



European Association of Urology



Original articles

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

Matteo Santoni^{a,†}, Thomas Büttner^{b,†}, Pasquale Rescigno^{c,*}, Ondrej Fiala^{d,e}, Nicolò Cavasin^f, Umberto Basso^f, Tarek Taha^g, Francesco Massari^{h,i}, Zin W. Myint^j, Luigi Formisano^k, Luca Galli^l, Sarah Scagliarini^m, Marc R. Matranaⁿ, Gaetano Facchini^o, Aristotelis Bamias^p, Carlo Messina^q, Francesca Zacchi^{r,s}, Ray Kopp Manneh^t, Giandomenico Roviello^u, Daniele Santini^v, Alexandr Poprach^w, Jiri Navratil^w, Michal Uher^w, Fabio Calabrò^x, Erin Pierce^m, Rossana Berardi^y, Gaetano Aurilio^z, Roubini Zakopoulou^o, Alessandro Rizzo^{aa}, Jawaher Ansari^{bb}, Mimma Rizzo^{cc}, Renato Bissoni^{dd}, Veronica Mollica^h, Lorena Incorvaia^{ee}, Gianpaolo Spinelli^{ff}, Xue Yan Jiang^{gg}, Robert Adam Chandler^{gg}, Francesco Grillone^{hh}, Franco Morelliⁱⁱ, Sebastiano Buti^{ij,kk}, Fernando C. Maluf^{ll,mm}, Fernando Sabino Marques Monteiro^{nn,oo}, Nicola Battelli^a, Camillo Porta^{pp}, Orazio Caffo^{qq,‡}, Andrey Soares^{oo,ll,‡}

^a Medical Oncology Unit, Macerata Hospital, Macerata, Italy; ^b Department of Urology, University Hospital Bonn, Bonn, Germany; ^c Translational and Clinical Research Institute, Centre for Cancer, Newcastle University, Newcastle upon Tyne, UK; ^d Department of Oncology and Radiotherapeutics, Faculty of Medicine, University Hospital in Pilsen, Charles University, Pilsen, Czechia; ^e Biomedical Center, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czechia; ^f Medical Oncology 1 Unit, Department of Oncology, Istituto Oncologico Veneto IRCCS, Padova, Italy; ^g Royal Marsden NHS Foundation Trust, London, UK; ^h Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; ⁱ Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; ^j Division of Medical Oncology, Department of Internal Medicine, Markey Cancer Center, University of Kentucky, Lexington, KY, USA; ^k Department of Medicine and Surgery, Federico II University, Naples, Italy; ^l Medical Oncology Unit 2, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; ^m UOC di Oncologia, Azienda Ospedaliera di Rilievo Nazionale Cardarelli di Napoli, Naples, Italy; ⁿ Department of Internal Medicine, Hematology/Oncology, Ochsner Medical Center, New Orleans, LA, USA; ^o Oncology Unit, S. Maria Delle Grazie Hospital, Pozzuoli, Naples, Italy; ^p 2nd Propaedeutic Department of Internal Medicine, ATTIKON University Hospital, National and Kapodistrian University of Athens, Athens, Greece; ^q Oncology Unit, ARNAS Civico, Palermo, Italy; ^r Section of Biomedicine Innovation-Oncology, University of Verona, Verona, Italy; ^s Section of Oncology, Department of Medicine, University of Verona, Verona University Hospital, Verona, Italy; ^t Clinical Oncology, Sociedad de Oncología y Hematología del Cesar, Valledupar, Colombia; ^u Department of Health Sciences, Section of Clinical Pharmacology and Oncology, University of Florence, Florence, Italy; ^v Division of Medical Oncology A, Policlinico Umberto 1, Rome, Italy; ^w Masaryk Memorial Cancer Institute, Faculty of Medicine, Masaryk University, Brno, Czechia; ^x Medical Oncology 1, IRCCS Regina Elena National Cancer Institute, Rome, Italy; ^y Clinica Oncologica e Centro Regionale di Genetica Oncologica, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italy; ^z Division of Cancer Prevention and Genetics, IRCCS European Institute of Oncology, Milan, Italy; ^{aa} IRCCS Istituto Tumori Giovanni Paolo II, Bari, Italy; ^{bb} Medical Oncology Department, Tawam Hospital, Al Ain, United Arab Emirates; ^{cc} Medical Oncology Unit, Azienda Ospedaliera Universitaria Consorziale Policlinico di Bari, Bari, Italy; ^{dd} UOC Oncologia Medica, Ospedale A. Murri, Fermo, Italy; ^{ee} Department of Precision Medicine in Medical, Surgical and Critical Care, Section of Medical Oncology, University of Palermo, Palermo, Italy; ^{ff} UOC Oncologia Territoriale Ausl Latina, Aprilia, Italy; ^{gg} Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne, UK; ^{hh} Unità Operativa di Oncologia Presidio Pugliese-Ciaccio, Azienda Ospedaliera Universitaria Renato Dulbecco, Catanzaro, Italy; ⁱⁱ Medical Oncology Unit, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia, Italy; ^{jj} Department of Medicine and Surgery, University of Parma, Parma, Italy; ^{kk} Medical Oncology Unit, University Hospital of Parma, Parma, Italy; ^{ll} Hospital Israelita Albert Einstein, São Paulo, Brazil; ^{mm} Hospital Beneficência Portuguesa, São Paulo, Brazil; ⁿⁿ Hospital Siro-Libanês, Brasília, Brazil; ^{oo} Latin American Cooperative Oncology Group, Porto Alegre, Brazil; ^{pp} Interdisciplinary Department of Medicine, Aldo Moro University of Bari, Division of Medical Oncology, AOU Consorziale Policlinico di Bari, Bari, Italy; ^{qq} Medical Oncology, Santa Chiara Hospital, APSS Trento, Trento, Italy

