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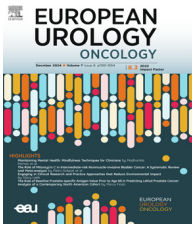

European Association of Urology

Apalutamide in Metastatic Castration-sensitive Prostate Cancer: Results from the Multicenter Real-world ARON-3 Study

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Abstract

Background and objective: Apalutamide (APA) is a treatment for metastatic castration-sensitive prostate cancer (mCSPC). In the ARON-3 study we investigated real-world experiences with APA treatment for mCSPC.

Methods: We retrospectively assessed real-world clinical outcomes for patients with mCSPC treated with APA in the ARON-3 study. Overall survival (OS) was calculated from APA initiation to death from any cause. PSA_{90} was defined as a prostate-specific antigen decline of ≥90% from baseline, and $PSA_{0.2}$ as achievement of a PSA level ≤0.2 ng/ml. Data for adverse events were retrospectively collected from electronic and paper charts and categorized according to Common Terminology Criteria for Adverse Events v5.0.

Key findings and limitations: We included 531 patients with mCSPC treated with APA. High-volume disease was reported for 214 patients (40%), and 56 (11%) had visceral metastases. Median OS was not reached. PSA_{90} was experienced by 461 patients (87%) and $PSA_{0.2}$ by 368 (69%). Median OS was significantly longer for patients with PSA_{90} or $PSA_{0.2}$ than for subjects without these responses ($p < 0.001$). The incidence of grade 3–4 fatigue was higher among elderly patients (≥80 yr) than among younger patients (19% vs 5%), but the incidence of other adverse events was comparable between the age groups.

Conclusions and clinical implications: APA is an effective and tolerable treatment for mCSPC in the real-world setting.

Patient summary: The ARON-3 project collects data for patients with prostate cancer treated in multiple centers worldwide to assess outcomes in the real-world setting. We analyzed data for patients with metastatic hormone-sensitive prostate cancer receiving apalutamide. Our results show that apalutamide is a safe and effective drug in the real-world setting as well as in clinical trials.

1. Introduction

The development of second-generation androgen receptor pathway inhibitors (ARPIs) has substantially improved survival outcomes for men with metastatic prostate cancer. ARPIs combined with androgen deprivation therapy (ADT) are therefore considered a standard of care in metastatic castration-sensitive prostate cancer (mCSPC), as recommended in the European Society of Medical Oncology and National Comprehensive Cancer Network guidelines [1,2]. Among several ARPIs available for this indication, apalutamide (APA) represents an agent of first choice for which administration is beneficial regardless of disease volume or risk [1,3].

APA competitively binds to the ligand-binding pocket of the androgen receptor (AR) with high affinity, downregulating DNA transcription induced by AR nuclear translocation and thereby exerting antiproliferative effects in prostate cancer cells [4]. On the basis of this rationale, the randomized, double-blind, phase 3 TITAN trial compared ADT + APA to ADT + placebo in 1052 patients with mCSPC [5]. Final survival analysis at median follow-up of 44.0 mo demonstrated potent antitumor activity, marked by median overall survival that was not reached and a crossover-adjusted 48% reduction in the risk of death in the APA + ADT arm [6]. APA treatment also resulted in a longer time to biochemical or radiographic progression and the development of castration-resistant disease [6]. Accordingly, both the US Food and Drug Administration and the European Medicines Agency approved the APA + ADT combination for mCSPC treatment in late 2019 [7,8].

Since then, strong APA antitumor activity has been observed in several real-world series, with a remarkably large proportion of patients exhibiting an early and deep biochemical response to APA treatment [9–11]. A post hoc analysis of the TITAN trial demonstrated that this response is associated with a further improvement in prognosis [12]. Meanwhile, quality of life was not negatively affected by APA in comparison to placebo in TITAN even though APA was commonly associated with treatment-emergent adverse events (AEs), especially rash in approximately a quarter of patients and frequent occurrence of fracture or hypothyroidism [5,13]. Therefore, a substantial number of patients require a dose reduction (up to 60%) or even discontinuation (~8.0%) [5,11]. Nevertheless, several studies suggest that APA has the most favorable AE profile among ARPIs approved for mCSPC [14,15].

