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Non-Metastatic Castration-Resistant Prostate Cancer Treated with Androgen Receptor Axis Targeting Agents – French Trends

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1. Abstract

1.1. Background: This study describes the real-world frequency, management and resource use of adverse events (AEs) of special interest in non-metastatic castration-resistant prostate cancer (nmCRPC) patients receiving androgen receptor axis targeting agents (ARATs), in France.

1.2. Methods: This was a retrospective chart review (January 1 to December 31, 2018).

1.3. Results: Of 270 patients, 59.3% had ≥1 AE. with fatigue/asthenia and hot flush most commonly reported. Of the cohort experiencing at least 1 AE, 18.5% received treatment for their AEs, 10.6% discontinued therapy, 4.2% had a hospitalization, and 3.2% had dose reductions.

1.4. Conclusion: More than half of nmCRPC patients treated with the ARATs, bicalutamide, abiraterone, apalutamide, or enzalutamide experienced AEs and a substantial proportion required management and incurred additional healthcare resource use.

2. Introduction

An estimated 64,955 new cases of prostate cancer (PC) were diagnosed in France in 2018, making it the most common cancer in men in this country [1]. In addition, 228,420 prevalent cases were estimated in France that year, and over 9,000 deaths occurred due to the disease. Non-metastatic castration-resistant prostate cancer (nmCRPC) is a distinct clinical state within the PC disease spectrum in men receiving androgen deprivation therapy who develop rising prostate-specific antigen (PSA) levels with castrate levels of serum testosterone but without evidence of detectable metastatic disease on imaging tests [2]. Clinically meaningful goals of treating nmCRPC patients are to delay metastatic disease and mortality while minimizing AEs and their impact on patients' daily lives, as well as avoiding or minimizing downstream healthcare resource utilization (HCRU) [3].

Treatment patterns for nmCRPC in France were last described in 2015-2017 [4]. A study conducted with real-world data found that nearly a quarter of patients received anti-androgens (ARATs; bicalutamide, enzalutamide, apalutamide) as first-line therapy after an nmCRPC diagnosis. Starting 2018 onwards, enzalutamide (September 2018) and apalutamide (January 2019), along with darolutamide (March 2020), have received regulatory approval for high-risk nmCRPC in Europe; these agents are now included in the guidelines from the European Society for Medical Oncology for the treatment of nmCRPC patients at high-risk of disease progression [5]. An Autorisation Temporaire d'Utilisation (ATU) de cohorte was in place for apalutamide in high-risk nmCRPC from February 2018 until February 2019 [6]; i.e., during the period in which data from physician charts were extracted for the current study (see Methods). Reimbursement in France for enzalutamide and apalutamide came about in 2020, and for darolutamide, in 2021. Thus, during the period covered by this study, enzalutamide had European Medicines Agency marketing authorization for high-risk nmCRPC without an ATU de cohorte for nmCRPC in place, whereas apalutamide was both authorized for use and covered under an ATU de cohort (from Feb 2018). Darolutamide, on the other hand, was neither approved nor enjoyed an ATU de cohort during this time frame, and hence, was not included in the current study. Abiraterone is not indicated for nmCRPC.The efficacy and adverse event (AE) profiles of newer ARATs have been described in their respective pivotal clinical trials [7-9]. Apalutamide, enzalutamide, and bicalutamide cross the blood-brain barrier and can potentially be associated with, or contribute to, some central nervous system (CNS) AEs [10]. Abiraterone has primarily been studied in patients with metastatic CRPC, with an AE profile characterized by mineralocorticoid excess (e.g., hypertension, hypokalemia, fluid retention), adrenocortical insufficiency, and hepatotoxicity [11, 12]. In addition, abiraterone use increased the risk of myocardial infarction, stroke, and arrythmias in prostate cancer patients which is consistent with data from clinical trials [13,14]

Patients with nmCRPC, although generally asymptomatic, can have multiple comorbidities and may take numerous medications, and as a result may be at elevated risk for falls and fall-related injuries [15]. Therefore, safety considerations are of particular importance for treatment selection in this patient population. Previous studies have shown that patients and their caregivers assign a high degree of importance to specific AEs of interest in nmCRPC, notably fatigue, falls, fractures, and cognitive impairment [16]. In the present study, we carried out a detailed medical chart-based review of a French cohort of non-metastatic CRPC (nmCRPC) patients treated with androgen receptor axis targeting agents which includes the ARATs, bicalutamide, apalutamide, enzalutamide as well as the androgen biosynthesis inhibitor, abiraterone. We undertook this study to better understand the frequency, management and resource use related to adverse events of special interest among nmCRPC, for French patients receiving ARATs.