† These authors contributed equally to this work.

‡ Joint senior authors.

* Corresponding author. Newcastle University Centre for Cancer, Translational and Clinical Research Institute, Paul O'Gorman Building, Framlington Place, Newcastle upon Tyne NE2 4HH, UK. Tel. +44 191 2336161.

E-mail address: pasquale.rescigno@newcastle.ac.uk (P. Rescigno).

Article info

Article history:

Received 2 October 2024
Received in Revised form
23 October 2024
Accepted 5 November 2024
Available online 29 November
2024

Associate Editor:

Elena Castro

Keywords:

Apalutamide
ARON-3 trial
Androgen receptor pathway
inhibitor
Castration-sensitive prostate
cancer
Hormone sensitive
Prostate cancer

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. PSA₉₀ was defined as a prostate-specific antigen decline of $\geq 90\%$ 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. PSA₉₀ was experienced by 461 patients (87%) and PSA_{0.2} by 368 (69%). Median OS was significantly longer for patients with PSA₉₀ 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.

© 2024 The Authors. Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

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]. Accord-

ingly, 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 ($\sim 8.0\%$) [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.

2. Patients and methods

2.1. Study design and population

We retrospectively analyzed clinical data for patients diagnosed at age ≥ 18 yr with mCSPC 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.

PSA₉₀ was defined as a $\geq 90\%$ 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 multi-variable 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 PSA₉₀ response was observed in 461 patients (87%). The median time to PSA₉₀ was 5.0 mo (95% CI 4.6–22.1). PSA₉₀ 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 PSA₉₀ response ($p < 0.001$; [Fig. 2](#)). The 2-yr OS rate was

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 PSA₉₀ subgroup, in contrast to 70% for the groups without a PSA₉₀ response ($p < 0.001$). There were no significant differences in median OS among the subgroups achieving PSA₉₀ 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 PSA₉₀ response ($p < 0.001$; [Supplementary Fig. 2](#)), with a 2-yr OS rate of 95% in the PSA₉₀ subgroup and 71% in the group without a PSA₉₀ 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, PSA₉₀, 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 PSA₉₀ rate of 87%, our findings confirm previous reports of 66–68% for PSA_{0.2} and 68–92% for PSA₉₀ [9–12,22]. As in TITAN, both PSA response parameters

