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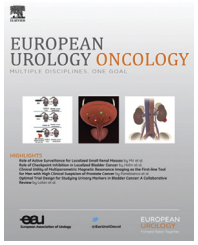

European Association of Urology

Real-world Outcomes of Sequential Androgen-receptor Targeting Therapies with or Without Interposed Life-prolonging Drugs in Metastatic Castration-resistant Prostate Cancer: Results from the Dutch Castration-resistant Prostate Cancer Registry

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Abstract

Background: Cross resistance between androgen-receptor targeting therapies (ARTs) (abiraterone acetate plus prednisone [ABI + P] or enzalutamide [ENZ]) for treatment of metastatic castration-resistant prostate cancer (mCRPC) may affect responses to second ART (ART2).

Objective: To establish treatment duration and prostate-specific antigen (PSA) response of ART2 in real-world mCRPC patients treated with or without other life-prolonging drugs (LPDs; ie, docetaxel, cabazitaxel, or radium-223) between ART1 and ART2.

Design, setting, and participants: Castration-resistant prostate cancer patients, diagnosed between 2010 and 2016 were retrospectively registered in Castration-resistant Prostate Cancer Registry (CAPRI). Patients treated with both ARTs were clustered into two subgroups: ART1 > ART2 or ART1 > LPD > ART2.

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Abiraterone acetate
Enzalutamide
Real-world outcomes
Cross resistance
Sequencing

Outcome measurements and statistical analysis: Outcomes were ≥50% PSA response and treatment duration of ART2. Descriptive statistics and binary logistic regression after multiple imputations were performed.

Results and limitations: A total of 273 patients were included with a median follow-up of 8.4 mo from ART2. Patients with ART1 > ART2 were older and had favourable prognostic characteristics at ART2 baseline compared with patients with ART1 > LPD > ART2. No differences between ART1 > ART2 and ART1 > LPD > ART2 were found in PSA response and treatment duration. Multivariate analysis suggested that PSA response of ART2 was less likely in patients with visceral metastases (odds ratio [OR] 0.143, $p = 0.04$) and more likely in patients with a relatively longer duration of androgen-deprivation treatment (OR 1.028, $p = 0.01$) and with ABI + P before ENZ (OR 3.192, $p = 0.02$). A major limitation of this study was missing data, a common problem in retrospective observational research.

Conclusions: The effect of ART2 seems to be low, with a low PSA response rate and a short treatment duration irrespective of interposed chemotherapy or radium-223, especially in patients with short time on castration, visceral disease, and ENZ before ABI + P.

Patient summary: We observed no differences in outcomes of patients treated with sequential abiraterone acetate plus prednisone (ABI + P) and enzalutamide (ENZ) with or without interposed chemotherapy or radium-223. In general, outcomes were lower than those in randomised trials, questioning the additional effect of second treatment with ABI + P or ENZ in daily practice.

1. Introduction

Annually, 3000 patients develop metastatic castration-resistant prostate cancer (mCRPC) in the Netherlands [1]. Multiple treatment options are available, including taxane (TAX) chemotherapy (docetaxel [DOC] and cabazitaxel [CAB]), androgen-receptor targeting therapies (ARTs; abiraterone acetate plus prednisone [ABI + P] and enzalutamide [ENZ]), and an alpha-emitting radioisotope (radium-223 [Ra-223]). One of the challenges is selecting the most optimal treatment sequence.

Sequencing of ARTs is of particular interest, since the two ARTs used target the androgen signalling pathway. Acquired resistance to ABI + P and ENZ is inevitable. Molecular mechanisms of resistance to both ARTs are similar and cross resistance is a common phenomenon [2]. Clinical findings from one prospective and several retrospective studies support this hypothesis, showing low prostate-specific antigen (PSA) responses of second ART (ART2), especially in patients treated with ENZ before ABI + P [3–6]. A short interval between both ARTs and progression on ART1 are related to low PSA responses [7,8].

The European Association of Urology advises the use of DOC after first-line ART because of concerns about cross resistance [9], but no solid evidence points to resensitisation following the "sandwich" use of TAX prior to ART2. One small retrospective study recently reported similar PSA responses (21–30%) in patients treated with both ARTs directly after each other or with TAX in between [10].

However, available data on the activity of ART2 are not easily translated into daily clinical practice, since data are based on small study populations (<150 patients) with highly selected patients either participating in early access programmes or treated in academic institutions, or on follow-up of patients who participated in randomised controlled trial.

The aim of this study is to investigate PSA response and treatment duration of ART2 depending on treatment sequence in a real-world setting. We provide outcomes on sequential ARTs or ARTs with interposed life-prolonging drugs (LPDs) such as TAX or Ra-223.

