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Original Research

Efficacy of cabazitaxel rechallenge in heavily treated patients with metastatic castration-resistant prostate cancer

Constance Thibault [a,b], Jean-Christophe Eymard [c], Alison Birtle [d], Michael Krainer [e], Giulia Baciarello [f], Aude Fléchon [g], Sylvestre Le Moulec [h], Dominique Spaeth [i], Brigitte Laguerre [j], Orazio Caffo [k], Jean-Laurent Deville [l], Phillipe Beuzeboc [m], Ali Hasbini [n], Marine Gross-Goupil [o], Carole Helissey [p], Mostefa Bennamoun [q], Anne-Claire Hardy-Bessard [r], Stéphane Oudard [a,b,*]

[a] *European Georges Pompidou Hospital, Paris, France*
[b] *René Descartes University, Paris V, France*
[c] *Jean Godinot Institute, Reims, France*
[d] *Lancashire Teaching Hospitals, Preston, UK*
[e] *Medical University of Vienna, Austria*
[f] *Gustave Roussy Institute, Villejuif, France*
[g] *Léon Bérard Center, Lyon, France*
[h] *Bergonie Institute, Bordeaux, France*
[i] *Gentilly Oncology Center, Nancy, France*
[j] *Eugène Marquis Center, Rennes, France*
[k] *Department of Medical Oncology Santa Chiara Hospital, Trento, Italy*
[l] *La Timone Hospital, Marseille, France*
[m] *Curie Institute, Paris, France*
[n] *Oncology Center Clinique Pasteur, Brest, France*
[o] *Centre Hospitalier Universitaire, Bordeaux, France*
[p] *Hôpital D'Instruction des Armées, Bégin, Saint Mandé, France*
[q] *Institut Mutaliste Montsouris, Paris, France*
[r] *Centre Amoricain D'Oncologie, CARIO, Plerin, Paris, France*

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Abstract ***Background:*** Treatment option in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (DOC), cabazitaxel (CABA)

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* *Corresponding author*: Georges Pompidou Hospital, 20 rue Leblanc, 75015 Paris, France.
E-mail address: stephane.oudard@aphp.fr (S. Oudard).

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Metastatic castration-resistant prostate cancer;
Rechallenge;
Overall survival;
Progression-free survival;
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Safety

and new hormone therapy (NHT) is limited. Rechallenge with DOC is limited because of cumulative toxicities. This study investigated the activity and safety of CABA rechallenge in mCRPC.

Patients and methods: Clinical data were collected retrospectively in 17 centres in Europe. Eligible patients had undergone rechallenge with cabazitaxel after three previous lines of treatment (DOC, NHT and CABA, in any order). Overall survival (OS) and progression-free survival (PFS) were estimated by the Kaplan–Meier method. Data on toxicities were collected.

Results: A total of 69 of 562 patients (Eastern Cooperative Oncology Group performance status 0–1 69%) were rechallenged with CABA (25 mg/m^2 q3w, 58%; 20 mg/m^2 q3w, 27.5%; other, 14.5%) for 1–10 (median 6) cycles; 76.8% received prophylactic granulocyte colony-stimulating factor. Median radiological or clinical PFS with CABA rechallenge was 7.8 months and 11.9 months with initial CABA therapy. OS was 13.7 months (95% confidence interval [CI]: 9.3–15.7) from the first CABA rechallenge cycle, 59.9 months (47.8–67.1) from the first life-extending therapy in mCRPC and 78.3 months (66.4–90.7) from mCRPC diagnosis. Best clinical benefit was improved (34.3%) or stable (47.8%). Lack of response to rechallenge occurred in 17.9% of patients (3.1% with initial CABA). The level of prostate-specific antigen decreased by $\geq$ 50% in 24% of patients at rechallenge (71% with initial CABA). There was no grade $\geq$III peripheral neuropathy or nail disorders.

Conclusions: CABA rechallenge may be a treatment option without cumulative toxicity in heavily pretreated patients with mCRPC who are still fit and had a progression >3 months after the last CABA injections.

1. Introduction

Docetaxel (DOC) was the first agent shown to improve overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC) and received US Food and Drug Administration and European Medicines Agency (EMA) approval for this indication in 2004 and 2005, respectively [1]. Since 2004, several new agents with different mechanisms of action have become available for the treatment of mCRPC contributing to further improve OS in patients with mCRPC [2]. These agents include the new hormonal therapies (NHT) such as abiraterone acetate (AA) and enzalutamide (ENZA), cabazitaxel (CABA), a next-generation taxane effective in resistant tumours [1], the radiopharmaceutical radium-223 and immunotherapy with sipuleucel-T.

