

ORIGINAL ARTICLE

Phase I/II trial of cabazitaxel plus abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel and abiraterone

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Background: Abiraterone and cabazitaxel improve survival in patients with metastatic castration-resistant prostate cancer (mCRPC). We conducted an open-label phase I/II trial of cabazitaxel plus abiraterone to assess the antitumor activity and tolerability in patients with progressive mCRPC after docetaxel (phase I), and after docetaxel and abiraterone (phase II) (NCT01511536).

Patients and methods: The primary objectives were to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of cabazitaxel plus abiraterone (phase I), and the prostate-specific antigen (PSA) response defined as a $\geq 50\%$ decrease confirmed ≥ 3 weeks later with this combination (phase II).

Results: Ten patients were enrolled in the phase I component; nine were evaluable. No DLTs were identified. The MTD was established as the approved doses for both drugs (cabazitaxel 25 mg/m² every 3 weeks and abiraterone 1000 mg once daily). Daily abiraterone treatment did not impact on cabazitaxel clearance. Twenty-seven patients received cabazitaxel plus abiraterone plus prednisone (5 mg twice daily) in phase II. The median number of cycles administered (cabazitaxel) was seven (range: 1–28). Grade 3–4 treatment-emergent adverse events included asthenia (in 5 patients; 14%), neutropenia (in 5 patients; 14%) and diarrhea (in 3 patients; 8%). Nine patients (24%) required dose reductions of cabazitaxel. Of 26 evaluable patients, 12 achieved a PSA response [46%; 95% confidence interval (CI): 26.6–66.6%]. Median PSA-progression-free survival was 6.9 months (95% CI: 4.1–10.3 months). Of 14 patients with measurable disease at baseline, 3 (21%) achieved a partial response per response evaluation criteria in solid tumors.

Conclusions: The combination of cabazitaxel and abiraterone has a manageable safety profile and shows antitumor activity in patients previously treated with docetaxel and abiraterone.

Key words: prostate cancer, abiraterone, cabazitaxel, combination

Introduction

Therapeutic options for men with metastatic castration-resistant prostate cancer (mCRPC) have evolved considerably with the approval of five therapies associated with improved overall survival

(OS): cabazitaxel (taxane chemotherapy), abiraterone and enzalutamide [androgen receptor (AR)-targeted therapies], radium 223 (bone-targeted), and sipuleucel-T (immunotherapy) [1]. These new treatments have improved OS in patients with mCRPC, but there is a need to provide robust evidence on how

these agents should be used, in sequence or combination, to achieve optimal medical management [2, 3].

Cabazitaxel is a second-generation taxane indicated for the treatment of patients with mCRPC pretreated with castration and docetaxel [4]. Phase I and II clinical studies have shown that neutropenia is the primary dose-limiting toxicity (DLT) [5, 6]. The recommended cabazitaxel dose was established as 25 mg/m² administered intravenously once every 3 weeks. A phase III randomized trial comparing cabazitaxel plus prednisone with mitoxantrone (TROPIC) found that cabazitaxel improved progression-free survival (PFS) and OS in patients with mCRPC who have progressed on prior docetaxel treatment [4]. Abiraterone is an inhibitor of CYP17, an enzyme required for androgen biosynthesis [7]. Two phase III randomized trials comparing abiraterone plus prednisone against prednisone alone in patients with mCRPC found that abiraterone significantly increased radiographic PFS and OS [8, 9]. Following these pivotal trials, cabazitaxel 25 mg/m² administered intravenously once every 3 weeks, and abiraterone 1000 mg administered once daily, were approved for use in patients with mCRPC who had previously received docetaxel.

An important potential therapeutic approach to be explored is the combined use of taxane-based chemotherapy and AR-targeted therapy, given their partially overlapping mechanisms of action and toxicities [10]. We hypothesized that the combination of an AR-targeted therapy and chemotherapy can maximize anti-tumor activity in patients with mCRPC previously treated with docetaxel.

Here we report the results of phase I/II trial (NCT01511536) of cabazitaxel plus abiraterone in patients with mCRPC who had previously received docetaxel and abiraterone. A dose escalation phase I study was conducted to determine the maximum tolerated dose (MTD) and DLTs of cabazitaxel-abiraterone combination. An expansion phase II study investigated the activity of cabazitaxel-abiraterone combination in terms of prostate-specific antigen (PSA) response rate. Secondary objectives included safety, pharmacokinetic (PK) profile, and assessment of the preliminary antitumor activity in terms of PFS, OS, and response rate.

