFS (6.6 mo) observed in group 3 in our study was unexpected because patients were mainly experiencing PSA-only progression at ART initiation and should, in theory, have had better prognosis. The greater number of prior hormonal therapies ($p = 0.002$) and the highest rate of short duration (<1 yr) or response to first ADT may suggest that these patients had primary resistance to ART [18]. To eliminate bias related to the recruitment period, a sensitivity analysis of TPP, rPFS, and OS for patients starting the first life-extending therapy in the same period was conducted. However, the results remained unchanged (Supplementary Table 1).

The shorter rPFS with DOC after ART is in agreement with several retrospective studies suggesting that DOC might lose some activity when administered after ART [11,15,19]. At progression after ART, DOC was associated with rates of PSA response ≥50% ranging from 25.7% to 38.0%, which is much lower than the PSA response observed with DOC in the first-line setting in the recent FIRSTANA trial (68.5%) [20].

Conversely, the activity of CABA in our cohort remained unchanged in second- and third-line settings. This is in agreement with results from a prospective randomised phase 2 trial that revealed no significant differences in PFS and OS with CABA between patients previously treated with ART and those with no previous ART [21]. Al Nakouzi et al [13] reported similar clinical data for CABA. PSA responses ≥50% were achieved in 28/79 patients (35%) previously treated with DOC and AA. Median PFS and OS were 4.4 and 10.9 mo, respectively. In the same article the authors reported that CABA decreased cell viability in vitro in both ENZA-sensitive and ENZA-resistant prostate cancer cells within the same range of concentrations. Xenograft models have also demonstrated that CABA is more active than DOC in tumours resistant to ENZA [22]. Conversely, some preclinical studies (but not all) suggest that DOC activity relies in part on direct targeting of the androgen receptor pathway [23,24]. Taken together, these data suggest that lower DOC activity after ART is probable and could be attributable to shared targets between DOC and ART, whereas CABA activity may be retained in the post-ART setting. Lastly, in multivariate analysis, the presence of visceral metastases, poor ECOG performance status, and pain were associated with poor OS, as previously reported [25].

Adverse events reported in this registry were in agreement with those reported in phase 3 trials. Taxanes are mainly associated with grade ≥3 neutropenia and its potential neutropenic complications (febrile neutropenia, neutropenic infections). Systematic prophylactic G-CSF initiated for cycle 1 is required on CABA, and should be considered in all patients aged ≥70 yr and those who have experienced hepatotoxicity during DOC therapy [25]. In patients judged unfit to receive the standard CABA dose regimen, a dose of 20 mg/m^2 is noninferior to 25 mg/m^2 in terms of OS [26]. The most common adverse events with ART were hypertension, hypokalaemia, and elevated transaminase underlining the need to regularly monitor for these toxicities in daily practice.

5. Conclusions

This large retrospective registry of mCRPC patients treated with three life-extending therapies (DOC, CABA, and one novel ART) suggests that CABA activity is not influenced by therapeutic sequence and does not appear to be correlated

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with response on ART. DOC activity might be lower when used after ART, but the data are insufficient to conclude that there is cross-resistance between DOC and ART. As new standards of care for mCRPC are emerging [27–29], the issue of therapeutic sequence is still crucial [30]. These retrospective data should be confirmed by well-conducted prospective trials.

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Acquisition of data: All authors.
Analysis and interpretation of data: Oudard, Delanoy.
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Appendix A. Supplementary data

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