While these trial insights provide meaningful information regarding the benefits and risks of APA in mCSPC, further analyses of real-world treatment patterns in large multicenter series are required to improve patient selection and overcome trial selection bias. The ARON-3 project (ClinicalTrials.gov NCT06200558) is a multicenter, international, retrospective study designed to collect real-world data for patients with prostate cancer. In this subset analysis, we focused on real-world experiences of APA treatment for mCSPC.

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2. Patients and methods

2.1. Study design and population

We retrospectively analyzed clinical data for patients diagnosed at age ≥18 yr with CSPC and confirmed metastatic disease. The study population included patients treated with APA from January 1, 2020 to May 31, 2024 in 29 oncological centers in nine countries (Supplementary Table 1). All the patients included had data available for age, tumor histology, Eastern Cooperative Oncology Group performance status (ECOG-PS), sites of metastases, previous surgery, dosage and duration of APA treatment, and prostate-specific antigen (PSA) response to APA. Clinical and pathological information was extracted at each participating center from the patients' medical and pathology reports for clinical use.

Patients with missing clinical or outcome data were excluded from the ARON-3 study. The study protocol was approved on April 18, 2024, by the ethics committee of the coordinating center (Marche Region, Italy; reference no. 2024 20, study protocol "ARON-3 study") and by the institutional review boards of participating centers. The study was conducted according to Good Clinical Practice and International Ethical Guidelines for Biomedical Research, and the protocol was designed on the basis of the ethical principles laid down in the Declaration of Helsinki on human experimentation.

2.2. Study objectives

The primary objective was to assess real-world clinical outcomes for patients with mCSPC treated with APA. Secondary objectives were to explore predictors of APA benefit and tolerability in the real-world setting, with a focus on elderly patients.

Data for time to PSA progression, time on treatment, and overall survival (OS) were collected. OS was calculated from the start of APA treatment to death from any cause. Time to PSA progression was defined as the time from the start of APA to the first PSA increase. Time on treatment was defined as the time from the start of APA to treatment interruption for any cause.

PSA_{90} was defined as a ≥90% decline in PSA from baseline, while $PSA_{0.2}$ was defined as achievement of PSA ≤0.2 ng/ml, as previously described [12].

Data on adverse events (AEs) were retrospectively collected from paper and electronic charts and categorized according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Data collection was restricted to severe AEs (SAEs), defined as CTCAE grade ≥3, and AEs leading to APA dose reduction or discontinuation.

2.3. Statistical analysis

OS was estimated using the Kaplan-Meier method and compared between subgroups using the log-rank test. Median follow-up, time on treatment, and time to PSA progression were also calculated using the Kaplan-Meier method. Landmark analysis was performed at the 12-mo time point to reduce potential biases related to follow-up time. Cox proportional-hazards models were used to compare multivariable effects on patient survival and to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Comparisons between subgroups were performed with the Fisher exact test. A p value <0.05 was considered statistically significant. Statistical analyses were conducted using MedCalc version 19.6.4 (MedCalc Software, Mariakerke, Belgium).

3. Results

3.1. Study population

Data for 531 patients treated with APA for mCSPC were extracted from the ARON-3 database (Supplementary Fig. 1). Median follow-up was 18.2 mo (95% CI 14.2–19.9) and 29 patients (5%) were dead at the time of analysis.

The median age was 70 (range 47–95) yr, with 53 patients aged ≥80 yr. ECOG-PS was 0 in 373 (70%), 1 in 135 (25%), 2 in 21 (4%), and 3 in two patients (1%). Gleason score at initial diagnosis was >7 in 66% of patients. Regarding metastasis status, 412 patients (78%) had de novo metastatic disease at prostate cancer diagnosis, while 119 patients (22%) presented with metachronous metastatic disease. Visceral metastases were observed in 56 patients (11%). High-volume disease was reported for 214 patients (40%). Median PSA was 22.6 (range 0.2–7793.0) ng/ml. All the patient characteristics are summarized in Table 1.

3.2. Survival outcomes

Median OS in the overall study population was not reached (Fig. 1). Median time on treatment with APA was 35.4 mo (95% CI 25.2–38.1).