3. Materials & Methods

3.1. Data Source

This was a two-phase, retrospective, multi-site medical chart review study conducted in France, using data collected from patient medical records. Physicians identified patients who were diagnosed with nmCRPC and treated with ARATs, and these physicians recorded any AEs experienced in a patient log. Detailed chart data were then collected for a randomly selected subset of patients who experienced at least one AE; the data included patient demographic and clinical characteristics, actions taken to manage AEs, and resulting HCRU. An ethics application for the study was filed with the Commission Nationale de l'Informatique et des Libertés (CNIL) and the Haut Conseil de l'Evaluation de la Recherche et de l'Enseignement Supérieur (HCERES) in January, 2020, prior to data collection.

3.2. Physician Investigators

Medical oncologists and urologists treating nmCRPC were randomly selected and recruited to serve as study investigators and were responsible for patient selection and data collection. Investigators were required to have managed and/or treated at least five patients with nmCRPC, have at least one patient prescribed one of the study drugs of interest; moreover, investigators were required not to be currently a consultant or investigator for a pharmaceutical company involved in CRPC treatment. In addition, physicians were required to attest that they were able to access patients' complete medical records and could systemically identify and record AEs in those records. Median follow-up time was 18 months.

3.3. Study Population

The study included adult patients diagnosed with nmCRPC who initiated treatment with abiraterone, bicalutamide, apalutamide, or enzalutamide between January 1, 2018 and December 31, 2018. Patients were required to have at least six months of follow-up from initiation of ARATs. Patients were followed until the date of last visit, death, or the end of the data collection period, whichever occurred first. Patients with a history of metastasis before CRPC diagnosis, current diagnosis or history of other primary cancers, or who were enrolled in an nmCRPC-related clinical trial, were excluded. Given the lack of regulatory approval and reimbursement, as well as limited use of darolutamide during the study period, it was not included in the present analysis.

3.4. Data Collection

AEs experienced by nmCRPC patients receiving ARATs were recorded using patient logs. AEs of special interest included in this analysis were aligned with the pivotal clinical trials of apalutamide and enzalutamide in nmCRPC, and of abiraterone in mCRPC (no phase 3 trials with abiraterone in nmCRPC have been conducted), and included the following: hypertension, cardiovascular events,

mental impairment disorder, hepatic impairment, neutropenia, seizure/convulsion, fracture, dizziness/vertigo, hypothyroidism, fatigue/asthenia, bone fracture, falls, rash, weight decrease, weight gain, cerebral ischemia, heart failure, fluid retention/peripheral edema, hypokalemia, hyperglycemia, and posterior reversible encephalopathy syndrome [17-19]; of note, no AEs of special interest were delineated in a pivotal trial of bicalutamide [20]. Within the subset of patients who had at least one reported AE, detailed data from randomly selected patient charts were collected. Patient demographics and data related to: 1) clinical characteristics; 2) ARAT treatment history; 3) type and severity of AE as judged by the treating physician; 4) whether treatment for the AE was required (yes or no); 5) actions taken by the physician regarding AE treatment (dose change, therapy discontinuation, or none); and 6) AE-related HCRU (including hospitalization, emergency department visits, outpatient/clinic visits, diagnostic labs, and imaging) were collected from time of nmCRPC diagnosis to the end of follow-up. Only AEs occurring in patients who continued to be non-metastatic were included; AEs occurring in the metastatic setting were excluded.

3.5. Statistical Analysis

As this is a descriptive study, a sample size of approximately 100 patients was targeted to provide an adequate representative sample for final analysis. The proportion of patients experiencing AEs was calculated among all included nmCRPC patients treated with ARATs. Categorical outcomes were summarized using the number and percentage in each category; confidence intervals around the percentage of patients experiencing adverse events were calculated using the Wilson score method. Continuous outcomes were summarized using mean, standard deviation (SD), and median. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

4. Results

Thirty-five physicians (18 medical oncologists, 17 urologists/urologist-oncologists) were recruited as study investigators. A total of 270 nmCRPC patients who initiated treatment with an ARAT were enrolled into the study. Among these, 160 patients experienced at least one AE, and 107 of these patients were randomly selected for further and more detailed characterization (Figure 1).