Although the optimal sequence of these agents is unknown, retrospective studies suggest that OS increases with the number of life-extending therapies received and sequential use of DOC, CABA and one NHT, showing a particularly long OS, whatever the order of administration [3,4]. However, once these three life-extending therapies have been exhausted, treatment options are limited, and there is a lack of clinical studies in this area.

Rechallenge with a previously used agent is one approach to the management of patients with disease relapse after all options have been used. However, there are several potential issues with this approach. First, prospective studies have evidenced cross-resistance in most patients between NHTs [5,6]; second, reuse of docetaxel may lose some activity after androgen receptor (AR)-targeted agents [7–10] and is associated with cumulative toxicity especially neurological toxicity [11]. Conversely, CABA, associated with less peripheral neuropathy than DOC [12], does not seem to be associated with cumulative toxicity [13] and retains its activity in patients with primary resistance to DOC [14] and those progressing with NHT [15]. Rechallenge with CABA may thus represent an interesting option in patients still fit to receive it.

This multicentre, retrospective study investigated the efficacy and safety of rechallenge with cabazitaxel in heavily pretreated patients with mCRPC previously treated with DOC, CABA and NHT.

2. Material and methods

2.1. Study design

Data from patients with mCRPC consecutively rechallenged with CABA were retrospectively collected (using an electronic case report form) between December 2013 and September 2016 at 17 centres in France, Italy, UK and Austria. To be eligible, all patients had to be previously treated with three life-extending therapies (DOC, one NHT and CABA) in any order. Patient clinical characteristics and activity of the first CABA treatment and CABA rechallenge were described. Efficacy assessments included prostate-specific antigen (PSA) response (confirmed PSA decrease of $\geq$50% from baseline), best clinical benefit (according to investigator

judgement based on European Cooperative Oncology Group performance status [ECOG-PS], pain and analgesic consumption), radiological and/or clinical progression-free survival or death (PFS) and overall survival (OS). Grade ≥III toxicities were collected. In addition, OS was examined from the first, second, third and fourth life-extending therapy (CABA rechallenge) to further characterise the impact of number of life-extending therapies on outcomes. Follow-up for all deceased patients was complete until the time of their death.

Imaging (bone scan with or without computed tomography [CT] scan for patients with measurable disease) was performed after every two or three cycles of CABA, at the physician's discretion.

2.2. Ethics

The study was approved by the Ethics Committee at each participating centre. Confidentiality approval was obtained from the Commission Nationale de l'Informatique et des Libertés.

2.3. Statistical analysis

Analyses were descriptive. OS and PFS were estimated by the Kaplan–Meier method. Hazard ratios (HRs) and 95% confidence interval (CI) values were calculated using a Cox proportional hazards model. The influence of CABA-free interval (<6 or ≥ 6 months) and CABA dose received (20 or 25 mg/m^2) on activity of CABA rechallenge was tested by Fishers exact test. A two-sided p-value of 0.05 was considered statistically significant. All analyses were conducted using SAS® software (SAS Institute, NC, USA).

3. Results

3.1. Patient characteristics

Clinical records of 562 patients treated with DOC, CABA and one NHT were reviewed. Of these, 69 underwent rechallenge with CABA and were included in this analysis. Treatment sequences were as follows: DOC→NHT→CABA (n = 51, 73.9%), DOC→CABA→NHT (n = 15, 21.7%) and NHT→DOC→CABA (n = 3, 4.3%). Among the 69 patients, 55% received other treatment(s) between the first CABA and CABA rechallenge, and 45% did not receive any other systemic treatment before the rechallenge. The previous treatment before CABA rechallenge was NHT (42%, n = 29), CABA (46%, n = 32), DOC (3%, n = 2) and other (9%, n = 6). The type of progression before CABA rechallenge was radiological (55%, n = 38), clinical without radiological progression (17.4%, n = 12) and PSA progression only (27.5%, n = 19). The main reasons for stopping the first CABA were treatment completed (73%, n = 49) and toxicity (9%, n = 6). Patient clinical characteristics at the first CABA therapy and CABA rechallenge are provided in Table 1. Of these 69 patients, 44.1% were diagnosed at metastatic stage, 46.8% had a Gleason 8–10 at diagnosis and 16.4% had a duration of response to ADT of less than 12 months.