The 2-yr OS rate was 91% for the ECOG-PS 0–1 group and 76% for the ECOG-PS ≥2 group ($p = 0.007$). Stratified by age, the 2-yr OS rate was 89% in the group aged <70 yr, 92% in the group aged ≥70 yr, and 91% in the group aged ≥80 yr ($p = 0.759$).

Median OS was not reached in the high-volume and low-volume disease groups ($p < 0.001$), with 2-yr OS rates of 82% and 96%, respectively ($p = 0.002$).

Further stratification revealed 2-yr OS rates of 95% for metachronous low-volume disease, 89% for de novo low-volume disease, 96% for metachronous high-volume disease, and 72% for de novo high-volume disease ($p < 0.001$; Fig. 1).

Median OS was not reached in the subgroups with only lymph node metastases (M1a) and only bone metastases (M1b), with 2-yr OS rates of 100% and 88%, respectively.

In the subgroup of 23 patients treated with APA after docetaxel, median OS was not reached and the 2-yr OS rate was 70%.

3.3. PSA dynamics

A PSA_{90} response was observed in 461 patients (87%). The median time to PSA_{90} was 5.0 mo (95% CI 4.6–22.1). PSA_{90} was achieved within 3 mo for 28% of these patients, between 3 and 6 mo for 29%, and after 6 mo for 43%. The median OS was not reached in the groups with and without a PSA_{90} response ($p < 0.001$; Fig. 2). The 2-yr OS rate was

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Table 1 – Patient characteristics (*n* = 531)

Parameter	Result
Median age, yr (range)	70 (47–95)
ECOG performance status, *n* (%)	
0	373 (70)
1	135 (25)
2	21 (4)
3	2 (1)
Gleason score at initial diagnosis, *n* (%)	
<7	35 (7)
7	145 (27)
>7	351 (66)
Metastatic status, *n* (%)	
De novo	412 (78)
Metachronous	119 (22)
Disease volume, *n* (%)	
Low volume	317 (60)
High volume	214 (40)
Metastatic stage, *n* (%)	
Exclusive metastases to distant lymph nodes (M1a)	70 (13)
Exclusive bone metastases (M1b)	179 (34)
Exclusive visceral metastases (M1c)	10 (2)
Multiple sites of metastasis	272 (51)
Visceral metastases, *n* (%)	56 (11)
Previous treatment with docetaxel for mCSPC, *n* (%)	23 (4)
Radiotherapy for localized CSPC, *n* (%)	68 (13)
Radical prostatectomy for localized CSPC	32 (6)
Median PSA before starting APA, ng/ml (range)	22.6 (0.2–7793.0)

APA = apalutamide; CSPC = castration-sensitive prostate cancer; ECOG = Eastern Cooperative Oncology Group; mCSPC = metastatic CSPC; PSA = prostate-specific antigen.

93% in the PSA_{90} subgroup, in contrast to 70% for the groups without a PSA_{90} response ($p < 0.001$). There were no significant differences in median OS among the subgroups achieving PSA_{90} at ≤3 mo, 3–6 mo, or >6 mo.

According to 12-mo OS landmark analysis, median OS was not reached in the groups with and without a PSA_{90} response ($p < 0.001$; Supplementary Fig. 2), with a 2-yr OS rate of 95% in the PSA_{90} subgroup and 71% in the group without a PSA_{90} response ($p < 0.001$).

A $PSA_{0.2}$ response was observed in 368 patients (69%). The median time to $PSA_{0.2}$ was 5.0 mo (95% CI 4.6–18.2). $PSA_{0.2}$ was achieved within 3 mo for 47% of these patients, between 3 and 6 mo for 48%, and after 6 mo for 5%. Median OS was not reached in the groups with and without a $PSA_{0.2}$ response ($p < 0.001$; Fig. 2). The 2-yr OS rate was 95% in the $PSA_{0.2}$ subgroup and 80% in the group with a $PSA_{0.2}$ response ($p = 0.002$).

According to the 12-mo OS landmark analysis, median OS was not reached in the groups with and without a $PSA_{0.2}$ response ($p = 0.036$; Supplementary Fig. 2), with 2-yr OS rates of 96% in the $PSA_{0.2}$ group and 85% in the group without a $PSA_{0.2}$ response ($p = 0.014$).

PSA increases were observed in 77 patients (15%), with a median time to PSA progression of 10.5 mo (95% CI 8.7–38.1).

