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ORIGINAL ARTICLE

Managing lines of therapy in castration-resistant prostate cancer: real-life snapshot from a multicenter cohort

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Abstract

Purpose To provide a snapshot of toxicities and oncologic outcomes of Abiraterone (AA) and Enzalutamide (EZ) in a chemo-naïve metastatic castration-resistant prostate cancer (mCPRC) population from a longitudinal real-life multicenter cohort.

Methods We prospectively collected data on chemo-naïve mCRPC patients treated with AA or EZ. Primary outcomes were PSA response, oncologic outcomes and toxicity profile. The Kaplan–Meier method was used to compare differences in terms of progression-free survival (PFS) between AA vs EZ and high- vs low-volume disease cohorts. Univariable and multivariable Cox regression analyses were performed to identify predictors of PFS. Toxicity, PSA response rates and oncologic outcomes on second line were compared with those observed on first line.

Results Out of 137 patients, 88 received AA, and 49 EZ. On first line, patients receiving EZ had significantly higher PSA response compared with AA (95.9% vs 67%, $p<0.001$), comparable toxicity rate (10.2% vs 16.3%, $p=0.437$) and PFS probabilities ($p=0.145$). Baseline PSA and high-volume disease were predictors of lower PFS probabilities at univariable analysis ($p=0.027$ and $p=0.007$, respectively). Overall, 28 patients shifted to a second-line therapy (EZ or radiometabolic therapy). Toxicity and PSA response rates on second line were comparable to those observed on first line (11.1% vs 12.4%, $p=0.77$; 73.1% vs 77.4%, $p=0.62$, respectively); 2-year PFS, cancer-specific and overall survival probabilities were comparable to those displayed in first-line cohort (12.1% vs 16.2%, $p=0.07$; 85.7% vs 86.4%, $p=0.98$; 71% vs 80.3%, $p=0.66$, respectively).

Conclusions Toxicity profile, PSA response rate and oncological outcomes were comparable between first-line and second-line courses in patients treated with either AA or EZ for mCRPC. Our findings showed the tolerability and oncological effectiveness, when feasible, of two lines of therapy other than chemotherapy.

keywords Castration-resistant prostate cancer · Metastatic disease · Systemic therapy · High volume disease · Androgen receptor targeted agent

Abbreviations

CRPC	Castration-resistant prostate cancer
EZ	Enzalutamide
AA	Abiraterone acetate
PFS	Progression-free survival
OS	Overall survival
HSMPC	Hormone-sensitive metastatic prostate cancer
AR	Androgen receptor
mCRPC	Metastatic castration-resistant prostate cancer
CSS	Cancer-specific survival
ADT	Androgen deprivation therapy
AP	Apalutamide
nmCRPC	Non-metastatic castration-resistant prostate cancer
FDA	Food and drug administration
ARTA	Androgen receptor-targeted agents

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Introduction

Castration resistance is a natural evolution of prostate cancer that appears even long time after diagnosis and androgen deprivation therapy. Medical oral drugs used to treat castration-resistant prostate cancer (CRPC) are useful tools

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to control disease progression avoiding or delaying chemotherapy. Both Enzalutamide (EZ) and Abiraterone (AA) have demonstrated improved radiologic progression-free survival (PFS) and overall survival (OS) versus placebo controls in chemo-naïve cohorts [1, 2].

Since patients with CRPC are eligible for multiple treatment lines, the preferred strategy is to individualize the plan by determining which drug is most appropriate as initial therapy. Similarly, no consensus exists for the drug sequencing after failure of a treatment line [3]. Careful monitoring is necessary to early identify resistance and promptly shift to alternative options.

Current guidelines provide many reasons that should be considered when selecting among available treatments such as performance status, symptoms, comorbidities, location and extent of disease, patient preference, and previous treatment for hormone-sensitive metastatic prostate cancer (HSMPC) [4, 5].