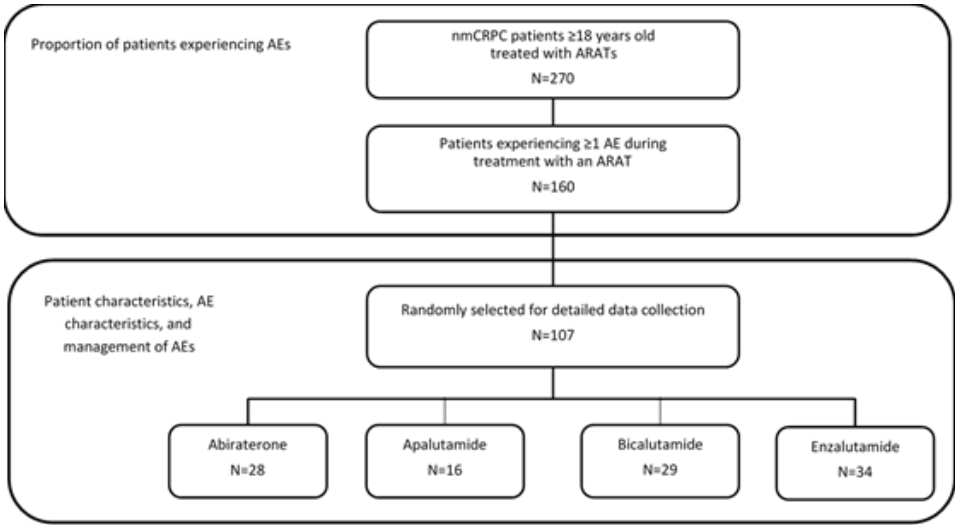

Figure 1: Distribution of Included Patients

AE, adverse event; ARAT, androgen receptor axis targeting agents; nmCRPC, non-metastatic castration-resistant prostate cancer

4.1. Physician Characteristics

Of the 35 physicians who collected data for the study, approximately half specialized in medical oncology (51.4%). The median number of total PC and nmCRPC patients managed/treated by each physician was 300 and 40, respectively. A large majority of physicians (94%) reported using PSA to monitor patients with nmCRPC, typically every 3 months, but only half of the physicians reported using PSA-DT as part of their routine management procedure.

4.2. Proportion of Patients Experiencing All-Grade AEs in the Overall Study Cohort

Included in the study were 270 patients (abiraterone, 85; apalutamide, 39; bicalutamide, 73; enzalutamide, 104; 25 patients received multiple therapies). Among the 270 patients, 160 (59.3%) experienced at least one AE. The most common AEs of any nature were fatigue/asthenia, reported in 39.6% of patients overall (abiraterone, 29.4%; apalutamide, 38.5%; bicalutamide, 31.5%; enzalutamide, 44.2%), and hot flush, reported in 18.9% of patients (abiraterone, 9.4%; apalutamide, 5.1%; bicalutamide, 37.0%; enzalutamide, 13.5%). Among the AEs of special interest, fatigue/asthenia was most common, followed by hypertension (overall, 11.5%; abiraterone, 22.4%; apalutamide, 0%; bicalutamide, 2.7%; enzalutamide, 9.6%) and fluid retention/peripheral edema (overall, 4.1%; abiraterone, 5.9%; apalutamide, 0%; bicalutamide, 1.4%; enzalutamide, 4.8%). Point estimates of the frequencies and their confidence intervals are found in Table 1.