3.4. Safety

SAEs were reported for 101 patients (19%). The most common grade 3–4 SAEs were fatigue (7%), skin rash (7%), hypertension (3%), and fractures (2%). In the group aged ≥80 yr the incidence of SAEs was 22%, with grade 3–4 fatigue reported for 19% of elderly patients, rash for 11%, fractures for 3%, and no cases of hypertension (Supplementary Table 2). Full-dose APA was received by 95% of the study population and 5% received an initial reduced dose. Some 13% of the patients had a dose reduction because of SAEs.

3.5. Univariate and multivariate analyses

In the overall study population, ECOG-PS, disease volume, PSA_{90}, $PSA_{0.2}$, and grade 3–4 rash were significantly associated with OS in univariate analyses. On multivariate analysis, only $PSA_{0.2}$ was significantly correlated with OS (Table 2).

4. Discussion

Following its marketing authorization in 2019, APA has been widely used in mCSPC, as reflected by our sizable cohort. To the best of our knowledge, our study represents the largest real-world series of patients treated with APA for mCSPC to date.

APA administration was associated with a decent OS, corroborating results from the phase 3 TITAN trial [6], although follow-up was considerably shorter in our analysis. While the cohorts had similar baseline characteristics in terms of age, PSA, disease volume, and previous treatment, our study also included patients with only lymph node metastases (M1a) and patients with ECOG-PS ≥2 [5].

Unlike advanced age, ECOG-PS ≥2 was a negative predictor of 2-yr OS in our study. This finding emphasizes the prognostic importance of ECOG-PS, as previously highlighted in advanced prostate cancer [16,17]. Since patients with ECOG-PS ≥2 were not included in the APA arm of the TITAN trial, real-world studies are necessary to overcome this lack of data [5]. However, the small proportion (5%) of these cases in our overall cohort reflects the usually favorable general condition of patients with mCSPC, so ECOG-PS might have limitations as a prognostic factor in this population. Karnofsky performance status, which provides more granular categorization of patients' abilities, could be a more reliable tool.

Another baseline variable associated with OS was de novo high-volume disease, which has been linked to worse OS prognosis in previous studies [18,19]. Given the development of triplet therapy (ADT + ARPI + docetaxel), identification of the subgroup of patients for whom ADT + ARPI treatment is not sufficient is required [20]. Complementary to previous reports, our results suggest a need for intensified treatment regimens for patients with de novo high-volume mCSPC [20,21]. By contrast, OS was similar for metachronous high-volume disease and low-volume mCSPC in our cohort. However, the limited numbers of cases should be noted.

The literature focus on biochemical response patterns to APA reflects the pivotal role of PSA in the disease and treatment perceptions by patients and physicians. With more than two-thirds of patients achieving $PSA_{0.2}$ and an even substantially higher PSA_{90} rate of 87%, our findings confirm previous reports of 66–68% for $PSA_{0.2}$ and 68–92% for PSA_{90} [9–12,22]. As in TITAN, both PSA response parameters