2. Patients and methods

2.1. Study design and setting

Castration-resistant Prostate Cancer Registry (CAPRI) is an investigator-initiated, observational, multicentre cohort study in 20 Dutch hospitals. Data collection started after approval by the local medical ethics committee and hospital board. The study design has been described before [11]. Castration-resistant prostate cancer patients were included retrospectively from 1 January 2010 until 31 December 2015, with regular updates of all data until 31 December 2017. All treatment decisions as well as the use of diagnostics, response measurements, and supportive care were made by treating physicians and were not protocol amended. CAPRI is registered in the Dutch Trial Registry as NTR3591.

2.2. Participants

Patients having mCRPC who were treated with both ABI + P and ENZ before 1 July 2017 with one line of TAX or Ra-223 between both ARTs were included in this analysis. Patients treated with DOC for metastatic hormone-sensitive prostate cancer were excluded.

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Outcomes were evaluated based on treatment sequence: (1) ABI + P directly followed by ENZ or vice versa (ART1 > ART2) and (2) ABI + P followed by ENZ or vice versa interposed with TAX or Ra-223 treatment (ART1 > LPD > ART2).

Additional subgroup analyses were performed based on the following parameters:

1 Sequence of ABI + P and ENZ: ABI + P before ENZ (ABI + P > ENZ) or ENZ before ABI + P (ENZ > ABI + P)
2 ART1 treatment duration: "long ART1 treatment" (ie, ART1 treatment duration ≥12 wk according to the Prostate Cancer Clinical Trials Working Group 3 [PCWG 3] criteria [12]) or "short ART1 treatment" (ie, ART1 treatment duration <12 wk)
3 Interval between ART1 and ART2: interval between ART1 and ART2 calculated as the time between stop of ART1 and start of ART2, with a cut-off of 40 d based on previous published work [7]

2.3. Study size

In all, 273 participants were included from a total of 3616 mCRPC patients.

2.4. Follow-up and data collection

Predefined and readily available data from medical records were retrospectively collected by trained data managers. Baseline characteristics (including performance score, symptoms, extent of disease, and laboratory values) were included in the analysis if they were documented from 6 wk before to 1 wk after the start of ART2. All patients were followed until death, loss to follow-up, or 31 December 2017. Follow-up duration was calculated from the start date of ART2 to the last recorded date.

2.5. Outcome

The primary outcome was PSA response. PSA response was defined as the maximum change from baseline PSA levels (in percentages) without confirmation of second measure. In case no decline was present, responses were measured at 12 wk (according to the PCWG 3 criteria for response measurement [12]) or, if treatment was for <12 wk, at the end of treatment or start of next treatment. PSA response was defined as a ≥50% PSA decline from baseline [12].

The secondary outcome was treatment duration, and was calculated as the interval between the start and stop of ART2. If the stop date was unknown, treatment duration was specified as the time (1) from the start of ART2 to the start of next treatment or (2) from the start of ART2 to death if ART2 was the last treatment. Patients still alive at the end of follow-up and without a new line of therapy were censored at the date of last known visit.

2.6. Statistical analysis

The sample size was not based on power calculations. Descriptive statistics were performed. To test the