Table 1: Proportion of Patients Receiving ARATs Who Experienced AEs

	All Patients	Abiraterone[a]	Apalutamide[a]	Bicalutamide[a]	Enzalutamide[a]
	(N = 270)	(N = 85)	(N = 39)	(N = 73)	(N = 104)
Any AE, proportion (95% CI)	59.3% (53.3%, 65.0%)	55.3% (44.7%, 65.4%)	56.4% (41.0%, 70.7%)	53.4% (42.1%, 64.4%)	52.9% (43.4%, 62.2%)
Adverse events that occurred in ≥5% of patients in any group, proportion (95% CI)					
Hot flush	18.9% (14.7%, 24.0%)	9.4% (4.8%, 17.5%)	5.1% (1.4%, 16.9%)	37.0% (26.8%, 48.5%)	13.5% (8.2%, 21.3%)
Diarrhea	5.9% (3.7%, 9.4%)	12.9% (7.4%, 21.7%)	0.0% (0.0%, 9.0%)	2.7% (0.8%, 9.5%)	2.9% (1.0%, 8.1%)
Nausea	4.1% (2.3%, 7.1%)	5.9% (2.5%, 13.0%)	0.0% (0.0%, 9.0%)	1.4% (0.2%, 7.4%)	4.8% (2.1%, 10.8%)
Adverse events of special interest, proportion (95% CI)[b]					
Fatigue or asthenia	39.6% (34.0%, 45.6%)	29.4% (20.8%, 39.8%)	38.5% (24.9%, 54.1%)	31.5% (22.0%, 42.9%)	44.2% (35.1%, 53.8%)
Hypertension	11.5% (8.2%, 15.8%)	22.4% (14.8%, 32.3%)	0.0% (0.0%, 9.0%)	2.7% (0.8%, 9.5%)	9.6% (5.3%, 16.8%)
Fluid retention/peripheral edema	4.1% (2.3%, 7.1%)	5.9% (2.5%, 13.0%)	0.0% (0.0%, 9.0%)	1.4% (0.2%, 7.4%)	4.8% (2.1%, 10.8%)
Mental impairment disorder[c]	3.0% (1.5%, 5.7%)	1.2% (0.2%, 6.4%)	0.0% (0.0%, 9.0%)	1.4% (0.2%, 7.4%)	5.8% (2.7%, 12.0%)
Seizure/convulsion	2.6% (1.3%, 5.3%)	2.4% (0.6%, 8.2%)	5.1% (1.4%, 16.9%)	2.7% (0.8%, 9.5%)	1.0% (0.2%, 5.2%)
Rash	2.6% (1.3%, 5.3%)	2.4% (0.6%, 8.2%)	5.1% (1.4%, 16.9%)	2.7% (0.8%, 9.5%)	1.0% (0.2%, 5.2%)
Headache	2.6% (1.3%, 5.3%)	1.2% (0.2%, 6.4%)	0.0% (0.0%, 9.0%)	0.0% (0.0%, 5.0%)	5.8% (2.7%, 12.0%)
Hypothyroidism	1.5% (0.6%, 3.7%)	0.0% (0.0%, 4.3%)	10.3% (4.1%, 23.6%)	0.0% (0.0%, 5.0%)	0.0% (0.0%, 3.6%)
Weight decrease	1.5% (0.6%, 3.7%)	0.0% (0.0%, 4.3%)	0.0% (0.0%, 9.0%)	0.0% (0.0%, 5.0%)	3.8% (1.5%, 9.5%)
Fracture	1.5% (0.6%, 3.7%)	0.0% (0.0%, 4.3%)	0.0% (0.0%, 9.0%)	1.4% (0.2%, 7.4%)	2.9% (1.0%, 8.1%)
Cardiovascular events	1.1% (0.4%, 3.2%)	0.0% (0.0%, 4.3%)	0.0% (0.0%, 9.0%)	1.4% (0.2%, 7.4%)	1.9% (0.5%, 6.7%)
Fall	0.7% (0.2%, 2.7%)	0.0% (0.0%, 4.3%)	5.1% (1.4%, 16.9%)	0.0% (0.0%, 5.0%)	0.0% (0.0%, 3.6%)
Hepatic impairment	0.4% (0.1%, 2.1%)	1.2% (0.2%, 6.4%)	0.0% (0.0%, 9.0%)	0.0% (0.0%, 5.0%)	0.0% (0.0%, 3.6%)

AE, adverse event; ARAT, androgen receptor axis targeting agents; CI, confidence interval

[a] 25 patients received more than 1 therapy (6 patients received 3 therapies). The specific AEs have been attributed to the respective therapy cohort, and therefore the Ns add to >100%.

[b] No patients experienced neutropenia, cerebral ischemia, heart failure, hypokalemia, hyperglycemia, weight gain, or posterior reversible encephalopathy syndrome.

[c] Included cognitive and attention disorders, memory impairment, mental and cognitive changes, and mental impairment disorder.

4.3. Patient and Treatment Characteristics in the Randomly Selected Subset Population

Detailed chart reviews were conducted in a 107-patient subset randomly selected from the 160 patients experiencing at least one AE to better understand initiation patterns, AE characteristics, and actions taken to address any relevant AEs. Within this subset, 28 patients received abiraterone, 29 received bicalutamide, 16 received apalutamide, and 34 received enzalutamide. The median duration of follow-up from ARAT initiation to discontinuation or loss to follow-up was 1.5 years (Q1-Q3, 1.3-1.8 years). Characteristics of the 107-patient subset who experienced at least one AE are shown in Table 2. Median age at the time of data collection across all treatments was 74 years (range, 54 to 90 years); 54% were past or current smokers, and 90% had an Eastern Cooperative Oncology Group (ECOG) score of 0-1 at the time of nmCRPC diagnosis. Among all patients, the 2 most common physician-reported rationales for initiating treatment with ARATs, were to prevent/delay metastasis (50.5%) and to counter a PSA-DT less than 10 months (47.7%). A PSA-DT less than 10 months was the most common rationale for treatment initiation with abiraterone and bicalutamide users (45.7%), while prevention/delay of metastasis was the most common rationale for treatment initiation among those treated with apalutamide and enzalutamide (60.0%).