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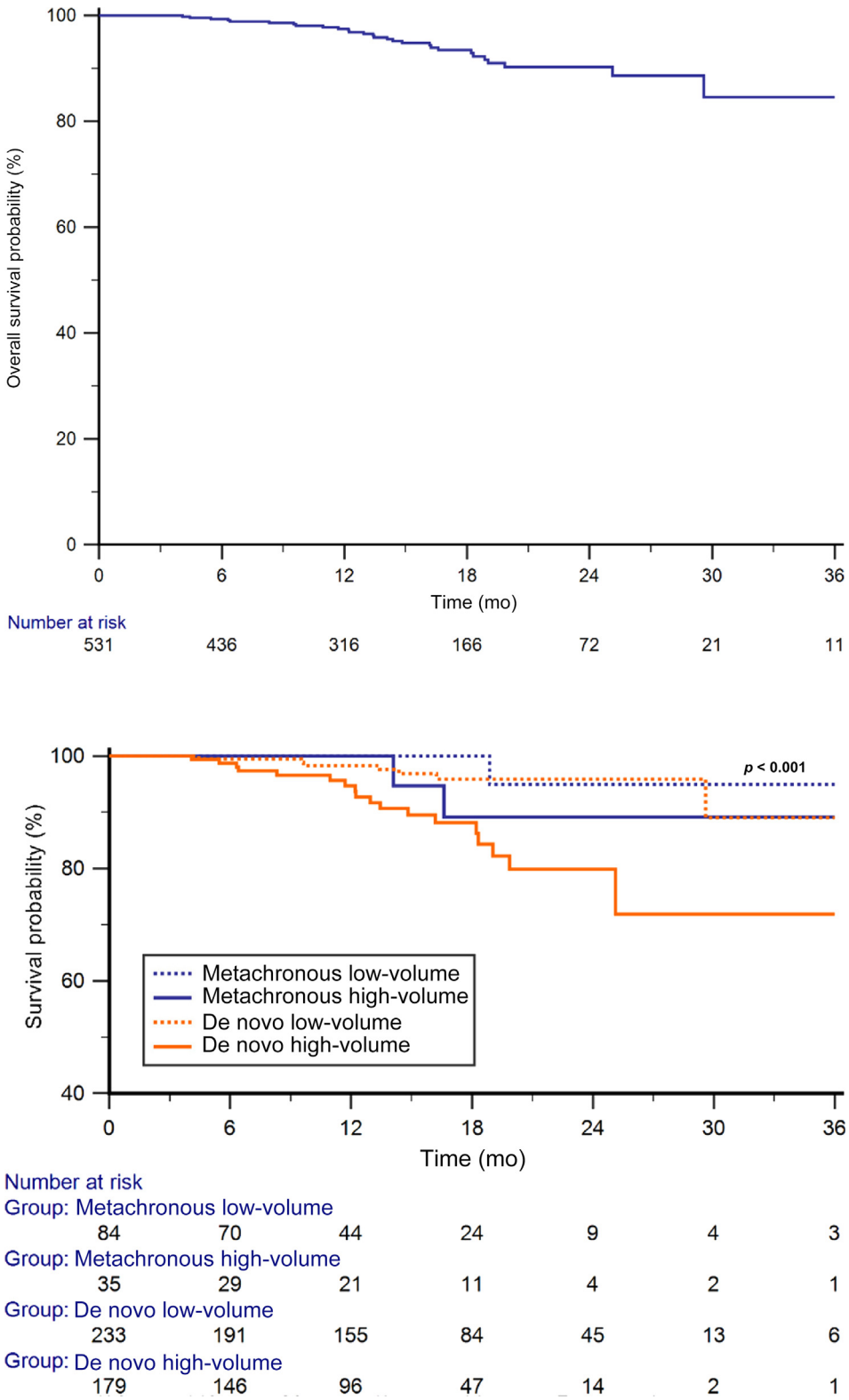

Fig. 1 – Overall survival in the study population stratified by disease volume (high vs low) and metastatic status (metachronous vs de novo).

exhibited predictive potential regarding OS [12]. $PSA_{0.2}$ was the only independent predictor of OS in multivariate analysis. These observations should prompt clinicians to monitor PSA in their patients with mCSPC being treated with APA to gather important prognostic information in a simple and straightforward manner.

Our SAE data confirm the tolerable safety profile of APA in mCSPC. Comparison of our findings to those from TITAN

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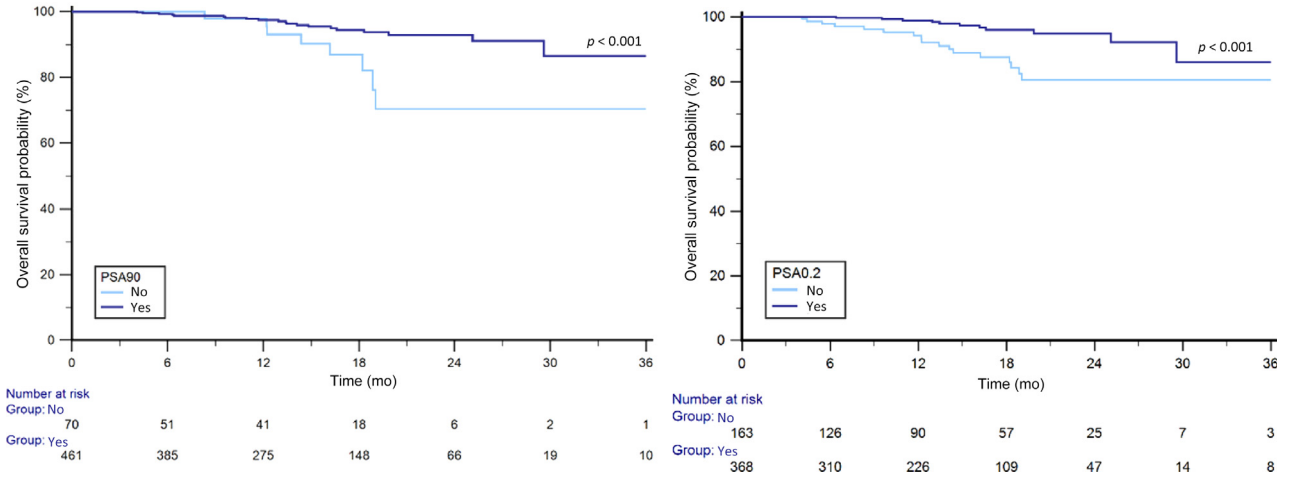