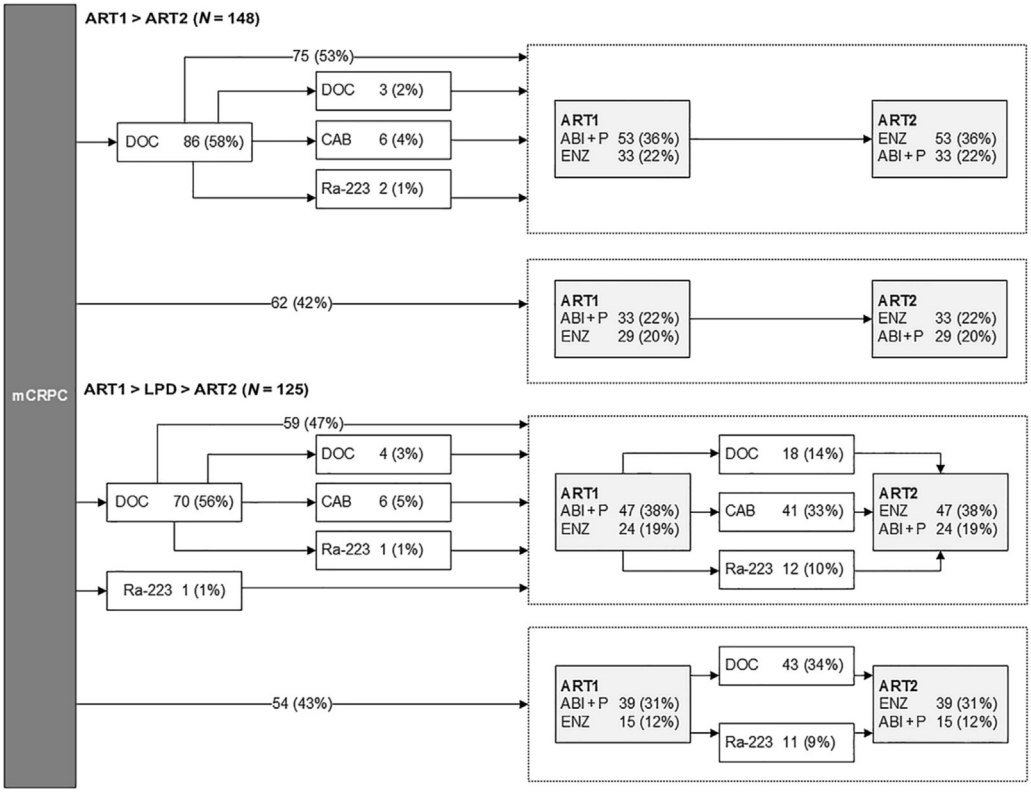

Fig. 1 – Flowchart of treatment sequencing in patients treated with both ARTs. ABI + P = abiraterone acetate plus prednisone; AR = androgen receptor; ART1 = first AR-targeting therapy; ART2 = second AR-targeting therapy; CAB = cabazitaxel; DOC = docetaxel; ENZ = enzalutamide; LPD = life-prolonging drug; mCRPC = metastatic castration-resistant prostate cancer; Ra-223 = radium-223.

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significance between subgroups, chi-square test, Mann-Whitney *U* test, and *t* test were used. Waterfall plots indicate PSA response per subgroup. Missing baseline characteristics were imputed using multiple imputations with Monte Carlo Markov Chain method. Binary logistic regression to assess the effect of baseline variables on PSA response was performed. A *p* value of <0.05 was considered statistically significant. IBM SPSS Statistics version 24.0 (IBM, Armonk, NY, USA) was used for all analyses.

3. Results

In total, 273 patients (8%) were treated with both ABI + P and ENZ before 1 July 2017. Of these patients, 148 were treated with ART1 > ART2 and 125 with ART1 > LPD > ART2, including 61 patients (48%) treated with DOC, 41 (33%) with CAB, and 23 (19%) with Ra-223 between ART1 and ART2 (Fig. 1).

In ART1 > ART, 86 patients (58%) received ABI + P > ENZ and 62 (44%) received ENZ > ABI + P compared with 86 patients (69%) with ABI + P > ENZ and 39 (31%) with ENZ > ABI + P in ART1 > LPD > ART2 (Fig. 1).

Median follow-up from ART2 was 8.4 mo (range 0.3–35.8 mo). At the end of the study, 202 all-cause deaths (74%) have occurred, 38 patients (14%) were lost to follow-up, and 33 (12%) were still in follow-up (median follow-up from ART2 of 11.1 mo).

3.1. Baseline characteristics

Patients in the ART1 > ART2 sequence were older at the start of ART2 than patients in ART1 > LPD > ART2 (75 vs 73 yr, $p < 0.01$; Table 1). ART1 > ART2 patients had favourable prognostic characteristics: less visceral metastases (12% vs 22%, $p = 0.04$), higher haemoglobin levels (7.5 vs 6.9 mmol/l, $p < 0.01$), lower lactate dehydrogenase (LDH) levels (240 vs 270 U/l, $p = 0.02$), and lower PSA levels (114 vs 170 μg/l, $p = 0.03$).

In ART1 > ART2, more patients had short ART1 treatment (<12 wk) than those in ART1 > LPD > ART2 (24% vs 11%, $p < 0.01$), but no differences in PSA response of ART1 were observed. In the ART1 > LPD > ART2 sequence, 24% of patients had a ≥50% PSA decline on interposed LPDs (28% on TAX and 9% on Ra-223; Table 1).

3.2. PSA response of ART2

PSA response of ART2 was similar in ART1 > ART2 to that in ART1 > LPD > ART2 (20% vs 18%, $p = 0.297$; Table 2 and Fig. 2). PSA response of ART2 in ART1 > ART2 was similar to PSA response of LPD in ART1 > LPD > ART2 (20% vs 24%, $p = 0.80$). PSA response of ART2 was lower in patients with ART1 treatment ≥12 wk than in patients with ART1 treatment <12 wk, but this did not reach statistical significance (18% vs 26%, $p = 0.08$). No differences in PSA response were found based on ABI + P and ENZ sequence, and interval between ART1 and ART2 (Table 3).