Median duration of ARAT therapy from initiation to discontinuation for any reason was 16 months (Q1-Q3, 8.9-19.1): 17 months (6.6-19.8) for abiraterone and bicalutamide and 15 months (10.6-17.3) for apalutamide and enzalutamide. During the study follow-up period (median, 1.5 years), 31.8% of nmCRPC patients progressed to metastasis (abiraterone/bicalutamide, 42.1%; apalutamide/enzalutamide, 20.0%).

4.4. AE Characteristics, Actions Taken to Address AEs, and Associated HCRU in the Subset Population

A total of 216 AEs were reported in the 107-patient subset. Eight AEs (3.7%) were grade 3, with 6.5% of patients experiencing at least one grade 3 AE. No grade 4 or 5 AEs were reported. Grade 3 AEs included fatigue/asthenia (2 patients; 1.9%), fluid overload/peripheral edema (2 patients; 1.9%), fracture (1 patient; 0.9%), hypothyroidism (1 patient; 0.9%), cardiovascular events (1 patient;

0.9%), and hypertension (1 patient; 0.9%).

Of the 216 AEs among the 107-patient subset, 40 (18.5%) AEs reported in 35 patients required treatment (Grade 1, 19.5%; Grade 2, 14.3%; Grade 3, 37.5%; unknown grade, 16.7%) (Figure 2). Other actions taken to manage AEs included discontinuation of anti-androgen therapy (23 AEs [10.6%] in 15 patients), dose reduction (7 AEs [3.2%] in 6 patients), and hospitalization (9 AEs [4.2%] in 8 patients).

AEs requiring hospitalization included fatigue/asthenia, fracture, peripheral edema, hypertension, decreased appetite, and other cardiovascular events, and 62.5% of these AEs were grade 3. Of the 3 patients experiencing cardiovascular events (unspecified), one had a history of coronary artery disease, one had a condition requiring anticoagulation, and one had no relevant comorbidities. Over a quarter of the patients experiencing AEs had at least 1 outpatient visit (including office/clinic visits, lab visits, and imaging visits) for the management of their AEs (Figure 3).

4.5. Other Reasons for ARAT Discontinuation

Sixty-five (60.7%) of the 107 patients (abiraterone, 67.9%; apalutamide, 31.3%; bicalutamide, 72.4%; enzalutamide, 58.8%) discontinued ARAT therapy during the follow-up period. The most common reason for treatment discontinuation was disease progression (32 patients, 30.0%); AEs were the second most common reason, with other reasons for discontinuation being patient choice and completion of planned treatment (Figure 4).

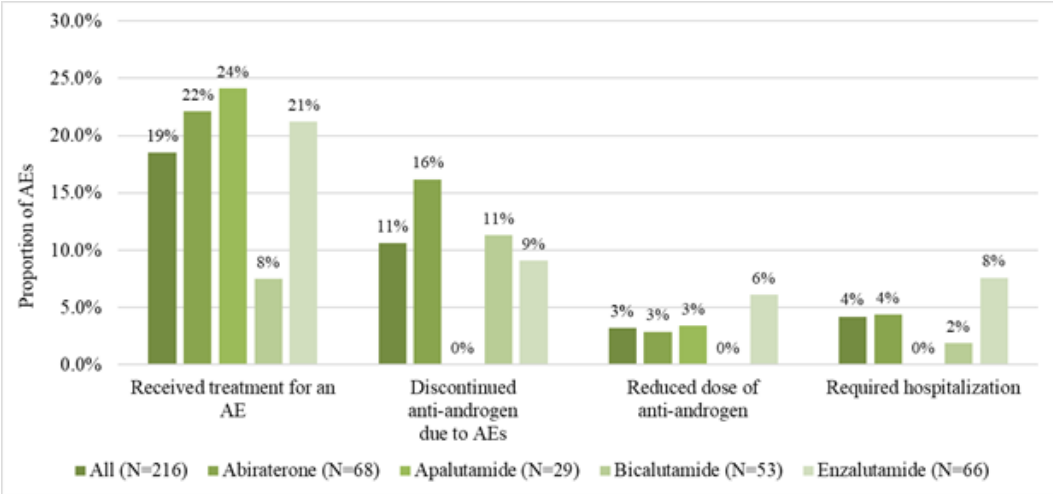

Figure 2: Actions Taken to Address AEs Occurring During ARAT Treatment[a]

AE, adverse event; ARAT, androgen receptor axis targeting agents

[a] Actions taken to address AEs are not mutually exclusive; multiple actions could have been taken.