Fig. 2 – Overall survival for the groups with and without PSA_{90} and $PSA_{0.2}$ responses. PSA = prostate-specific antigen; PSA_{90} = ≥90% PSA decline from baseline; $PSA_{0.2}$ = PSA response to ≤0.2 ng/ml.

Table 2 – Univariate and multivariate analysis results for overall survival

Covariate	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (≥70 vs <70 yr)	1.72 (0.78–3.80)	0.181		
ECOG-PS (≥2 vs <2)	5.34 (1.84–15.5)	**0.002**	1.40 (0.25–7.90)	0.704
Gleason score (<7 vs ≤7)	2.70 (0.80–9.16)	0.110		
De novo vs metachronous metastasis	2.27 (0.68–7.51)	0.181		
High-volume vs low-volume disease	4.37 (1.91–9.98)	**<0.001**	2.19 (0.84–5.67)	0.107
PSA_{90} response (yes vs no)	0.32 (0.14–073)	**0.007**	0.41 (0.16–1.04)	0.061
$PSA_{0.2}$ response (yes vs no)	0.28 (0.13–0.60)	**0.001**	0.26 (0.10–0.66)	**0.005**
APA dose reduction (yes vs no)	1.48 (0.50–4.34)	0.474		
Grade 3–4 fatigue (yes vs no)	0.83 (0.19–3.56)	0.797		
Grade 3–4 rash (yes vs no)	3.03 (1.02–9.02)	**0.047**	3.45 (0.96–12.35)	0.057
Grade 3–4 hypertension (yes vs no)	0.97 (0.67–2.54)	0.961		
Grade 3–4 fracture (yes vs no)	1.35 (0.18–10.09)	0.772		

APA = apalutamide; CI = confidence interval; ECOG-PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; PSA = prostate-specific antigen; PSA_{90} = ≥90% PSA decline from baseline; $PSA_{0.2}$ = PSA response to ≤0.2 ng/ml.

revealed similar rates of CTCAE grade ≥3 rash, fracture, and fatigue [5]; however, fatigue seems to be a more relevant issue in the elderly population. Hypertension was considerably less frequent than in the phase 3 trial, possibly because of differences in evaluation and screening procedures in real-world practice [5]. However, potential cohort bias should be considered when generalizing these findings, as rash seems to occur more frequently in Asian populations [11,23]. In our cohort, which mainly comprised European patients, this ethnic group was under-represented. This is reflected by the dose reduction rate in our cohort, which was consistent with the TITAN trial [5] but substantially lower than the rate reported for a Japanese cohort [11].

The main limitations of our study are the retrospective nature of the analyses, which might have affected the CTCAE grading of toxicities, the short follow-up, and multicenter collection of data.

5. Conclusions

This subset analysis of the ARON-3 project examined the main clinical outcomes of apalutamide treatment for metastatic castration-sensitive prostate cancer. Our real-world data corroborate the efficacy and safety profile observed in the phase 3 TITAN trial. Despite severe adverse events in 19% of patients, especially rash and fatigue, tolerability remains acceptable.

Author contributions: Pasquale Rescigno had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Santoni, Büttner.
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Analysis and interpretation of data: Santoni, Büttner, Rescigno, Fiala.
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Appendix A. Supplementary data

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