3.3. Treatment duration

At the end of follow-up, 9% of ART1 > ART2 patients were still on treatment compared with 3% of ART1 > LPD > ART2 patients. Fig. 3 shows median treatment duration of ART2:

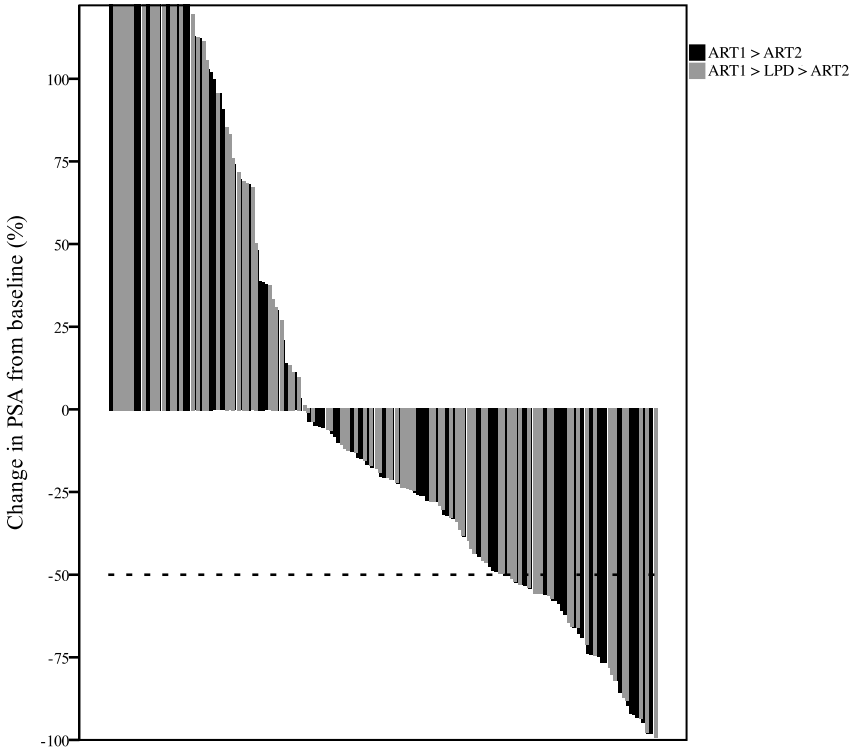

Fig. 2 – Waterfall plot of PSA response during second AR-targeting therapy (ART2). Maximum percentage change from baseline PSA per patient. The dotted line indicates the threshold of ≥50% PSA decline. AR = androgen receptor; ART1 = first AR-targeting therapy; LPD = other life-prolonging drug (docetaxel, cabazitaxel, or radium-223); PSA = prostate-specific antigen.

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Table 1 – Baseline characteristics at the start of second AR-targeting therapy.

N = 273		ART1 > ART2 *N* = 148	ART1 > LPD > ART2 *N* = 125	*p* value
Age (yr)	Median (range)	75 (53–80)	73 (50–90)	0.002 **
	≥75 yr (%)	54	38	0.010 *
Charlson score (%)	6	57	69	0.147
	7–8	35	22	
	9–10	7	8	
	>10	1	1	
	Missing	0	0	
ECOG PS (%)	0	16	17	0.172
	1	35	40	
	≥2	29	18	
	Missing	20	25	
Opioid use (%)	Yes	16	23	0.968
	No	22	33	
	Missing	62	44	
Disease state (%)	N0/N1/Nx	14/41/45	20/38/42	0.260
	M0/M1/Mx (bone)	5/80/15	3/82/14	0.554
	M0/M1/Mx (visceral)	44/12/45	34/22/44	0.016 *
Gleason score (%)	≤7	34	37	0.715
	8–10	53	53	
	No histology	1	2	
	Metastasis biopsy	1	1	
	Missing	10	7	
Time castration to mCRPC (mo)	Median (IQR)	14.3 (8–27)	13.4 (9–22)	0.725
	Missing (%)	0	0	
Hb (mmol/l)	Median (IQR)	7.5 (6.8–8.2)	6.9 (6.0–7.8)	<0.001 **
	Missing (%)	10	7	
ALP (U/l)	Median (IQR)	129 (88–224)	144 (86–258)	0.581
	Missing (%)	11	10	
LDH (U/l)	Median (IQR)	240 (190–283)	270 (204–364)	0.017 *
	Missing (%)	30	22	
PSA (μg/l)	Median (IQR)	114 (32–391)	170 (85–444)	0.033 *
	Missing (%)	8	7	
Number of lines prior to ART2 (%)	1	42	0	<0.001 **
	2	51	43	
	3	7	48	
	4–5	0	9	
ART1 treatment (%)	ENZ	42	31	0.068
	ABI + P	58	69	
Treatment duration of ART1 (mo)	Median (IQR)	7.1 (3.1–13.6)	7.4 (5.2–12.3)	0.869
	≤12 wk (%)	24	11	0.005 **
PSA response to ART1 (%)	≥50% PSA decline	51	54	0.442
	<50% PSA decline	35	30	
	PSA response missing	14	16	
Time between discontinuation of ART1 and start of ART2 (mo)	Median (IQR),	<1 (0–2), 27	7 (5–10), 33	<0.001 **
	missing (%)[a]	53	0	
	<40 d (%)	20	67	
	≥40 d (%)			
Interposed LPD [b] (%)	Docetaxel	NA	49	
	Cabazitaxel		33	
	Radium-223		18	
Treatment duration of interposed LPD [b] (cycles)	Median (range)	NA	6 (1–15)	
	≥6 cycles (valid %)		68	
	≥10 cycles (valid %)		16	
	Missing (%)		5	
PSA response to interposed LPD [b] (%)	≥50% PSA decline	NA	24	
	<50% PSA decline		49	
	PSA response missing		27	