Patients and methods

Patient population

The study enrolled patients aged ≥ 18 years with histologically or cytologically confirmed mCRPC, previously treated with a docetaxel-containing regimen. Patients had documented progressive disease, and an Eastern Cooperative Oncology Group performance status of 0–1. All patients had progressive disease documented by rising PSA. In phase I, in addition to rising PSA, progressive disease must have been documented by an increase in non-measurable/measurable disease and/or the appearance of new lesions. In phase II, enrolled patients had progressive disease documented by rising PSA only, and had received abiraterone for ≥ 3 months, which they were continuing to receive before study entry (full eligibility criteria in [supplementary Table S1](#), available at *Annals of Oncology* online). The study was approved by the institutional review board at each study center and was conducted in compliance with guidelines for Good Clinical Practice. Patients provided written informed consent before study participation.

Study design and treatment

This was a phase I/II, multicenter, open-label, dose escalation, and dose expansion study of cabazitaxel plus abiraterone and prednisone in patients with mCRPC previously treated with docetaxel. In the phase I part of the study, cohorts of three to six patients received one of two cabazitaxel dose levels (20 or 25 mg/m²) by 1-h intravenous infusion on day 1 of each 3-weekly cycle, according to a standard 3 + 3 dose escalation design. The recommended dose of cabazitaxel was determined as 20 and 25 mg/m² in early phase I studies [5, 6]; therefore both doses were assessed in combination with abiraterone. All patients also received oral abiraterone 1000 mg once daily in fasting conditions and oral prednisone 5 mg twice daily. DLTs during Cycles 1 and 2 in phase I were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (AE) [11] as grade 3–4 non-hematologic AE, or hematologic toxicity defined as febrile neutropenia (fever $\geq 38.5^\circ\text{C}$ of unknown origin, without infection, with grade 3–4 neutropenia), grade 4 neutropenia lasting > 7 days, grade 4 thrombocytopenia or grade 3 thrombocytopenia complicated by hemorrhage. Treatment delay of > 2 weeks due to delayed recovery was considered a DLT. Prophylactic use of granulocyte-colony stimulating factor (G-CSF) was not permitted during Cycle 1, but allowed in subsequent cycles in the case of neutropenia-related DLTs (for details, see [supplementary information](#), available at *Annals of Oncology* online). The phase II part of the study was an open-label, multicenter study to evaluate safety and tolerability and to assess the activity of cabazitaxel plus abiraterone at the MTD determined in phase I. Treatment was not limited to a certain number of cycles and continued until disease progression, unacceptable toxicity, investigator's decision, or withdrawal of consent. Radiologic disease progression was defined according to Response Evaluation Criteria In Solid Tumors (RECIST 1.1.) [12].

PK assessments

For cabazitaxel PK parameters, blood samples were collected from all patients at predetermined time points during the phase I and phase II parts of the study. Further details are available in the [supplementary information](#), available at *Annals of Oncology* online.

Efficacy assessments

The primary endpoint of the phase II part of the study was PSA response rate, defined as a decline of serum PSA from baseline of $\geq 50\%$ confirmed at least

3 weeks later. PSA was assessed at baseline and every 3 weeks during study treatment. Tumor assessments by computed tomography scan and bone scan were performed at baseline and every 12 weeks thereafter. Tumor response was evaluated according to RECIST 1.1. [12].

Statistical considerations

In prior studies, the PSA response rate was 29% ($N=797$) in patients with mCRPC who received abiraterone post-docetaxel [8], and 39% ($N=329$) in patients who received cabazitaxel post-docetaxel [4, 8]. Therefore, in this study for patients receiving abiraterone plus cabazitaxel post-docetaxel, the null hypothesis was set as a 25% PSA response rate, versus an alternative hypothesis of a 50% PSA response rate (an absolute difference of 25%); to reject the null hypothesis, a cohort of 26 patients would have approximately 83% power with a type I error rate of 5%, using a one-sided exact binomial test.