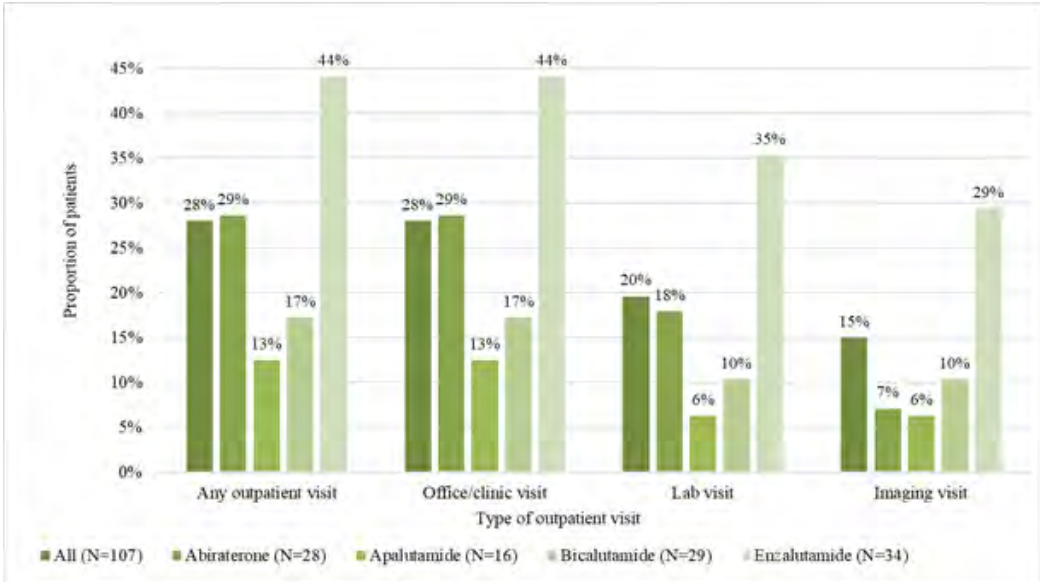

Figure 3: Outpatient Resource Use for AE Management

AE, adverse event

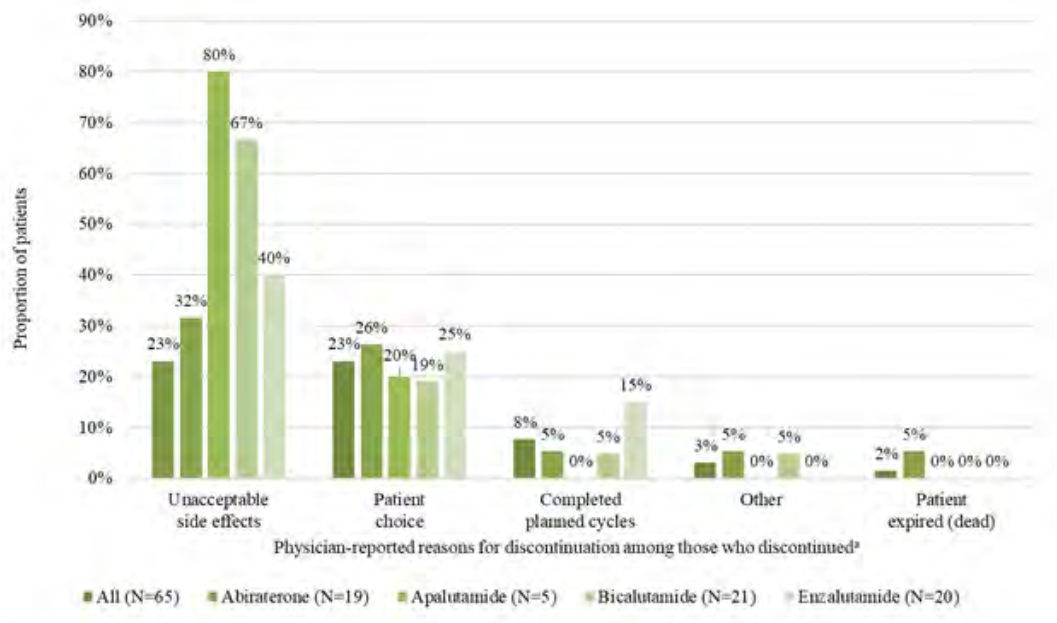

Figure 4: Reasons for Anti-Androgen Discontinuation Other Than Disease Progression

[a] Reasons for discontinuation are not mutually exclusive; multiple reasons could have been and therefore the percentages do not add up to 100%.