3.2. Cabazitaxel rechallenge details and activity

CABA treatment modalities are described in Table 2. Compared with initial CABA therapy, at rechallenge, more patients were receiving a 20 mg/m^2 starting dose (27.5% versus 13.0%) or another CABA schedule (mainly 16 mg/m^2 every 2 weeks; 14.5% versus 4.3%), the median number of CABA cycles was lower (6 versus 9) and prophylactic granulocyte colony-stimulating factor (G-CSF) use was more common (76.7% versus 66.6%). At CABA rechallenge, clinical response was clinical benefit in 34.3% of the patients (50.0% with the first CABA), stable in 47.8% (46.9% with the first CABA) and 17.9% had a clinical progression (3.1% with the first CABA). Confirmed PSA response of at least 50% was observed in 23.8% of patients (70.8% with the first CABA). Median PFS with CABA rechallenge was

Table 1
Patient characteristics at initiation of the first CABA and CABA rechallenge.

Characteristic	First CABA (n = 69)	CABA rechallenge (n = 69)
Median age	68 (49–85)	70 (51–86)
Metastatic sites		
Lymph node	40.0%	36.2%
Bone	90.0%	94.2%
Visceral	8.7%	10.1%
Tumour burden		
Low volume	26.2%	17.2%
High volume[a]	73.8%	82.8%
Type of progression		
PSA only	24.6%	27.5%
Radiological	59.4%	55.1%
Clinical	36.2%	52.2%
ECOG-PS		
0–1	88.7%	69.1%
2+	11.3%	30.9%
Pain	54.4%	69.6%
Narcotic analgesics	52.9%	65.9%
PSA, ng/ml (range)	88.6 (4.0–3159)	170 (3.8–9692)
Cabazitaxel-free interval		
Median (months)	NR	8.9 (3.1–32.6)
3–6 months	NR	34.3%
6–9 months	NR	16.4%
9–12 months	NR	16.4%
>12 months	NR	32.8%

Values are median (range) or percentage of patients.
CABA = cabazitaxel; ECOG-PS = European Cooperative Oncology Group Performance Status; PSA = prostate-specific antigen; NR = not relevant.
[a] High volume definition: visceral metastases and/or four or more bone metastases with ≥one beyond pelvis.

Table 2
Modalities and activity of the first CABA therapy and CABA rechallenge.

% Patients	First CABA	CABA rechallenge
CABA initial dose		
25 mg/m^2 q3w	82.6%	58.0%
20 mg/m^2 q3w	13.0%	27.5%
16 mg/m^2 q2w	4.3%	14.5%
N cycles (range)	9 (3–22)	6 (1–10)
Prophylactic G-CSF, %	66.6%	76.8%
Best clinical benefit[a]		
Improved	50.0%	34.3%
Stable	46.9%	47.8%
Progression	3.1%	17.9%
PSA response		
≥50%	70.8%	23.8%
Radiological and/or clinical PFS[b]		
Median [95% CI]	11.9 [10.6–14.5]	7.8 [4.6–10.1]
OS		
Median [95% CI]	30.65 [24.3–37.8]	13.7 [9.3–15.7]

CABA = cabazitaxel; CI = confidence interval; G-CSF = granulocyte colony-stimulating factor; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen.
[a] Best clinical benefit based on ECOG-PS, pain and analgesic consumption.
[b] Time to radiological progression as per PCWG2 or symptomatic progression or death.

7.8 months (95% CI 4.6–10.1) and 11.9 months (95% CI 10.6–14.5) with the first CABA (Fig. 1). Median follow-up from the start of the first life-extending therapy was 46.9 months. Median OS at initiation of CABA rechallenge was 13.7 months (95% CI, 9.3–15.7) versus 30.65 months (95% CI, 24.3–37.8) at initiation of the first CABA treatment. OS calculated from mCRPC diagnosis (disease progression with the first ADT), first, second and third life-extending therapies in mCRPC were 78.3 [66.4; 90.7], 59.9 [47.8–67.1], 46.4 [35.1–51.2] and 27.1 [23.9–34.7] months, respectively (Fig. 2).