Results

Patient characteristics and study drug exposure

Overall, a total of 37 patients with mCRPC were enrolled onto the study; 10 onto the dose escalation phase I and 27 onto the

dose expansion phase II components, between 28 March 2012 and 18 June 2014 at 4 centers. All patients received at least one cycle of cabazitaxel plus abiraterone. Baseline demographics and disease characteristics are shown in [supplementary Table S2](#), available at *Annals of Oncology* online. In the phase I part of the study, patients with progressive mCRPC after docetaxel treatment were enrolled. In the phase II part of the study all patients had progressed on docetaxel, received at least 3 months of abiraterone, and continued treatment with abiraterone, prior to study entry.

Patients and safety

In the phase I dose escalation part of the study, 9 out of 10 patients were evaluable for DLTs. Three patients receiving cabazitaxel 20 mg/m² and six patients receiving cabazitaxel 25 mg/m² completed two treatment cycles without experiencing any DLTs. The MTD of the combination was established as the full and approved dose of both agents (cabazitaxel 25 mg/m² once every 3 weeks and abiraterone 1000 mg once daily). The median number of cabazitaxel plus abiraterone treatment cycles administered per patient was six (range 4–20).

In phase II (expansion), 27 patients received cabazitaxel (25 mg/m² every 3 weeks) in combination with continuous abiraterone (1000 mg once daily). The median number of treatment cycles administered per patient was 7 (range 1–28) and 8 (1–28) for cabazitaxel and abiraterone, respectively. Eight patients (30%) required a reduction of the cabazitaxel dose and three patients (11%) required a reduction of the abiraterone dose ([supplementary Table S3](#), available at *Annals of Oncology* online) during study treatment. In phase II of this study, 19 patients (70%) received G-CSF after the first treatment cycle. Thirteen patients (48%) discontinued the study due to an AE.

AEs were similar across the phase I and phase II parts of the study. The most common treatment emergent AEs (TEAEs) possibly related to study treatment are listed in [Table 1](#) (both phases) and [supplementary Table S4](#) (phase I), available at *Annals of Oncology* online. The majority of treatment-related TEAEs were grade 1–2 in severity. The most frequent all-grade treatment-related TEAEs in the phase I part of the study were nausea (50%), asthenia (40%), and diarrhea (40%). One patient presented with grade 3 diarrhea, considered to be related to concurrent infection. In the phase II part of the study, the most common all-grade TEAEs possibly related to study treatment were asthenia (59%), nausea (41%), and diarrhea (41%). The most common grade 3–4 AEs were hematologic toxicities; only one patient (3.7%) experienced febrile neutropenia. The most common grade 3–4 hematologic laboratory abnormalities were neutropenia ($n = 15$; 56%), leukopenia ($n = 14$; 52%), and lymphopenia ($n = 13$; 48%). Six patients died within 30 days of study treatment due to disease progression ($n = 2$; 7%) and AEs ($n = 4$; 15%) including pneumonia, acute renal failure, septic shock, and acute coronary syndrome, all assessed as not related to study treatment ([supplementary information](#), available at *Annals of Oncology* online). There were three additional deaths due to disease progression by the end of the study. Overall, AEs were similar to those previously reported in the cabazitaxel phase III TROPIC trial and the abiraterone phase III COU-AA-301 trial [4, 8].

Table 1. Patients experiencing possibly related TEAEs in $\geq 10\%$ of patients and laboratory abnormalities

Patients, n (%)	Phase I (N = 10)		Phase II (N = 27)	
	Grade ≥ 3	All grades	Grade ≥ 3	All grades
Any possibly related TEAE	3 (30.0)	10 (100)	12 (44.4)	27 (100)
Asthenia	1 (10.0)	4 (40.0)	4 (14.8)	16 (59.3)
Nausea	0	5 (50.0)	0	11 (40.7)
Diarrhea	1 (10.0)	4 (40.0)	2 (7.4)	11 (40.7)
Decreased appetite	0	2 (20.0)	1 (3.7)	9 (33.3)
Dyspnea	0	2 (20.0)	1 (3.7)	7 (25.9)
Neutropenia	0	0	5 (18.5)	5 (18.5)
Vomiting	0	0	1 (3.7)	5 (18.5)
Stomatitis	0	3 (30.0)	0	2 (7.4)
Hypokalemia	0	1 (10.0)	0	3 (11.1)
Dysgeusia	0	2 (20.0)	0	2 (7.4)
Fatigue	1 (10.0)	2 (20.0)	0	2 (7.4)
Laboratory abnormalities				
Anemia	0	10 (100.0)	2 (7.4)	27 (100.0)
Leukopenia	3 (30.0)	9 (90.0)	14 (51.9)	23 (85.2)
Neutropenia	2 (20.0)	9 (90.0)	15 (55.6)	19 (70.4)
Lymphopenia	0	7 (70.0)	13 (48.1)	24 (88.9)
Thrombocytopenia	0	4 (40.0)	1 (3.7)	16 (59.3)

TEAEs, treatment-emergent AE.