Table 2: Patient Demographic and Clinical Characteristics in the 107-Patient Subset

	All Patients (N = 107)	**Abiraterone (N = 28)**	**Apalutamide (N = 16)**	**Bicalutamide (N = 29)**	**Enzalutamide (N = 34)**
Age at most recent visit (years)					
Mean (SD)	73.8 (7.2)	74.5 (7.3)	72.4 (6.5)	75.0 (5.2)	72.8 (8.7)
Median (Q1-Q3)	74.0 (69.0-79.0)	75.0 (71.5 to 79.5)	72.0 (68.5 to 76.5)	75.0 (71.0 to 77.0)	73.0 (67.0 to 81.0)
Body mass index at most recent visit					
N	90	21	14	28	27
Mean (SD)	25.2 (2.2)	24.6 (2.1)	25.4 (2.5)	25.7 (2.3)	25.2 (2.2)
Median (Q1-Q3)	25.3 (23.6- 26.6)	23.8 (23.4 to 26.2)	25.8 (23.3 to 27.1)	25.4 (24.3 to 27.2)	25.3 (23.8 to 26.5)
Charlson Comorbidity Index,[a] N (%)					
0	91 (85.0%)	24 (85.7%)	13 (81.3%)	25 (86.2%)	29 (85.3%)
1	12 (11.2%)	3 (10.7%)	2 (12.5%)	4 (13.8%)	3 (8.8%)
2+	4 (3.7%)	1 (3.6%)	1 (6.3%)	0 (0.0%)	2 (5.9%)
Age at nmCRPC diagnosis (years)					
Mean (SD)	72.7 (7.2)	73.5 (7.4)	71.3 (6.5)	74.0 (5.2)	71.7 (8.7)
Median (Q1-Q3)	73.0 (68.0-78.0)	74.0 (70.5 to 78.0)	70.5 (67.5 to 75.5)	74.0 (70.0 to 76.0)	72.0 (65.0 to 79.0)
ECOG score at nmCRPC diagnosis, N (%)					
0	67 (62.6%)	18 (64.3%)	10 (62.5%)	15 (51.7%)	24 (70.6%)
1	29 (27.1%)	7 (25.0%)	5 (31.3%)	11 (37.9%)	6 (17.6%)
2	11 (10.3%)	3 (10.7%)	1 (6.3%)	3 (10.3%)	4 (11.8%)
Gleason score at nmCRPC diagnosis, N (%)					
6 or lower	4 (3.7%)	2 (7.1%)	0 (0.0%)	0 (0.0%)	2 (5.9%)
7	18 (16.8%)	2 (7.1%)	3 (18.8%)	7 (24.1%)	6 (17.6%)
8 to 10	48 (44.9%)	18 (64.3%)	6 (37.5%)	11 (37.9%)	13 (38.2%)
Unknown	37 (34.6%)	6 (21.4%)	7 (43.8%)	11 (37.9%)	13 (38.2%)
PSA at nmCRPC diagnosis					
N	93	22	16	29	26
Mean (SD)	16.4 (15.2)	16.2 (11.2)	21.2 (24.3)	21.7 (14.2)	7.6 (6.1)
Median (Q1-Q3)	12.0 (6.0-25.0)	10.0 (8.0 to 25.0)	13.9 (5.9 to 28.2)	20.6 (13.0 to 30.0)	5.8 (4.1 to 8.0)

ECOG, Eastern Cooperative Oncology Group; Q1-Q3, range between the first quartile (Q1) and third quartile (Q3); nmCRPC, non-metastatic castrate-resistant prostate cancer; PSA, prostate specific antigen; SD, standard deviation.

[a] Charlson Comorbidity Index was calculated using patient comorbidities present from nmCRPC diagnosis through the end of the study period.

5. Discussion

This is the first real-world study to examine the frequency and burden of AEs among nmCRPC patients in France treated with ARATs using data abstracted from patient charts. When one considers all AE grades, more than half of the treated nmCRPC patients experienced AEs. This study highlights their downstream consequences, with 14% of patients with AEs discontinuing ARAT treatment with a median follow-up time of 18 months, 18.5% requiring treatment, and 4.2% needing hospitalization within a year and half of treatment initiation.