ABI + P = abiraterone acetate plus prednisone; ALP = alkaline phosphatase; AR = androgen receptor; ART1 = first AR-targeting therapy; ART2 = second AR-targeting therapy; ECOG PS = Eastern Cooperative Oncology Group performance score; ENZ = enzalutamide; Hb = haemoglobin; IQR = interquartile range; LDH = lactate dehydrogenase; LPD = life-prolonging drug; mCRPC = metastatic castration-resistant prostate cancer; NA = not available; PSA = prostate specific antigen.

[a] Patients with missing ART1 stop date.

[b] Characteristics of interposed life-prolonging treatment in ART1 > LPD > ART2.

* Significant at $p < 0.05$.

** Significant at $p < 0.01$.

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Table 2 – PSA response and treatment duration of second AR-targeting therapy.

N = 273			ART1 > ART2 *N* = 148	ART1 > LPD > ART2 *N* = 125	*p* value
PSA response	Median change from baseline [a] (IQR)		−21% (−56% to +46%)	−18% (−50% to +73%)	0.315
	≥50% PSA decline (%)				
	<50% PSA decline (%)		20	18	0.297
	Missing (%)		45	57	
			35	25	
Treatment duration of ART2	Median (IQR), censored (%) [b]		3.2 (1.9–7.5), 9	3.2 (1.8–5.9), 3	0.042 *
	≤3 mo (valid %)		52	49	
	>3 mo (valid %)		48	51	0.621
PSA response on line after ART1 [c]	≥50% PSA decline (%)		20	24	0.801
	<50% PSA decline (%)		45	49	
	Missing (%)		35	27	

AR = androgen receptor; ART1 = first AR-targeting therapy; ART2 = second AR-targeting therapy; IQR = interquartile range; LPD = life-prolonging drug; PSA = prostate-specific antigen.
[a] Measured as relative change from baseline value (negative values indicate a PSA decline, positive values a PSA increase).
[b] Still on treatment at the end of follow-up.
[c] PSA response rate of ART2 in ART1 > ART2 and of interposed LPD in ART1 > LPD > ART2.
* Significant at $p < 0.05$.

Table 3 – PSA response and treatment duration of second AR-targeting therapy based on different subgroups.

		ABI + P and ENZ sequence			ART1 treatment duration			Interval between ART1 and ART2		
		ENZ > ABI + P *N* = 101	ABI + P > ENZ *N* = 172	*p* value	≥12 wk *N* = 223	<12 wk *N* = 50	*p* value	<40 d *N* = 119	≥40 d *N* = 154	*p* value
PSA response	≥50% PSA decline (%)	14	23	0.159	18	26	0.078	20	19	0.461
	<50% PSA decline (%)	51	50		53	38		45	54	
	Missing (%)	36	27		29	36		35	27	
Treatment duration (mo)	Median (IQR)	3.2 (1.8–7.3)	3.2 (1.9–5.9)	0.158	3.2 (1.9–6.7)	3.2 (1.8–5.8)	0.573	3.2 (1.9–6.4)	3.2 (1.8–6.5)	0.364
	Censored (%) [a]	12	3		6	6		8	5	
	≤3 mo (valid %)	55	48	0.276	51	49	0.825	53	48	0.437
	>3 mo (valid %)	45	52		49	51		47	52	

ABI + P = abiraterone acetate plus prednisone; AR = androgen receptor; ART1 = first AR-targeting therapy; ART2 = second AR-targeting therapy; ENZ = enzalutamide; IQR = interquartile range; PSA = prostate-specific antigen.
[a] Still on treatment at the end of follow-up.