There are few reports directly comparing the efficacy AA and EZ, although several retrospective studies have shown the decreased efficacy of the second-line androgen receptor (AR)-targeting therapy after progression on the first-line therapy [6, 7].

The evidences supporting the use of AA and EZ in chemo-naïve CRPC need to be further confirmed in real-life cohorts to overcome strict inclusions criteria of registration studies and clinical trials [8].

In this study, we provide a snapshot of toxicities and oncologic outcomes of AA, and EZ in a chemo-naive CPRC population from a longitudinal real-life multicenter cohort.

Materials and methods

Study cohort

Between October 2012 and July 2018, data on chemo-naïve metastatic CRPC (mCRPC) patients, who received either AA or EZ as first- or second-line treatment at five centers, were prospectively collected. All patients had castrate levels of testosterone (< 50 ng/dl), with ongoing androgen deprivation therapy (ADT) and increasing PSA levels.

Schedule of treatments

All mCRPC patients received 1000 mg of AA plus 10 mg of Prednisone or 160 mg of EZ daily as first line of therapy. The selection of drug as first treatment option for mCRPC was arbitrarily made by oncologists or urologists according to different criteria (such as age, comorbidities, patient compliance, drugs availability). Patients experiencing significant toxicity or disease progression were shifted to a second line of therapy. Salvage chemotherapy was prescribed after early failure of first-line drug and after progression during second treatment line.

Clinical staging and follow-up

All patients were staged for disease progression under ADT using CT scan and bone scan. Choline PET/CT scan was performed based on physician discretion when conventional imaging was negative. PSMA PET/CT was performed in case of negative choline PET/CT scan. A physical examination and laboratory routine biochemistry were carried out at baseline and subsequently at four-week intervals.

Patients were visited monthly and imaging re-evaluation was performed every 6 months regardless of PSA levels and symptoms. Clinical features, treatment outcomes and toxicity events were recorded at each visit. Presence of bone, visceral and lymph node metastases at any site different by pelvic nodes were criteria used to define metastatic (m) disease. High-volume disease was defined as bulky positive nodes (≥ 5 cm) or more than six bone metastases.

Outcomes

Primary outcomes included PSA response, progression-free survival (PFS) and toxicity profile at both first line and second line.

PSA response was defined as a decline at 12 weeks equal to or greater than 50% in the PSA relative to the baseline. PFS was defined as time from the first dose of AA or EZ to the first radiographic evidence of progression [9].

Treatment-related toxicity was graded according to the National Cancer Institute Common Terminology Criteria for adverse events 4.02 toxicity scale [10].

Toxicity, PSA response rates and oncologic outcomes [PFS, cancer-specific survival (CSS) and overall survival (OS)] on second line were compared with those observed on first line.

Statistical analysis

Continuous and categorical variables were compared using Student *t* and Chi-Square tests, respectively. Significance threshold was set at $p < 0.05$ for any test.

The therapeutic effectiveness of AA vs EZ and the role of established prognosticators were assessed with the Kaplan–Meier method and the log rank test was applied to assess statistical significance between groups. Univariable and multivariable Cox Regression analyses were performed to identify predictors of PFS. Survival probabilities were computed at 12, 24 and 36 months after the start of treatment. Statistical analysis was performed using the Statistical Package for Social Science (SPSS, IBM, v.22.0, Armonk, NY).

Results

Overall, 137 chemo-naive CRPC patients received AA or EZ as a first-line therapy. Baseline global clinical features of the whole cohort are reported in Table 1. Forty patients were staged using choline PET/CT Scan. PSMA PET/CT detected distant metastasis in ten patients with negative choline PET/CT. Eighty-eight (64.2%) patients received AA and 49 (35.8%) received EZ. The two subgroups of patients (AA and EZ) were not homogeneous for local treatments ($p < 0.001$). The EZ cohort displayed a higher rate of nodal and high-volume disease ($p = 0.02$ and $p < 0.001$, respectively)and a longer length of ADT ($p = 0.001$) versus AA cohort. (Table 2).