Phase II expansion study: antitumor activity

Overall 26 patients were evaluable for assessment of antitumor activity in the phase II part of the study; 12 achieved a PSA response [46.2%; 95% confidence interval (CI): 26.6–66.6]; the null hypothesis of a 25% PSA response rate was therefore rejected ($P < 0.01$). The percentage of patients with a $\geq 30\%$ PSA decrease from baseline was 61.5% (16/26; 95% CI: 42.8–80.2) ([Figure 1](#)). For the 14 patients evaluable for tumor response according to RECIST 1.1. [12], the response rate was 21.4% (3/14; 95% CI: 4.7–50.8); an additional 7 patients (50.0%) had a best response of stable disease ([Table 2](#)). Of the 12 patients demonstrating a PSA response, 6 maintained the response for at least 6 months, and 1 maintained the response for over 12 months. The median duration of PSA response was 6.7 months (95% CI: 3.3–9.6 months). The median PSA–PFS was 6.9 months (95% CI: 4.1–10.3 months). There was no statistically significant difference in PSA response between patients who did or did not have a response with prior docetaxel and abiraterone treatment ([supplementary Table S5](#), available at *Annals of Oncology* online).

Pharmacokinetics

PK data are presented in [Table 3](#). Abiraterone mean maximum concentration (C_{max}) [221 ng/mL; coefficient of the variation (CV) 84%] and mean area under the concentration-time curve from 0 to 24 h (AUC_{0-24h}) (872 ng*h/mL; CV 43%) observed in the phase I and phase II parts of the study were in accordance with data reported in the literature for abiraterone given as a single agent, indicating that cabazitaxel did not affect abiraterone steady-state exposure ([supplementary Table S6](#), available at *Annals of Oncology* online).

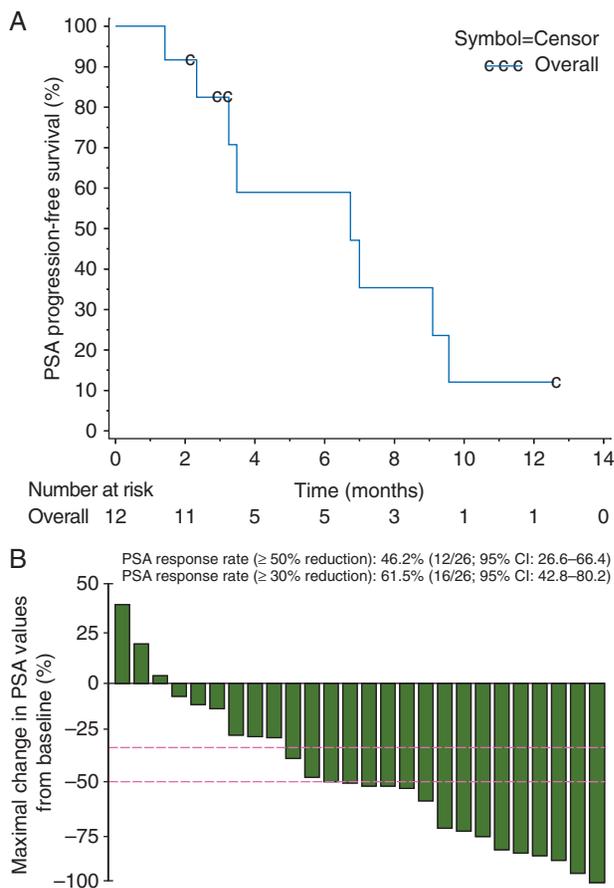


Figure 1. PSA response (phase II part of study, efficacy population). (A) Duration of PSA response: PSA–PFS in patients with an initial PSA response. (B) Maximal decline in PSA from baseline. CI, confidence interval; PSA, prostate-specific antigen.

online). Cabazitaxel exposure after repeated daily oral administration of abiraterone (mean plasma clearance 26.1–31.4 across phase I and phase II) was comparable to previous studies of cabazitaxel monotherapy at 25 mg/m² [13]. This suggests that daily abiraterone treatment does not significantly alter cabazitaxel clearance. Repeated abiraterone exposure observed when abiraterone 1000 mg/day was administered concomitantly with cabazitaxel at 20 or 25 mg/m² (C_{max} = 217 ng/mL and AUC_{0-24h} = 916 ng⁴h/mL) was consistent in both phases.