The median cabazitaxel-free interval (time from the last CABA cycle in the first line to CABA rechallenge) was 8.9 months (range 3.1–32.6) and was >6 months for 66% of the patients. Time relapsed since the last CABA cycle in the first line to CABA rechallenge did not significantly impact the activity of CABA rechallenge, either when median time (>8.9 versus ≤ 8.9 months) or a 6-month cut-off was considered. Hence, among patients with a CABA-free interval >6 and ≤ 6 months, 85.7% and 74.0% had improved/stable symptoms (p = 0.319), and 26.8% and 19% had a PSA response of ≥50% (p = 0.551). Similarly, the starting dose of CABA at rechallenge (25 mg/m^2 versus 20 mg/m^2) did not significantly impact the rate of improved/stable symptoms (p = 1.0) or PSA response rate (p = 0.383).

3.3. Safety

CABA rechallenge had a manageable tolerability profile (Table 3). Most patients (76.8%) received prophylactic G-CSF during CABA rechallenge. Adapted dose/regimen was more common at rechallenge (27.5% had a starting dose of 20 mg/m^2 and 14.5% had a 16 mg/m^2 every 2 weeks mg/m^2).The proportion of patients experiencing grade III/IV adverse events was slightly lower during CABA rechallenge than during the first dose of cabazitaxel (Table 3). There was no grade ≥III peripheral neuropathy or nail disorders.

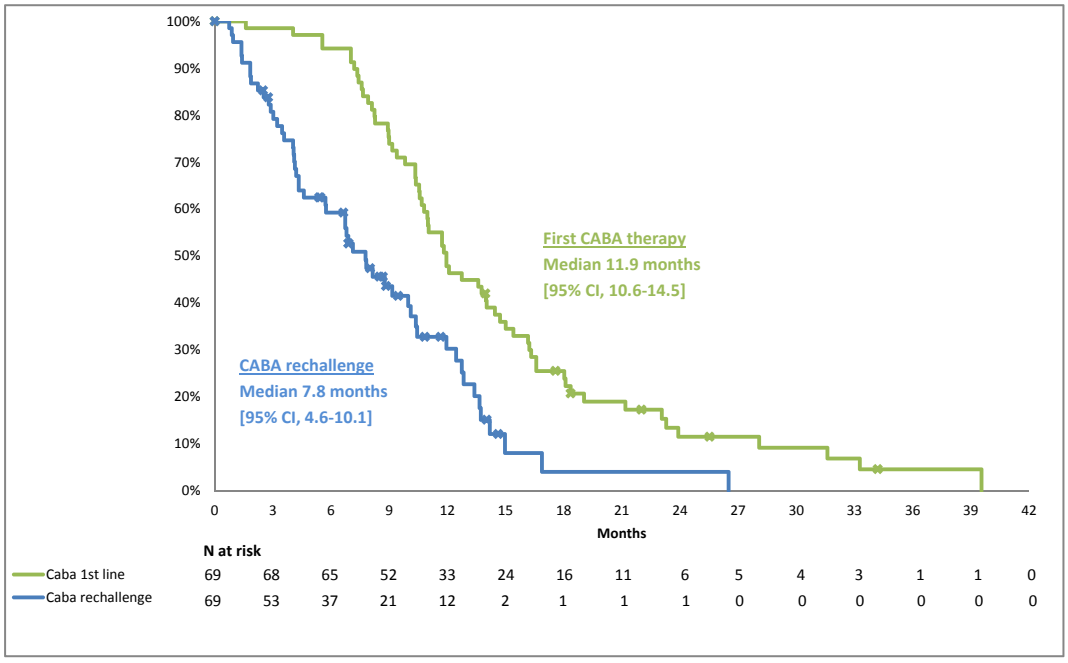

Fig. 1. Radiological and/or clinical progression-free survival after cabazitaxel given as the first-line therapy and rechallenge. CABA = cabazitaxel; CI = confidence interval.