Table 1 Clinical features of the whole cohort

Clinical features	Median or *N* (IQR or %)
Age (years)	76 (71–82)
ECOG	
0	93 (67.9)
1	44 (32.1)
ISUP grade group (%)	
NA	6 (4.4)
1	6 (4.4)
2	18 (13.1)
3	38 (27.7)
4	34 (24.8)
5	35 (25.5)
Baseline staging PCa (%)	
cT	
x	48 (35)
T1	4 (2.9)
T2	22 (16.1)
T3	63 (46)
cN	
0	113 (82.5)
1	24 (17.5)
cM	
0	102 (74.5)
1	35 (25.5)
Local treatment (%)	
Radical prostatectomy	27 (19.7)
Radiation therapy	35 (25.5)
None	48 (35)
Both	27 (19.7)
ADT length (mo)	27 (9–65)
ADT lines (*N*)	2 (2–2)
Time to CRPC (years)	5 (2–9)
PSA CRPC (ng/dl)	9.7 (3.5–29.7)
cN CRPC (%)	
Nx	33 (24.1)
N0	49 (35.8)
N1	55 (40.1)
High-volume disease (%)	44 (32.1)
Follow-up (mo)	17 (10–27)

The PSA response rate was 77.4% (higher for EZ cohort, 95.9% vs 67% respectively, $p < 0.001$). Toxicity rate was 12.4% (comparable between AA and EZ cohorts, 10.2% vs 16.3%, respectively $p = 0.437$), with 2% rate of high-grade adverse events recorded only in EZ cohort (Table 3). Seventeen (15.7%) patients underwent salvage chemotherapy after first-line failure. Two-year PFS, CSS and OS probabilities were 21%, 76.7% and 74.8%, respectively.

At univariable Cox regression analysis, PSA value and high-volume disease were significant predictors of PFS in first line of therapy ($p = 0.027$ and $p = 0.007$, respectively). None of these variables was found to be independent predictors of PFS at multivariable Cox regression analysis.

At Kaplan–Meier analysis, high-volume disease was a significant predictor of lower PFS probabilities (log rank $p = 0.01$ and $p = 0.015$, respectively), while AA and EZ showed comparable PFS (log rank $p = 0.145$) probabilities (Fig. 1).

Overall, 28 patients shifted to a second-line therapy: EZ was prescribed in 19 cases and radiometabolic therapy in 9 patients (Radium-223 and Lutetium-177 in 7 and 2 cases, respectively).

On second line, toxicity profile and the PSA response probability were comparable to first line (11.1% vs 12.4%, [$p = 0.77$] and 73.1% vs 77.4%, [$p = 0.62$], respectively). Moreover 2-year PFS, CSS and OS probabilities were comparable to those displayed on first line (12.1% vs 16.2% [$p = 0.07$], 85.7% vs 86.4% [$p = 0.98$] and 71% vs 80.3% [$p = 0.66$], respectively) (Fig. 2). Four (14.8%) patients underwent salvage chemotherapy after progression.

Discussion

Availability of multiple drugs has changed the treatment course and the natural history of patients with CRPC; and the administration of multiple consecutive treatments has become very common. The main reasons for treatment discontinuation are either disease progression or clinically significant adverse events. Herein, we report clinical data from a real-life setting about toxicity and oncologic outcomes of mCRPC patients receiving either AA or EZ as first-line and EZ or radio-metabolic therapy as second-line treatment.

In the available literature, there are some retrospective studies reporting AA and EZ safety and oncologic effectiveness in different lines of therapy but evidences from the only ongoing multicenter randomized Phase III trial comparing AA and EZ are awaited [11].