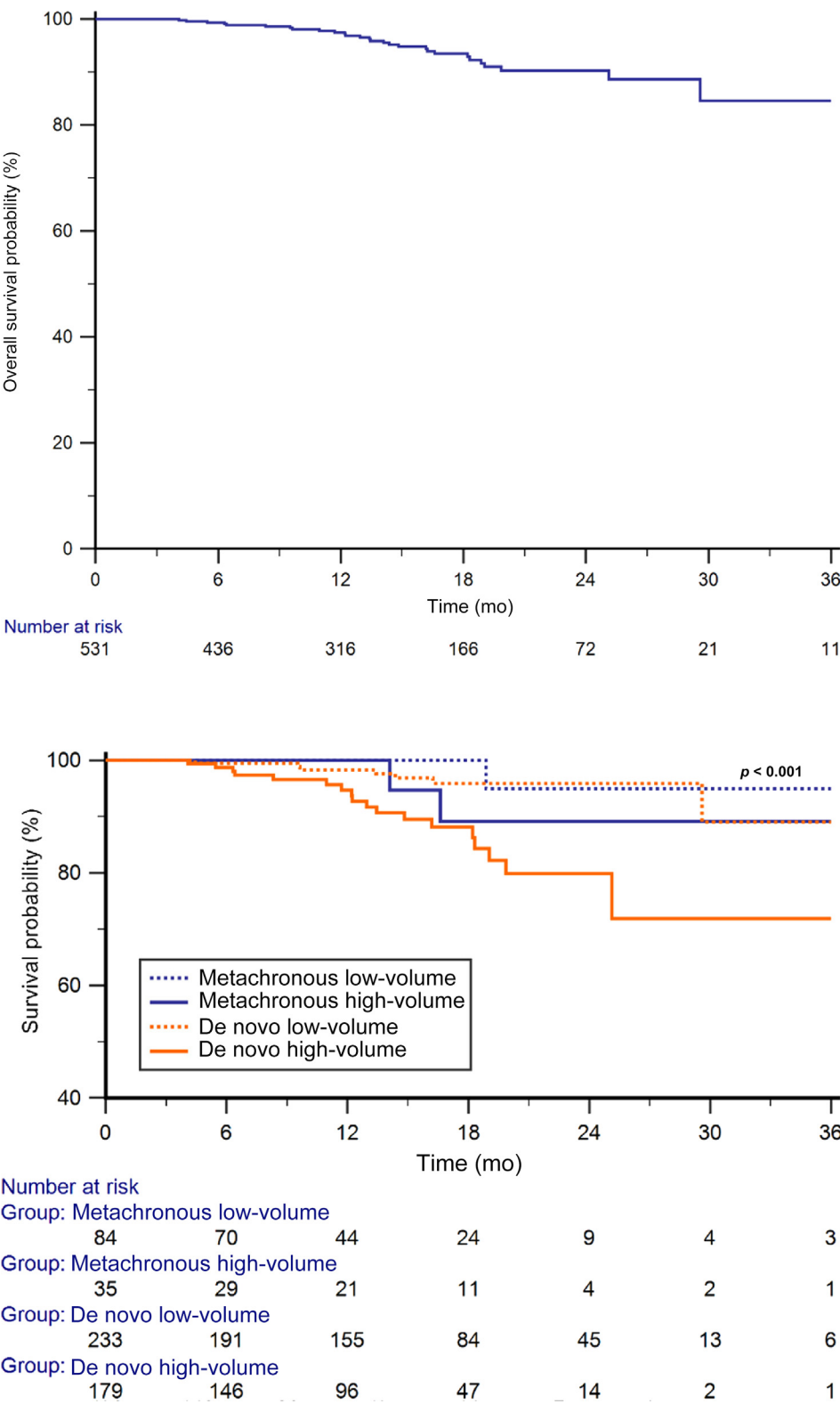


Fig. 1 – Overall survival in the study population stratified by disease volume (high vs low) and metastatic status (metachronous vs de novo).