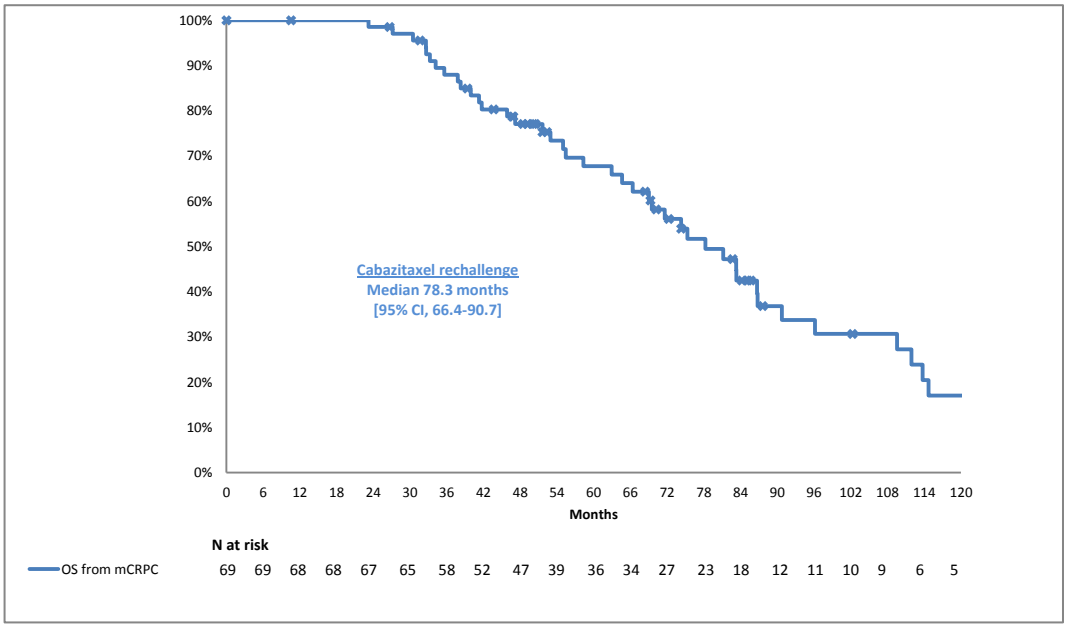

Fig. 2. Overall survival from mCRPC diagnosis. CI = confidence interval; mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival.

4. Discussion

This study is the first to report the efficacy and safety of CABA rechallenge in patients with mCRPC who had previously received three different life-extending therapies (DOC, one NHT and CABA). No prospective clinical trial has addressed this question as of now. Our results suggest that rechallenge with CABA in the fourth-line setting is associated with improved/stable symptoms in 33.8%/48.5% of patients, a median radiological or clinical PFS of 7.8 months and a median OS from CABA rechallenge initiation of 13.4 months. Calculated from mCRPC diagnosis and the first life-extending therapy received, median OS reached 78.3 and 59.9 months, respectively. Although the activity of CABA rechallenge appeared slightly reduced as compared with the first CABA therapy, which is expected because heavily pretreated patients usually have more resistant tumours, such good outcomes may reflect a certain patient selection. Indeed, patients rechallenged with CABA were mainly good responders to initial CABA therapy (although no specific inclusion criterion was specified in the protocol) with only 3% of non-responders. The tolerance of CABA rechallenge was acceptable in our study. Only 8.7% patients had grade III/IV treatment-related toxicities, and 16% had a dose reduction with CABA rechallenge. The safety profile tended to be better with CABA rechallenge if compared with the first CABA. However, fewer patients with CABA rechallenge received a dose of 25 mg/m^2 of CABA (58% versus 83%), and the use of prophylactic G-CSF was more frequent (77% versus 67%).

Reuse of the same anticancer therapy after disease progression is often considered to be futile owing to drug resistance. However, there are many examples in oncology showing that an effective drug can be reused with a high likelihood of response which may be attributed to reversible and epigenetic resistance mechanisms [16]. Hence, several retrospective studies have reported a clinical benefit with DOC rechallenge [11,17–20]. However, these studies were conducted at the time DOC was the unique life-extending therapy available in mCRPC which means that DOC rechallenge was given in the second-line setting while CABA rechallenge in our study was given in the fourth-line setting in patients previously treated with DOC, AA or ENZA and CABA. We believe CABA rechallenge might be a better option in the new mCRPC landscape for several reasons. First, DOC rechallenge usage is limited by its cumulative and bothersome toxicity (mainly nail disorders and sensory neuropathy) [11]. This does not seem to be the case with CABA in our trial as in the literature [21]. Second, there is increasing evidence that DOC loses some activity in patients progressing with NHT [7–9], whereas CABA has shown in a prospective randomised phase II trial to retain its activity in such patients [22]. This is likely explained by a greater tumour penetration of CABA than DOC in resistant tumours [23].