Table 2 First-line treatment—clinical features

Clinical features	Mean or *N* (SD or %)		
	Enzalutamide (*N* = 49)	Abiraterone (*N* = 88)	*p* value
Age (years)	74.2 (9.1)	76.8 (7.3)	0.065
ECOG			0.70
0	32 (65.3)	61 (69.3)	
1	17 (34.7)	27 (30.7)	
CCI	4 (1.4)	3 (1.2)	0.62
ISUP grade group (%)			0.40
NA	4 (8.2)	2 (2.3)	
1	3 (6.1)	3 (3.4)	
2	5 (10.2)	13 (14.8)	
3	14 (28.6)	24 (27.3)	
4	9 (18.4)	25 (28.4)	
5	14 (28.6)	21 (23.9)	
Baseline staging PCa (%)			
cT			0.33
x	18 (36.7)	30 (34.1)	
T1	3 (6.1)	1 (1.1)	
T2	6 (12.2)	16 (18.2)	
T3	22 (44.9)	41 (46.6)	
cN			0.16
0	37 (75.5)	76 (86.4)	
1	12 (24.5)	12 (13.6)	
cM			0.41
0	39 (79.6)	63 (71.6)	
1	10 (20.4)	25 (28.4)	
Local treatment (%)			< 0.001
Radical prostatectomy	7 (14.3)	20 (22.7)	
Radiation therapy	16 (32.7)	19 (21.6)	
None	14 (28.6)	34 (38.6)	
Both	12 (24.5)	15 (17)	
ADT length (mo)	60.2 (55.4)	37.9 (46.3)	0.017
ADT lines (*N*)	2.1 (0.4)	2.1 (0.4)	0.70
Time to CRPC (years)	5.9 (5.1)	5.9 (4.9)	0.98
PSA CRPC (ng/dl)	8 (3–21.9)	9.8 (3.5–34)	0.59
cN CRPC (%)			0.02
Nx	18 (36.7)	15 (17)	
N0	9 (18.4)	40 (45.5)	
N1	22 (44.9)	33 (37.5)	
High-volume disease (%)	19 (38.8)	21 (23.9)	< 0.001
Follow-up (mo)	19.7 (16.8)	19.5 (11)	0.935

In a multicentric retrospective study comparing 113 chemo-naïve CRPC patients treated with AA first and then shifted to EZ, versus 85 patients treated with EZ first and then AA, Terada et al. showed comparable PSA response rate and PFS ($p = 0.353$ and $p = 0.412$) in first-line setting, while a significant advantage favoring EZ in second-line setting was observed ($p = 0.011$ and $p = 0.009$, respectively) [12]. Similarly, in a series of 50 patients AA–EZ versus 45 EZ–AA, there was no significant difference for all clinical outcomes, with the exception of significantly higher second-line PSA response rates in EZ cohorts (EZ, 30% vs AA, 6.4%, $p = 0.004$). These data would support, to date, the use of AA in first-line setting [13]. Likewise in our series, no patients had AA in second-line setting; also, toxicity rate was comparable between AA and EZ cohorts ($p = 0.437$). Despite comparable 2-year PFS between AA and EZ cohorts (log rank $p = 0.145$), PSA response rate was higher for EZ cohort ($p < 0.001$) also in a first-line setting.

Table 3 First-line treatment—adverse events

Variable *N* (%)	Enzalutamide (*N* = 49)	Abiraterone (*N* = 88)	*p* value
Adverse events	8 (16.3)	9 (10.2)	0.437
Any grade ≥ 3 adverse event	1 (2)	0	0.232
Most common adverse events			0.156
Hypertension	2 (4.1)	3 (3.4)	
New onset	1 (2.05)	1 (1.1)	
Worsening	1 (2.05)	2 (2.3)	
Fatigue	4 (8.2)	0	
Osteoporotic fracture	1 (2)	0	
Hepatic impairment	1 (2)	2 (2.3)	
Nausea	0	1 (1.1)	
Headache	0	1 (1.1)	
Thrombocytopenia	0	2 (2.3)	