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

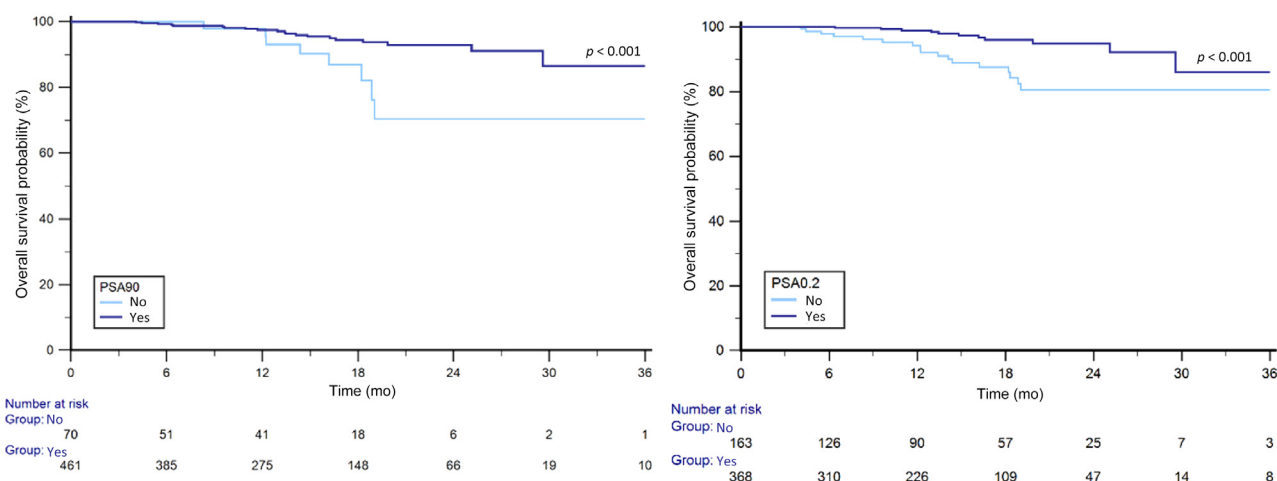


Fig. 2 – Overall survival for the groups with and without PSA₉₀ and PSA_{0.2} responses. PSA = prostate-specific antigen; PSA₉₀ = ≥90% PSA decline from baseline; PSA_{0.2} = PSA response to ≤0.2 ng/ml.

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 (0.14–0.73)	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; PSA₉₀ = ≥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 multi-center 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.

Acquisition of data: Cavašin, Basso, Taha, Formisano, Galli, Scagliarini, Messina, Zacchi, Kopp Manneh, Roviello, Pierce, Berardi, Aurilio, Zakopoulou, A. Rizzo, Ansari, Navratil, Uher, Chandler, Maluf, M. Rizzo, Bisonni, Mollica, Incorvaia, Spinelli, Jiang, Grillone, Morelli.

Analysis and interpretation of data: Santoni, Büttner, Rescigno, Fiala.

Drafting of the manuscript: Santoni, Büttner, Rescigno, Fiala, Massari, Myint, Matrana, Facchini, Bamias, Santini, Poprach, Calabrò, Buti, Marques Monteiro, Battelli, Porta, Caffo, Soares.

Critical revision of the manuscript for important intellectual content: Santoni, Büttner, Rescigno.

Statistical analysis: Santoni, Büttner.

Obtaining funding: None.

Administrative, technical, or material support: Rescigno.

Supervision: Caffo, Soares.

Other: None.

Financial disclosures: Pasquale Rescigno certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Aristotelis Bamias reports honoraria, advisory fee, or research support from Pfizer, BMS, AstraZeneca, MSD, Roche, Janssen, Ipsen, Bayer, and Merck. Rossan Bernardi received honoraria for advisory boards from Astra Zeneca, Bayer, Boehringer Ingelheim, Eisai, Gilead, Lilly, Menarini, Merck; as Invited Speaker from Incyte; and Institutional funding from Astra Zeneca, Pfizer, Roche. Sebastiano Buti reports honoraria for speaker and advisory roles from BMS, Pfizer, MSD, Ipsen, Roche, Eli Lilly, AstraZeneca, Pierre-Fabre, Novartis, Merck, Gentili, and Astellas. Thomas Büttner reports speaker honoraria from Astellas and travel fees from Ipsen and MSD. Ondrej Fiala reports honoraria from Novartis, Janssen, Merck, BMS, MSD, Pierre Fabre, and Pfizer for consultations and lectures unrelated to this project. Lorena Incorvaia reports honoraria from BMS and Ipsen outside the submitted work. Gaetano Facchini reports research support and/or honoraria from Astellas, Janssen, Ipsen, and AstraZeneca outside the submitted work. Francesco Grillone reports honoraria from Merck, Astellas, Bayer, Ipsen, MSD, and Pfizer outside the submitted work. Francesco Massari reports research support and/or honoraria from Astellas, BMS, Janssen, Ipsen, MSD, and Pfizer outside the submitted work. Carlo Messina reports speaker fees from Astellas, Janssen, Bayer, and Ipsen; advisory and consulting fees from Janssen, Bayer, and Ipsen; and travel grants from Janssen, Bayer, and Ipsen. Fernando Sabino Marques Monteiro reports research support from Janssen, Merck Sharp & Dohme, and honoraria from Janssen, Ipsen, Bristol-Myers Squibb, and Merck Sharp & Dohme. Zin W. Myint reports research support from Merck outside the submitted work. Alexandr Poprach reports payments or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from BMS, Ipsen, Roche, Astellas, Merck, Eisai, MSD, Novartis, and Pfizer outside the submitted work. Camillo Porta reports honoraria from Angelini Pharma, AstraZeneca, BMS, Eisai, Exelixis, Ipsen, Merck, and MSD, and a protocol steering committee role for BMS, Eisai, and MSD. Pasquale Rescigno reports payments or honoraria for advisory board roles, presentations, speaker bureaus, manuscript writing, educational events, or travel support from AstraZeneca, Janssen, Pfizer, Merck, MSD Italy, Bayer, and Ipsen outside the submitted work. Mimma Rizzo reports honoraria for a speaker/consultant role from MSD, AstraZeneca, Bristol-Myers Squibb, Gilead, Janssen, and Merck Serono outside the submitted work. Daniele Santini received honoraria as Speaker/advisory for MSD, BMS, AstraZeneca, Janssen, Astellas, Pfizer, Novartis, Adium, Ipsen, Janssen, Bayer, Eli Lilly, Roche, Daiichi Sankyo. Matteo Santoni reports research support and honoraria from Janssen, Bristol-Myers Squibb, Ipsen, MSD, Astellas, A.A.A., and Bayer outside the submitted work. Sarah Scagliarini received honoraria as Speaker/Advisor from Ipsen, MSD, BMS, Eisai, Astellas, Gentili, MERCK, J&J outside the submitted work. Andrey Soares reports honoraria from Janssen, Pfizer, Bayer, AstraZeneca, Astellas Pharma, Merck Serono, Sanofi, Ipsen, and Adium; a consulting or advisory role for Astellas Pharma, Janssen, Roche, Bayer, AstraZeneca, MSD, Bristol-Myers Squibb, Adium, Ipsen, Pfizer, and Novartis; institutional research funding from Bristol-Myers Squibb, Astellas, and AstraZeneca; travel and accommodation expenses from Bayer, Janssen, Ipsen, Adium, MSD, and Merck Serono; and ownership of Brazilian Information Oncology