3.2 mo (interquartile range [IQR] 1.9–7.5 mo) in ART1 > ART2 and 3.2 mo (IQR 1.8–5.9 mo) in ART1 > LPD > ART2 ($p = 0.04$). Patients with ART1 > ART2 had higher probability of longer treatment duration (hazard ratio 0.773, 95% confidence interval 0.603–0.993, $p = 0.04$). Patients with a response to ART2 had a median treatment duration of 7.3 mo (IQR 4.1–13.0 mo).

No differences were observed in ART2 treatment duration between ABI + P and ENZ sequence, ART1 treatment duration, and interval between ART1 and ART2 (Table 3).

3.4. *Multivariate analyses*

Eighty-three patients (30%) were excluded from multivariate binary logistic regression due to missing PSA response of ART2 (Table 4). There was no difference in PSA response of ART2 between ART1 > ART2 and ART1 > LPD > ART2 (odds ratio [OR] 0.890, $p = 0.89$). Visceral metastases were associated with lower PSA response rates (OR 0.143, $p = 0.04$), while longer time on androgen-deprivation therapy (OR 1.028, $p = 0.01$) and ABI + P before ENZ (OR 3.192, $p = 0.02$) were associated with higher PSA response rates (Table 4).

After the exclusion of 32 patients treated with ART1 for <12 wk from multivariate analysis, time on androgen-deprivation therapy remained the only significant factor for PSA response (OR 1.034, $p = 0.02$).

4. Discussion

In this retrospective analysis of real-world data, we reported outcomes of sequential treatment with both ARTs with or without interposed TAX or Ra-223. To our knowledge, this is the largest multicentre population in which patients are treated according to the views and opinions of their medical oncologists and urologists. Outcomes therefore reflect current daily practice.

Patients with ART1 > ART2 had better prognostic factors at the start of ART2 (less visceral disease, higher haemoglobin, lower LDH, and lower PSA) than ART1 > LPD > ART2 patients. One could speculate that physicians decided to administer TAX or Ra-223 rather than the other ART in

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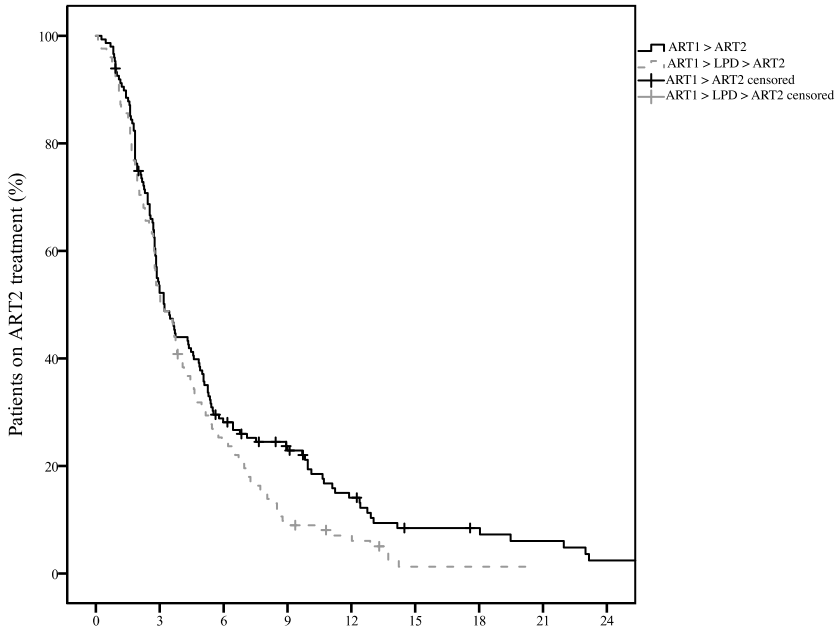

Fig. 3 – Treatment duration (in months) during second AR-targeting therapy (ART2). AR = androgen receptor; ART1 = first AR-targeting therapy; LPD = other life-prolonging drug (docetaxel, cabazitaxel, or radium-223).

younger patients with more adverse prognostic factors, and seemingly have little faith in a meaningful response to ART2 in patients with progression on ART1. This seems unjustified based on similar response rates to ART2 in ART1 > ART2 (20%) to that on LPDs in ART1 > LPD > ART2 (24%).