Discussion

Findings from this phase I/II study showed that in patients with mCRPC who had previously received docetaxel, the administration of cabazitaxel in combination with abiraterone was generally well tolerated when both agents were administered at the approved doses. The tolerability profile was consistent with the established safety profiles of cabazitaxel and abiraterone monotherapy [4, 8]. There was no evidence of a PK interaction between cabazitaxel and abiraterone. The combination had clinically important antitumor activity. The rate of 50% PSA declines from baseline [12 of 26 evaluable patients (46.2%)] and tolerability supports the future evaluation of this combination. Of note, a recent phase III PROSELICA trial demonstrated the non-inferiority of cabazitaxel 20 mg/m² versus 25 mg/m² with respect

Table 2. PSA response and tumor response (phase II)

	Cabazitaxel 25 mg/m² + abiraterone 1000 mg/day
PSA response (N = 26), n (%)	
PSA response	12 (46.2)
95% CI	26.6–66.6
P-value ^a	0.006
Duration of PSA response (N = 12) ^b	
Number of patients progressed after initial response, n (%)	8 (66.7)
Median duration of response in months (95% CI)	6.7 (3.3–9.6)
Probability of maintaining response at 3 months	0.825 (0.604–1.000)
Probability of maintaining response at 5 months	0.589 (0.271–0.907)
PFS (N = 26) ^c	
Number of patients with progression (%)	11 (42.3)
Median PFS in months (95% CI)	NC (4.7–NC)
Probability of PFS at 3 months ^d	0.762 (0.594–0.929)
Probability of PFS at 5 months ^d	0.677 (0.492–0.862)
Tumor response (N = 14), n (%)^c	
Complete response	0
Partial response	3 (21.4)
Stable disease	7 (50.0)
Progressive disease	3 (21.4)
Not evaluable/missing data	1 (7.1)
ORR (N = 14), n (%)	
ORR	3 (21.4)
95% CI	4.7–50.8

^aBased on the one-sided exact binomial test conducted on the null hypothesis of a 25% response rate.

^bSix patients in phase II received 10 or more cycles of cabazitaxel and did not have PSA progression.

^cEight patients completed 10 cycles of treatment and had not progressed by RECIST criteria at study completion.

^dRefer to Kaplan–Meier curve (supplementary Figure S1, available at *Annals of Oncology* online) for the interpretation of probability of PFS. CI, confidence interval; NC, not calculable; ORR, objective response rate; PFS, progression-free survival; PSA, prostate-specific antigen.

to OS [14]. In this trial, cabazitaxel 20 mg/m² maintained at least 50% of the OS benefit previously observed for cabazitaxel 25 mg/m² versus mitoxantrone in the TROPIC trial [4], and may have an improved safety profile [14]. These results should be considered in future trials of cabazitaxel combinations.

The overall safety profile of cabazitaxel plus abiraterone was consistent with the safety profiles of each individual component. The most frequent side effects were asthenia and neutropenia, with one patient experiencing febrile neutropenia. The rate of febrile neutropenia observed in the TROPIC trial was 8% for the cabazitaxel plus prednisone treatment arm (n/N = 28/371) [4]. Proactive management of neutropenia may have reduced the risk of febrile neutropenia in this study as most patients (70%) received G-CSF after the first treatment cycle. The frequency of

Table 3. PK parameters of cabazitaxel and abiraterone

Mean \pm SD (Median) [CV%]	Cabazitaxel		
	Phase I Cycle 1 <i>n</i> = 10	Phase I Cycle 2 <i>n</i> = 10	Phase II <i>N</i> = 24
	Dose, mg/m ²	46.3 \pm 7.04 (45.0) [15.2]	45.4 \pm 8.12 (45.0) [17.9]
<i>t</i> _{1/2z} , h	115 \pm 43.9 111 (38.3)	157 \pm 68.0 154 (43.3)	91.6 \pm 62.6 68.4 (68.3)
<i>C</i> _{max} , ng/mL			330 \pm 187 (334) [56.7]
AUC, ng*h/mL			817 \pm 117 (840) [14.3]
CL, L/h/m ²	30.7 \pm 4.16 (29.8) [13.6]	26.1 \pm 7.34 (28.7) [28.1]	31.4 \pm 4.67 (30.1) [14.9]
V _{ss} , L/m ²	3790 \pm 1640 (3719) [43.3]	4531 \pm 2270 (4028) [50.1]	2711 \pm 2493 (1738) [91.9]