(BIO), all outside the submitted work. Gian Paolo Spinelli served as Speaker/advisory for BMS, Janssen, Novartis, Roche. Roubini Zakopoulou receive funding for clinical research from MSD, BMS, Ipsen; and Speaker/advisory from MSD, BMS, AstraZeneca, Janssen, Astellas, Ipsen, Janssen, Bayer. The remaining authors have nothing to disclose.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euo.2024.11.005>.

References

- [1] Schaeffer EM, Srinivas S, Adra N, et al. Prostate cancer, version 4.2023, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw* 2023;21:1067–96.
- [2] Parker C, Castro E, Fizazi K, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020;31:1119–34.
- [3] Merseburger AS, Agarwal N, Bhaumik A, et al. Apalutamide plus androgen deprivation therapy in clinical subgroups of patients with metastatic castration-sensitive prostate cancer: a subgroup analysis of the randomised clinical TITAN study. *Eur J Cancer* 2023;193:113290. <https://doi.org/10.1016/j.ejca.2023.113290>.
- [4] Clegg NJ, Wongvipat J, Joseph JD, et al. ARN-509: a novel antiandrogen for prostate cancer treatment. *Cancer Res* 2012;72:1494–503. <https://doi.org/10.1158/0008-5472.Can-11-3948>.
- [5] Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2019;381:13–24. <https://doi.org/10.1056/NEJMoa1903307>.
- [6] Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. *J Clin Oncol* 2021;39:2294–303. <https://doi.org/10.1200/jco.20.03488>.
- [7] European Society of Medical Oncology. EMA recommends extension of therapeutic indications for apalutamide. Press release; December 17, 2019. <https://www.esmo.org/oncology-news/ema-recommends-extension-of-therapeutic-indications-for-apalutamide>.
- [8] US Food and Drug Administration. FDA approves apalutamide for metastatic castration-sensitive prostate cancer. Press release; September 17, 2019. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-apalutamide-metastatic-castration-sensitive-prostate-cancer>.
- [9] Lowentritt B, Pilon D, Khilfeh I, et al. Attainment of early, deep prostate-specific antigen response in metastatic castration-sensitive prostate cancer: a comparison of patients initiated on apalutamide or enzalutamide. *Urol Oncol* 2023;41:253.e1–e9. <https://doi.org/10.1016/j.urolonc.2023.03.003>.
- [10] Lowentritt B, Pilon D, Waters D, et al. Comparison of prostate-specific antigen response in patients with metastatic castration-sensitive prostate cancer initiated on apalutamide or abiraterone acetate: a retrospective cohort study. *Urol Oncol* 2023;41:252.e19–. <https://doi.org/10.1016/j.urolonc.2023.03.013>.
- [11] Tohi Y, Kato T, Kobayashi K, et al. Real-world prostate-specific antigen response and progression to castration-resistant prostate cancer among men with metastatic castration-sensitive prostate cancer treated with apalutamide: a multi-institutional study in the Chu-shikoku Japan Urological Consortium. *Jpn J Clin Oncol* 2024;54:167–74. <https://doi.org/10.1093/jjco/hyad143>.
- [12] Chowdhury S, Bjartell A, Agarwal N, et al. Deep, rapid, and durable prostate-specific antigen decline with apalutamide plus androgen deprivation therapy is associated with longer survival and improved clinical outcomes in TITAN patients with metastatic castration-sensitive prostate cancer. *Ann Oncol* 2023;34:477–85. <https://doi.org/10.1016/j.annonc.2023.02.009>.
- [13] Agarwal N, McQuarrie K, Bjartell A, et al. Health-related quality of life after apalutamide treatment in patients with metastatic

- castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study. *Lancet Oncol* 2019;20:1518–30. [https://doi.org/10.1016/s1470-2045\(19\)30620-5](https://doi.org/10.1016/s1470-2045(19)30620-5).
- [14] Mori K, Mostafaei H, Sari Motlagh R, et al. Systemic therapies for metastatic hormone-sensitive prostate cancer: network meta-analysis. *BJU Int* 2022;129:423–33. <https://doi.org/10.1111/bju.15507>.
- [15] Santoni M, Massari F, Rizzo A, et al. Apalutamide or enzalutamide in castration-sensitive prostate cancer: a number needed to treat analysis. *Tumori J* 2022;109:157–63. <https://doi.org/10.1177/03008916221090323>.
- [16] Dolan RD, Daly L, Sim WMJ, et al. Comparison of the prognostic value of ECOG-PS, mGPS and BMI/WL: implications for a clinically important framework in the assessment and treatment of advanced cancer. *Clin Nutr* 2020;39:2889–95. <https://doi.org/10.1016/j.clnu.2019.12.024>.
- [17] Assayag J, Kim C, Chu H, Webster J. The prognostic value of Eastern Cooperative Oncology Group performance status on overall survival among patients with metastatic prostate cancer: a systematic review and meta-analysis. *Front Oncol* 2023;13:1194718. <https://doi.org/10.3389/fonc.2023.1194718>.
- [18] Finianos A, Gupta K, Clark B, Simmens SJ, Aragon-Ching JB. Characterization of differences between prostate cancer patients presenting with de novo versus primary progressive metastatic disease. *Clin Genitourin Cancer* 2018;16:85–9. <https://doi.org/10.1016/j.clgc.2017.08.006>.
- [19] Shiota M, Terada N, Saito T, et al. Differential prognostic factors in low- and high-burden de novo metastatic hormone-sensitive prostate cancer patients. *Cancer Sci* 2021;112:1524–33. <https://doi.org/10.1111/cas.14722>.
- [20] Hoeh B, Garcia CC, Wenzel M, et al. Triplet or doublet therapy in metastatic hormone-sensitive prostate cancer: updated network meta-analysis stratified by disease volume. *Eur Urol Focus* 2023;9:838–42. <https://doi.org/10.1016/j.euf.2023.03.024>.
- [21] Sathianathan NJ, Pan HYC, Lawrentschuk N, et al. Emergence of triplet therapy for metastatic castration-sensitive prostate cancer: an updated systematic review and network meta-analysis. *Urol Oncol* 2023;41:233–9. <https://doi.org/10.1016/j.urolonc.2022.10.016>.
- [22] Sánchez JC, Picola N, Rodriguez-Vida A, et al. Apalutamide for prostate cancer: Multicentre and multidisciplinary real-world study of 227 patients. *Cancer Med* 2023;12:21969–77. <https://doi.org/10.1002/cam4.6769>.
- [23] Yang Z, Shao Y, Huang H, Liu Y, Wang Z, Wang Y. Real-world analysis of apalutamide-associated skin rash in Chinese patients with prostate cancer. *World J Urol* 2024;42:171. <https://doi.org/10.1007/s00345-024-04880-y>.