We believe our findings may be useful for oncologists in everyday clinical practice, but the results need to be interpreted with caution because of several limitations. First is the retrospective design and its inherent biases. Second, all the patients rechallenged with CABA were still fit for a fourth line of treatment and for chemotherapy, which is not representative of the usual population of mCRPC after several treatments. Third, none of the patients rechallenged had a progression under or in the 3 months after the last CABA injection. The main

Table 3
Safety of cabazitaxel.

Adverse event	First CABA	CABA rechallenge
Number of patients (%)		
Any Grade III/IV event	15 (21.7)	7 (10.1)
Treatment-related Grade III/IV event	14 (20.3)	6 (8.7)
Serious treatment-related events	6 (8.7)	0
Events necessitating dose reduction	13 (18.8)	11 (15.9)
Events necessitating dose delay	11 (15.9)	16 (23.2)
Main grade III/IV adverse events, N		
Neutropenia	8	7
Febrile neutropenia	1	0
Anaemia	4	0
Thrombopenia	0	1
Diarrhoea	1	0
Haematuria	1	0
Cholestasis	1	0

CABA = cabazitaxel.

reason for stopping the first CABA was the end of the treatment (73%). Therefore, the population of our study can be considered as responsive to the first CABA, which can explain the higher PSA response at the first CABA in our study than in TROPIC trial. Fourth, none of the patients in our study received carboplatin before CABA rechallenge, and only one received it after. We do not know which is the better option between CABA rechallenge and carboplatin. Moreover, several data have been recently published about the frequency of germinal and somatic DNA repair defects in mCRPC, and carboplatin is known to be effective in those patients. In our study, we did not know the frequency of DNA repair defects. We therefore do not know if CABA rechallenge is a good option for patients with DNA repairs deficiency.

In our cohort, 27% of patients were rechallenged at a dose of 20 mg/m^2. Although numbers are rather small, we did not evidence a significant reduction in CABA activity as compared with the standard 25 mg/m^2. This is in agreement with PROSELICA phase III results showing that a CABA 20 mg/m^2 dose was better tolerated and non-inferior to CABA 25 mg/m^2 dose in terms of OS although anti-tumour activity was numerically higher with 25 mg dose [24]. In the first-line setting, FIRSTANA also showed that CABA 20 mg/m^2 was better tolerated than CABA 25 mg/m^2 and DOC 75 mg/m^2 [12]. Although CABA 25 mg/m^2 may have a manageable toxicity in elderly patients receiving prophylactic G-CSF [25,26], starting with a 20 mg/m^2 dose may be appropriate in patients with very advanced disease because they may not be fit enough to receive the standard dose. In a German retrospective trial of patients with mCRPC treated with CABA in the second-to sixth-line setting, 39.2% received a starting dose of 20 mg/m^2 or other adapted regimens because of a poor general condition [27]. All lines considered, median OS and PFS with CABA were 10 and 3.9 months, respectively, which is shorter than those in our cohort in the fourth line (13.4 and 7.8 months, respectively). In addition, three patients in the German cohort experienced fatal adverse events, whereas we did not observe any toxic death in our cohort. This may reflect either a better selection of patients considered fit to receive chemotherapy or a better proactive prevention and management of chemotherapy-related side-effects in our study. It is well known that best supportive care measures are crucial to optimise outcomes in patients with advanced prostate cancer. Indeed, a subanalysis of TROPIC phase III trial concluded that proactive management of CABA adverse events (mainly neutropenic complications) was associated with a lower rate of discontinuation due to adverse event, less severe toxicity and better OS [28]. Another approach aimed at improving the tolerability of taxanes in heavily pretreated patients may be to give them every 2 weeks [25]. We have conducted in our institution a pilot study suggesting that CABA administered at a dose of 16 mg/m^2 every 2 weeks was active with a manageable tolerability in heavily pretreated patients [29]. A phase III randomised trial comparing CABA 25 mg/m^2 every 3 weeks versus CABA 16 mg/m^2 every 2 weeks in patients aged $\geq$70 years is currently ongoing (NCT02961257).