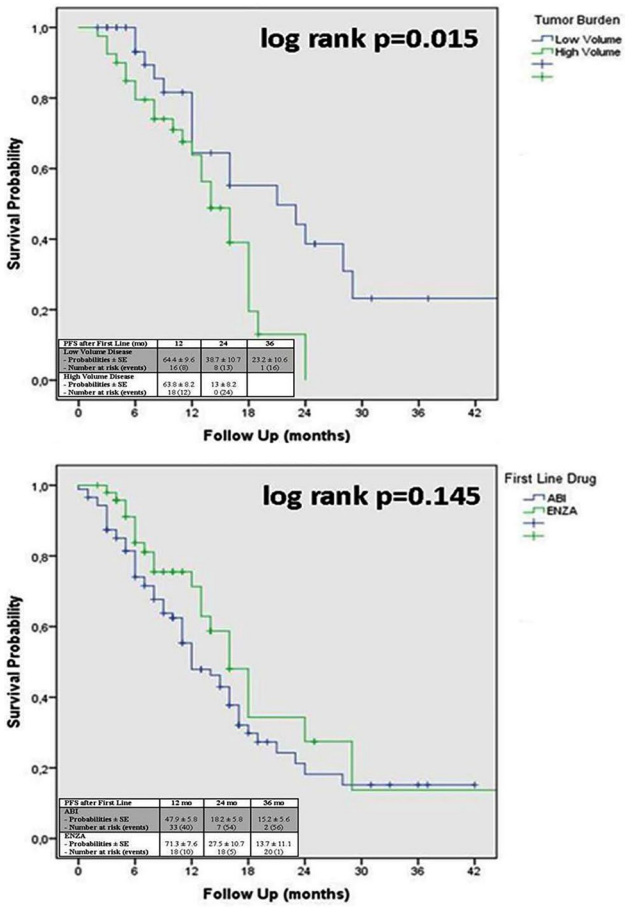

Fig. 1 Kaplan–Meier curves showing progression-free survival (PFS) probability in first-line therapy