AEs were somewhat less commonly reported in this study compared to the rates reported in apalutamide and enzalutamide clinical trials [8, 9]. This difference is likely due to the protocol-driven management in the clinical trials, i.e., diligent real-time monitoring vs. real-world practice. At a qualitative level, however, the results are consistent with the enzalutamide and apalutamide pivotal trials in that fatigue, hot flush, and hypertension were among the most common AEs reported [8, 9]. AE rates in this study were also comparable to those in a similar study conducted in the United States among 699 patients receiving apalutamide or enzalutamide. In this study, the most common AEs experienced by patients with nmCRPC were fatigue/asthenia (34.3%), hot flush (13.9%), and arthralgia (13.6%) [21]. Caution needs to be exercised to draw inference across different studies, but at a qualitative level there appears to be some consistency amongst the more frequent AEs, lending further credence to our findings. Although comparison between treatments was not an objective of this study, hot flush, hypertension, diarrhea, and peripheral edema appeared to be more common in patients receiving abiraterone, consistent with its known AE profile [11].

This study has several strengths. This is the first real-world study in France to examine the frequency and burden of AEs among an nmCRPC patient population treated with ARATs using data abstracted directly from patient charts. Because data were collected in this way, we were able to evaluate detailed clinical information, including treatments, AE grade, and ECOG and Gleason scores that are not commonly available from other sources (e.g., healthcare claims data). Study investigators identified patients diagnosed with nmCRPC, and thus we were not reliant on algorithms and other methods to rule out metastatic CRPC and potential misclassification.

The limitations of this study should be acknowledged in interpreting its results. As previously discussed, AEs may generally be under-documented in retrospective medical records analysis such as chart reviews. Information collected on the physician profile form, such as patient case-load and practice patterns, are likely to have been estimated by the participating investigators. The patient characteristics, treatment patterns, AEs, and associated HCRU in nmCRPC patients represent the populations and practices of participating physicians/sites and may vary from non-participating sites.

6. Conclusion

This study provides data on the prevalence and impact of AEs in patients with nmCRPC receiving bicalutamide, abiraterone, apalutamide, or enzalutamide in a real-world French clinical practice setting. The study highlights the burden of managing AEs, with 18.5% of AEs requiring treatment, 10.60% resulting in discontinuation of ARAT treatment, and 4.2% requiring hospitalization over an 18-month period. The results are broadly consistent with the AE profiles observed in clinical trials. Importantly, the study highlights the importance of AEs in nmCRPC and the impact on downstream AE management and HCRU associated with those AEs, in a French real world setting. Future studies may provide further insights as the nmCRPC treatment landscape continues to evolve.

7. Summary Points

- An estimated 64,955 new cases of prostate cancer (PC) were diagnosed in France in 2018, making it the most common cancer in French men.
- Non-metastatic castration-resistant PC (nmCRPC) is a distinct clinical state within the PC disease spectrum in men receiving androgen deprivation therapy who develop rising prostate-specific antigen (PSA) levels with castrate levels of serum testosterone but without evidence of detectable metastatic disease on imaging tests
- Clinically meaningful goals of treating nmCRPC patients are to delay metastatic disease and mortality while minimizing AEs and their impact on patients' daily lives, as well as avoiding or minimizing downstream healthcare resource utilization (HCRU)
- The efficacy and adverse event (AE) profiles of newer anti-androgens (ARATs) have been described in their respective pivotal clinical trials, but there is a lack of real-world data showing the AE rates of these agents in patients outside of clinical studies.
- This study helps to fill that gap by characterizing AEs among patients with nmCRPC receiving ARATs (bicalutamide, abiraterone, apalutamide, or enzalutamide) in a real-world French clinical practice setting and describes the management of their respective AEs.
- Thirty-five physicians were recruited as study investigators. And a total of 270 nmCRPC patients who initiated treatment with an ARAT were enrolled into the study.
- Nearly 60% (160 out of 270) nmCPRC experienced at least one AE which highlights the burden of managing AEs, with 18.5% of AEs requiring treatment, 10.6% resulting in discontinuation of ARAT treatment, and 4.2% requiring hospitalization over a median follow-up period of 18-months.

- Broadly consistent with the AE profiles observed in clinical trials, the results of this real-world study of nmCRPC patients provide relevant context to how these agents are used in actual practice in France.
- The study also highlights the importance of AEs in nmCRPC and the impact on downstream HCRU associated with those AEs.

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