We observed a PSA response of ART2 in 20% of patients with or without interposed TAX or Ra-223, and a median treatment duration of 3 mo. PSA response is in line with previously published reports on ART2 (4–30% [4–6,13–16]), but low compared with phase III randomised controlled trials for ABI + P and ENZ (62–78% in chemotherapy-naïve and 38–54% in postchemotherapy treatment [17–20]). Low PSA responses and short treatment duration can be a result of cross-resistance between ABI + P and ENZ. Mechanisms of resistance are complex and not completely understood, but it is proposed that they include both androgen receptor (AR)-dependent mechanisms (eg, AR aberrations, including amplification, genomic structural variants, or splice variants such as AR-V7) and AR-independent mechanisms (eg, neuroendocrine transformation or glucocorticoid receptor overexpression) [2]. Since mechanisms of resistance are overlapping between ABI + P and ENZ, cross resistance may lead to low efficacy of ART2.

However, a low PSA response rate and a short treatment duration of ART2 can also be the result of the advanced disease state. Most patients were treated with ART2 in line 3 (47%) or line ≥4 (30%). An Italian multicentre study showed that the biochemical response rates decreased to 38%, 24%, and 16%, respectively, on second, third, and fourth lines irrespective of the treatment sequence [21].

Presence of visceral disease and shorter time between the start of androgen-deprivation therapy and mCRPC were predictive of a poor PSA response of ART2. Visceral disease and rapid time to castration resistance are known prognostic factors for overall survival [22,23], but can possibly impact PSA response due to a correlation between survival and PSA response rate [24,25].

We hypothesised that patients who discontinued ART1 due to other reasons than progression would have better effect of ART2, since resistance (either primary or acquired) to ART1 has not occurred. Since the exact reason of discontinuation was not easily evaluable due to missing values and the absence of strict progression criteria, treatment duration was used as a proxy for the reason of discontinuation. Toxicity mainly occurs in the initial months, making a duration of <12 wk an indicator of toxicity. These patients tended to have higher PSA response rates than patients with ART1 treatment ≥12 wk (26% vs 18%), but this difference was not clinically relevant.

Treatment sequence of ABI + P and ENZ has also been argued to affect the response of ART2 with favourable effects for ABI + P > ENZ than for ENZ > ABI + P [4–7,13,26,27]. In our study, patients with ABI + P > ENZ also had better PSA response rates of ART2 (OR 3.192, $p = 0.02$) without differences in treatment duration. The beneficial effect of ABI + P > ENZ on PSA response did not hold after exclusion of patients with ART1 treatment <12 wk (OR 2.060, $p = 0.19$).

We used PSA kinetics and treatment duration as indicators for treatment efficacy of ART2, but the effect on overall survival and progression-free survival could not be estimated. Post hoc analyses of phase III trials of ABI + P and ENZ demonstrated a strong correlation between PSA kinetics during ABI + P and ENZ and overall survival [24,25].

Although the PSA response rate of ART2 is fairly low and median treatment duration is short, patients who had a PSA response of ART2 had a clinically relevant duration of ART2 treatment (7.3 mo). ART2 may therefore offer a benefit in a

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Table 4 – Univariate and multivariate binary logistic regression for PSA response.

	Univariate analysis of original data				Multivariate analysis of pooled data after imputation ($N = 190$)		
	N	OR	95% CI	*p* value	OR	95% CI	*p* value
Age (yr), cont.	190	1.027	0.986–1.069	0.199	1.013	0.959–1.070	0.643
Charlson score							
6	127	REF	–	–	REF	–	–
7–8	52	0.613	0.345–1.545	0.266	0.582	0.216–1.565	0.283
>9	11	0.815	0.384–5.033	0.684	1.162	0.206–6.563	0.865
ECOG PS							
0	36	REF	–	–	REF	–	–
1	81	0.707	0.259–1.452	0.412	0.396	0.140–1.120	0.081
≥2	38	0.895	0.304–2.184	0.814	0.495	0.125–1.963	0.316
Opioid use							
No	54	REF	–	–	REF	–	–
Yes	40	1.196	0.470–3.042	0.707	1.312	0.463–3.719	0.609
Disease state							
N1 vs N0	107	0.629	0.265–1.494	0.293	0.696	0.221–2.192	0.532
M1 vs M0 (bone)	162	1.239	0.241–6.369	0.798	5.414	0.702–41.770	0.104
M1 vs M0 (visceral)	91	0.340	0.104–1.111	0.074	0.143	0.023–0.879	0.037
Gleason score (%)							
≤7	65	REF	–	–	REF	–	–
8–10	104	0.578	0.293–1.139	0.113	0.692	0.287–1.668	0.411
Time castration to mCRPC (mo), cont.	190	1.020	1.004–1.036	0.013 *	1.028	1.006–1.050	0.013 *
Hb (mmol/l), cont.	183	0.979	0.727–1.317	0.888	0.706	0.424–1.177	0.180
ALP (U/l), cont.	183	1.000	0.999–1.002	0.720	1.000	0.998–1.002	0.760
LDH (U/l), cont.	151	1.000	0.998–1.001	0.500	1.000	0.998–1.002	0.725
PSA (μg/l), cont.	190	1.000	1.000–1.0001	0.931	1.000	0.999–1.000	0.535
Docetaxel prior to ART1							
No	75	REF	–	–	REF	–	–
Yes	115	0.717	0.377–1.362	0.309	0.667	0.292–1.525	0.337
Treatment sequence							
ENZ > ABI + P	65	REF	–	–	REF	–	–
ABI + P > ENZ	125	1.652	0.819–3.334	0.161	3.192	1.195–8.529	0.021 *
Treatment sequence							
ART1 > ART2	95	REF	–	–	–	–	–
ART1 > LPD > ART2	94	0.713	0.376–1.349	0.298	0.890	0.359–2.206	0.890
Treatment duration of ART1 (wk)							
>12	158	REF	–	–	REF	–	–
≤12	32	2.018	0.915–4.453	0.082	3.293	0.978–11.094	0.054
≥50% PSA decline on ART1							
No	56	REF	–	–	REF	–	–
Yes	109	0.914	0.442–1.888	0.807	1.125	0.395–3.207	0.824