Mean \pm SD (Geometric mean) [CV%]	Abiraterone		
	Phase I <i>n</i> = 9	Phase II <i>n</i> = 26	Phases I and II <i>N</i> = 35
<i>C</i> _{trough,ss1} , ng/mL	7.38 \pm 4.39 (6.18) [60]	9.99 \pm 13.0 (NA) [130]	9.32 \pm 11.4 (NA) [122]
<i>t</i> _{max} ^a , h	2.00 (1.00–4.33)	2.00 (1.00–6.00)	2.00 (1.00–6.00)
<i>C</i> _{max} , ng/mL	221 \pm 186 (168) [84]	216 \pm 152 (171) [71]	217 \pm 159 (170) [73]
AUC _{0–24h} , ng*h/mL	872 \pm 372 ^b (804) [43]	928 \pm 466 (798) [50]	916 \pm 443 (799) [48]

Profiles of two patients (one in phase I and one in phase II) were excluded from descriptive statistics.

^aMedian (min–max).

^b*n* = 7, AUC_{0–24h} not calculated in two patients due to aberrant data at 24 h.

AUC, area under the concentration–time curve; AUC_{0–24h}, AUC from 0 to 24 h; *C*_{max}, maximum concentration observed; CL, plasma clearance; *C*_{trough,ss1}, concentration observed before dose intake during repeated administration at steady state; CV, coefficient of the variation; NA, not applicable; SD, standard deviation; *t*_{1/2z}, terminal half-life; V_{ss}, steady-state volume of distribution.

gastrointestinal toxicities in this study was similar to the rates reported in the TROPIC trial for the cabazitaxel arm [4]; however, these data should be interpreted with caution due to the small cohort size. The PK assessments and analysis in this study do not provide evidence of any drug–drug interactions between cabazitaxel and abiraterone. Mean trough plasma concentrations of cabazitaxel plus abiraterone were similar to those observed in previous combination therapy and monotherapy studies [15, 16].

In this population, cabazitaxel plus abiraterone combination therapy demonstrated significant antitumor activity. A PSA response was reported in 12 of 26 patients (46.2%), which is higher than the PSA response rates observed in the phase III trials of abiraterone (COU-AA-301) [8], and cabazitaxel in the

post-docetaxel setting (TROPIC) [4], where 29% and 39% of patients, respectively, demonstrated a \geq 50% decline in PSA levels. However, cross-trial comparisons should be interpreted with caution due to the broad CIs associated with these small cohorts. Nonetheless, these phase II results are encouraging because the patient population differed from that of the TROPIC study, having received a greater number of prior treatments. These results warrant further evaluation of cabazitaxel plus abiraterone in this population of patients [17–19]. Several studies have retrospectively investigated the efficacy of cabazitaxel as a third-line treatment after docetaxel and abiraterone, and suggest that cabazitaxel remains active after docetaxel and abiraterone treatment with declines of PSA from baseline of \geq 50% observed in 35–39% of patients [20, 21]. The response rate in our prospective phase II cabazitaxel and abiraterone combination study indicates that this combination is at least as active as cabazitaxel alone [4]. Randomized trials to ascertain the optimal sequencing and/or combination of these and other novel agents are urgently needed to maximize patient benefit, as is the clinical qualification of predictive biomarkers of response including AR-splice variant 7 expression, phosphatase, and tensin homolog loss and broader genomic studies to deliver improved care for men with mCRPC [22, 23].

Conclusions

In summary, cabazitaxel and abiraterone administered as a combination treatment can be administered at the approved dose of both monotherapies (25 mg/m²/1000 mg) with these being generally well tolerated. This combination had antitumor activity in patients with mCRPC previously treated with docetaxel and abiraterone. The AE profile of this combination did not identify any overlapping toxicities or present any new safety concerns. Further studies are warranted to better define which patients with mCRPC would benefit most from this combinational approach.

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