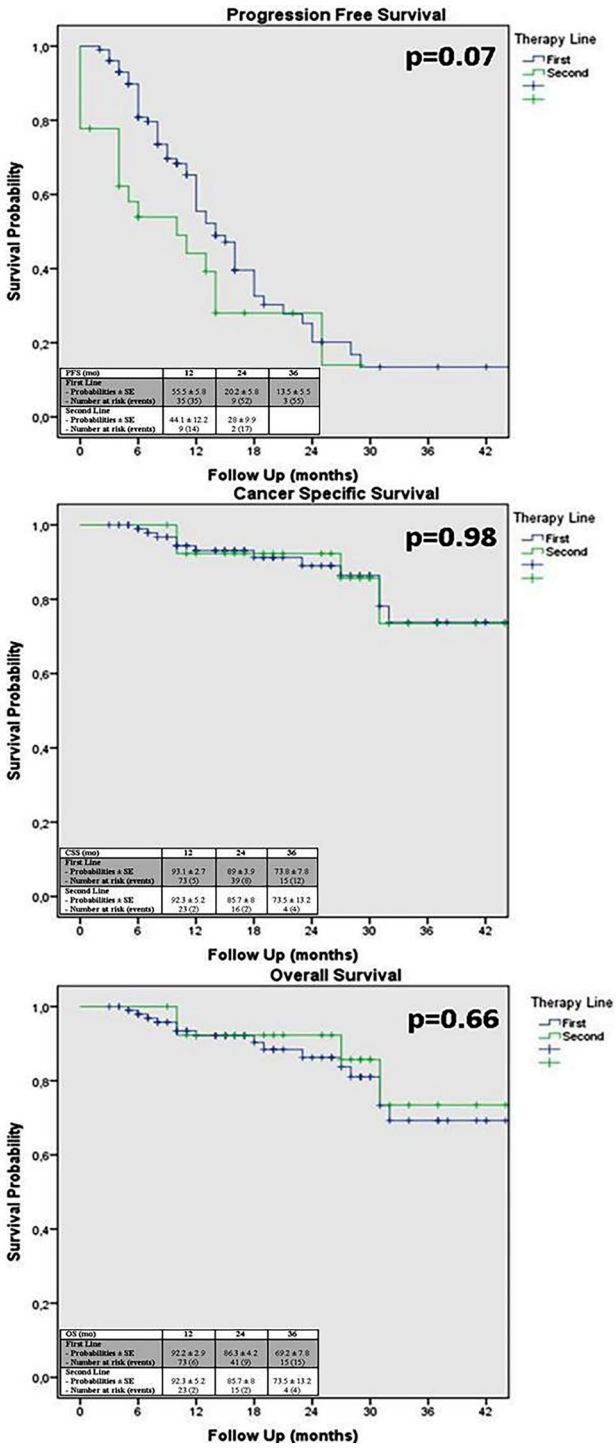

Fig. 2 Kaplan–Meier curves showing progression-free survival (PFS), cancer-specific survival (CSS) and overall survival (OS) between first and second lines of therapy

Overall, AA and EZ were widely adopted in clinical practice, thanks to a favorable toxicity profile compared with chemotherapy. A recent meta-analysis showed how AA was found to significantly increase the risk of both

cardiac toxicity and hypertension, whereas EZ significantly increases the risk of hypertension [14]. Another meta-analysis reported how AA was related to increased risk of cardiovascular events, while EZ was related to increased risk of fatigue [15]. In our series, toxicity rate was comparable between AA and EZ cohorts in first-line ($p = 0.437$) setting and the main adverse events were hypertension for AA cohort and fatigue for EZ. In second-line setting, toxicity events were comparable to those observed in first line ($p = 0.77$).

Disease progression during ADT outlines a move to the castration-resistant state. The definition of CRPC patients, according to the European Association of Urology guidelines, is castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either: (1) three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or (2) radiological progression [16]. The evidence of distant disease by imaging is considered the breakthrough between the metastatic versus non-metastatic state.

The oncologic effectiveness of AA and EZ for mCRPC in chemo-naïve patients has been widely reported [1, 2], while only recent evidences showed the role of EZ and Apalutamide (AP) for non-metastatic CRPC (nmCRPC) in a pre-chemotherapy setting.

A phase III, double-blind, randomised study of EZ in nmCRPC (PROSPER) versus placebo performed on 1401 patients, showed how EZ treatment resulted in significantly improved metastasis-free survival (MFS) (median 36.6 mo vs 14.7 mo for EZ and placebo, respectively; HR = 0.29; $p < 0.0001$). These data led to the approval of EZ by the Food and Drug Administration (FDA) for the treatment of nmCRPC patients [17]. Similarly, the SPARTAN Trial demonstrated significant benefits of AP versus placebo in nmCRPC patients (median 40.5 vs 16.5 mo, respectively; HR 0.28, $p < 0.001$) [18].

In mCRPC patients, high-volume disease proved to be a significant predictor of overall survival and was included in a prognostic model [19] but the therapeutic role of EZ and AA on metastatic high-volume CRPC is debated. The PREVAIL study demonstrated clinically significant benefit in men with chemo-naïve mCRPC treated with EZ either with or without visceral disease, low- or high-volume bone disease, or lymph node only disease [20]. A subgroup of 110 patients from PREVAIL study with low PSA levels (< 10 ng/ml) and high tumor burden (number of bone metastasis > 4 and/or visceral metastasis) treated with EZ displayed similar probability of radiologic progression than low-volume disease versus placebo [21].

Conversely, there are evidences supporting the role of early chemotherapy for metastatic and high-volume disease in hormone-sensitive prostate cancer (HSPC) [19, 20]. Data from CHAARTED trial showed in a cohort of patients with high-volume disease, defined as the presence of visceral metastases and/or ≥ four bone metastases with at least one outside of the vertebral column and pelvis, improved OS with chemohormonal therapy versus ADT alone (median 51.2 vs 34.4 months; HR 0.63; 95% CI 0.50–0.79; $p < 0.001$) [22]. Moreover, in a subgroup analysis from STAMPEDE trial restricted to patients with metastatic prostate cancer, the addition of docetaxel-based chemotherapy to long-term ADT resulted in a prolonged OS. [23].