Finally, we and others have reported that DOC rechallenge had a reduced activity in patients rapidly progressing after the last DOC cycle [17,30]. In a cohort of 39 patients with mCRPC rechallenged with DOC, those progressing within 3 months after the last DOC cycle had a median PFS of 3.4 months versus 6.3 months in those progressing >3 months ($p = 0.04$) [17,30]. In a large retrospective cohort of 270 patients, we also observed a strong relationship between progression-free interval and outcome on DOC rechallenge [11,30]. Patients progressing >6 months after the last DOC cycle had greater PSA response rates (54.9%) and symptom relief (25.7%) than those progressing more rapidly although there was no OS benefit versus a non-taxane regimen. In the present study, the progression-free interval did not seem to influence the activity of CABA rechallenge. There was only a trend to a better response in patients with a progression-free interval >6 months.

To conclude, we do think that for patients still fit for chemotherapy (PS 0–2) after NHT, DOC and CABA, who had a progression > 3 months after the last CABA injection, CABA rechallenge might be a treatment option.

5. Conclusion

This retrospective study suggests that rechallenge with CABA is a feasible and effective therapeutic option in heavily pretreated patients with mCRPC who well responded to a first CABA treatment and were still fit to receive chemotherapy. There was no evidence of

cumulative toxicity during CABA rechallenge. These results must be confirmed by prospective randomised clinical studies.

Conflict of interest statement

Stéphane Oudard certifies that all conflicts of interest, including specific financial interests, relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g. employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties or patents filed, received or pending), are the following: CT declares to be a consultant, a member of speakers bureau and scientific advisory boards and a recipient of travel support for participation in medical meetings from Sanofi and Astellas; J-C.E declares to be a consultant, a member of speakers bureau and scientific advisory boards and a recipient of travel support for participation in medical meetings from Sanofi, Janssen, Astallas, Pfizer, Novartis and Sandoz; AB declares to be an advisory board member of Janssen, Astellas, Bayer and Roche and received an educational grant from Sanofi-Aventis; MK declares to have an advisory role or expert testimony for Jannsen, Astellas, Dendreon, Sanofi-Aventis and Medivation and Financing of Scientific Research from BMS, Astellas, Medivation, Pfizer, Sotio, Sanofi-Aventis; GB declares to be at a the scientific advisory boards of Sanofi, Janssen and has travel support for participation in medical meetings from Sanofi, Astellas, Janssen, Astra Zeneca; AF declares to be a consultant, a member of speakers bureau and the scientific advisory boards and a recipient of travel support for participation in medical meetings from Sanofi, Astellas, Bayer, Janssen; DS declares to be a a member of the scientific advisory board of Sanofi, Novartis, Roche and Astra Zeneca and a recipient of travel support for participation in medical meetings from Janssen, Novartis, Roche and Pierre Fabre Oncology; BL declares to be a consultant, a member of speakers bureau and the scientific advisory boards and a recipient of travel support for participation in medical meetings from Sanofi, BMS, Bayer, Janssen, Pfizer, Novartis and Merck; OC declares honoraria as a speaker or advisor for Astellas, Bayer, Janssen and Sanofi; J-L D declares to be a consultant, a member of speakers bureau and the scientific advisory boards and a recipient of travel support for participation in medical meetings from Sanofi, Astellas, Janssen, Pfizer and Novartis; PB declares honoraria as a speaker or advisor for Sanofi and Jansen; AH declares to be a member of scientific advisory boards and a recipient of travel support for participation in medical meetings from Sanofi, Astellas, Janssen, Pfizer, Novartis and Ferring; MGG declares to be a consultant, a member of the speakers bureau and the scientific advisory boards and a recipient of travel support for participation in medical meetings from Sanofi, BMS, Astellas, Bayer, Janssen, Pfizer, Novartis, Roche and MSD; CH declare to be a member of the scientific advisory boards and a recipient of travel support for participation in medical meetings from Sanofi, Astellas, Janssen and Roche; MB declares to be a consultant, a member of the speakers bureau and the scientific advisory boards and a recipient of travel support for participation in medical meetings from Sanofi, BMS, Astellas, Janssen, Novartis and Amgen; SO declares to be a consultant, a member of the speakers bureau and the scientific advisory boards and a recipient of travel support for participation in medical meetings from Sanofi, BMS, Astellas, Janssen, Novartis, Ipsen, Pfizer, Roche and MSD ; all other authors have declared no conflicts of interest.

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JCE has reported consulting and speaker's bureau remuneration from Sanofi, JLD has received honoraria from Janssen-Cilag, Astellas, Sanofi, PB has received honoraria from Sanofi and SO has reported consulting and speaker's bureau remuneration from Sanofi and travels and accommodations paid by Sanofi.

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