ABI + P = abiraterone acetate plus prednisone; ALP = alkaline phosphatase; AR = androgen receptor; ART1 = first AR-targeting therapy; ART2 = second AR-targeting therapy; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance score; ENZ = enzalutamide; Hb = haemoglobin; IQR = interquartile range; LDH = lactate dehydrogenase; LPD = life-prolonging drug; mCRPC = metastatic castration-resistant prostate cancer; OR = odds ratio; PSA = prostate-specific antigen; REF = reference category.
* Significant at $p < 0.05$.

selected patient population, which may include patients who are AR copy neutral and those without AR-V7 [2].

Monitoring treatment efficacy in mCRPC is complex [28]. The decision to discontinue treatment should not be based on a single indicator for progression, but on the association between different outcome measures (eg, clinical, biochemical, patient-reported outcomes, and imaging) [12]. Consistent evaluation and reporting of clinical, biochemical, and radiologic changes during treatment are advised, since these can aid future research of treatment efficacy in daily practice [12].

The first limitation of our study was the high number of missing values, which is inherent to the retrospective design. Missing values on baseline characteristics reflect incomplete evaluation of patients or lack of structured reporting in daily practice. This underlines the need for better documentation at the start of a new treatment. Imputation of missing baseline data offers a valid solution for multivariate analysis. However, 83 patients (30%) were excluded from the imputed analysis, which decreased the statistical power. Moreover, because of the retrospective database, the sample size was not based on power calculations, but on patients available matching the study population criteria.

The second limitation was the fact that this study was not able to capture all data on treatment decisions. Other factors than the known patient and disease characteristics may play a role in the decision for a particular sequence, for example, preferences of both patients and physicians. In sequencing ABI + P and ENZ, the possible contraindications for prednisone could also be considered. These unknown factors may affect outcomes. Furthermore, biomarkers could not be evaluated in our patient population.

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Accumulating evidence points at a subgroup, identified by noninvasive biomarkers, that benefits from ART2. These limitations indicate the need of prospective research in a large population to confirm the findings of this retrospective research and putative predictive biomarkers; such research work is currently being conducted (eg, CARD study [ClinicalTrials.gov identifier NCT02485691] and phase 2 randomised cross-over trial of ART [NCT02125357]).

5. Conclusions

In conclusion, our study suggests that PSA response rates of ART2 are low with a short treatment duration irrespective of sequencing both ARTs directly after each other or with interposed TAX or Ra-223. The effect of ART2 seems to be low, especially in patients with short time on castration, visceral disease, and ENZ before ABI + P. Further prospective research incorporating other outcome measures such as overall and progression-free survival, pain, and quality of life is necessary to aid in the optimal treatment decision after ART1 and to possibly identify subgroups that can benefit from ART2.

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Study concept and design: Kuppen, Westgeest, van den Eertwegh, Uyl-de Groot, Gerritsen.
Acquisition of data: Kuppen, Westgeest.
Analysis and interpretation of data: Kuppen.
Drafting of the manuscript: Kuppen.
Critical revision of the manuscript for important intellectual content: Westgeest, van den Eertwegh, van Moorselaar, van Oort, Coenen, van den Bergh, Mehra, Somford, Bergman, ten Bokkel Huinink, Fossion, Geenen, Hendriks, van de Luijtgaarden, Polee, Weijl, van de Wouw, de Wit, Uyl-de Groot, Gerritsen.
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