We defined high-volume disease as "bulky positive nodes (≥ 5 cm) or more than six bone metastases. No patients of this cohort met CHAARTED criteria [22]. As a fact, no patient was M1c, with most being M1b. STAMPEDE trial provided criteria based on risk classes at diagnosis (Gleason score, PSA, treatment failure after primary treatment), however focused on hormone-sensitive patients [23]. Therefore, in our cohort, few patients had PSA > 20 at enrollment, since progression to castration-resistant status was monitored during ADT. Patients with high-volume disease according to CHAARTED, or with PSA levels > 20, were included in this cohort only when unfit for chemotherapy.

Therefore, our data do not allow us to draw any conclusion about the potential role of AA or EZ versus docetaxel-based chemotherapy in mCRPC patients. Notwithstanding, high-volume mCRPC cohort had significantly lower PFS compared with low-volume mCRPC cohort ($p = 0.015$).

With regard to the optimal treatment sequence, an observational retrospective real-life study reported improved PSA response rate (adjusted odds ratio = 2.27, $p = 0.005$) and longer time to PSA progression (adjusted HR = 0.66; $p = 0.010$) with second-line chemotherapy in mCRPC, following early progression after AA or EZ compared with second-line androgen receptor-targeted agents (ARTA) [21]. Similarly, another retrospective series showed a favorable PFS of ARTA-Docetaxel sequence than ARTA–ARTA sequence (HR 0.38; 95% CI 0.24–0.59; $p < 0.001$) [25].

Despite these reports of lower oncologic efficacy of a second-line treatment course with ARTA after progression of a first-line ARTA [9–24], in our real-life cohort, patients receiving a second treatment line rather than chemotherapy, had similar PFS, CSS, OS probability and safety profile compared with first-line cohort (12.1% vs 6.2% [$p = 0.07$], 85.7% vs 86.4% [$p = 0.98$], 71% vs 80.3% [$p = 0.66$] and 11.1% vs 12.4%, [$p = 0.77$], respectively).

Many limitations of this study are related to its "real-life" nature. There is a clear selection bias of patients, indications, the use of PET/CT scan for the definition of metastatic disease, the choice of drug and shift to another treatment line, as well as the lack of central radiologic review for clinical staging and the lack of central laboratory test evaluation. This bias is likely to be significant, due to contemporary availability of multiple clinical trials including AA, EZ, AP, Radium-223 or Lutetium-177; therefore, most of patients

enrolled in this real-life study represent the cohort of patients not recruited in clinical trials. In fact, when reporting comparable PFS in second-line treatment, we acknowledge strong selection bias, with a large proportion of patients who experienced significant toxicity precluding adoption of a second-line treatment, or diffuse bone or visceral metastatic spread requiring adoption of docetaxel-based chemotherapy schedule.

Conclusions

We report clinical data from a real-life setting about toxicity and oncologic outcomes of patients treated with either AA or EZ for mCRPC. Toxicity profile, PSA response rate and oncological outcomes were comparable between first-line and second-line courses. Our findings showed the tolerability and the oncological effectiveness of two lines of therapy, when feasible, with androgen receptor-targeted agents or radiometabolic therapy in a chemo-naïve setting.

Authors' contribution MF: project development, data collection, data analysis, manuscript writing; RM: data collection, data analysis; CN: data collection; LC: data collection, data analysis, manuscript editing; FC: data collection; GT: data collection; CL: data collection; RSF: data collection; GT: data collection; UA: data collection; AB: data collection; SG: data collection; SG: data collection; JG: data collection; LS: data collection; AT: data collection; MG: project development, data analysis; GS: project development, data analysis, manuscript writing, manuscript editing

Compliance with ethical standards

Informed consent All patients have signed the informed consent for data collection and follow-up.

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