PROTOCOL

1. General information[1]

1.1 Title:

Utilization patterns of oral therapies in prostate cancer in Tuscany: a retrospective observational study based on regional administrative databases.

1.2 Protocol version:

2.0 dated 12 june 2026

1.3 Personnel Responsible for Conducting the Study

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1.4 Conflicts of Interest: None to declare.

2. Abstract

Background: Prostate cancer is one of the most common cancers among men worldwide. The introduction of second-generation androgen receptor inhibitors (ARIs) has substantially changed the treatment of prostate cancer across different disease settings. Given their increasing use in clinical practice and the limited availability of real-world evidence on utilization patterns and clinically relevant outcomes, further evaluations based on administrative healthcare data are warranted.

Objectives: The primary objective of this study is to describe the utilization patterns of oral therapies for prostate cancer in Tuscany, with particular focus on abiraterone, apalutamide, enzalutamide, and darolutamide. Secondary objectives are to characterize the demographic and clinical profile of treated patients, describe treatment discontinuation and switching patterns, and evaluate the occurrence of major cardiovascular and other clinically relevant adverse events associated with these therapies.

Methods: This is a retrospective descriptive observational cohort study based on the regional administrative healthcare databases of Tuscany. All residents of Tuscany aged ≥18 years with at least one dispensing of abiraterone, apalutamide, enzalutamide, or darolutamide between 2016 and 2025 will be included. Patients will be classified as first-line users, new users beyond first-line therapy, or prevalent users. Drug utilization patterns will

be described according to calendar year and Regional Healthcare Area. Demographic and clinical characteristics, including comorbidities and concomitant medications, will be evaluated among first-line users and new users beyond first-line therapy. Treatment discontinuation, treatment switching, and clinically relevant adverse events resulting in hospitalization or emergency department visits, including cardiovascular events, acute kidney injury, acute liver injury, and fractures, will be evaluated during follow-up using validated algorithms based on administrative healthcare data.

Results: The study will provide a comprehensive overview of the use of oral therapies for prostate cancer in routine clinical practice in Tuscany. The study will generate real-world evidence on prescribing patterns, patient characteristics, treatment pathways, and clinically relevant safety outcomes, supporting clinicians and regional healthcare decision-makers in optimizing the use of these therapies.

3. Amendments and Updates

Description: Documents all protocol amendments and updates to ensure transparency.

Version date	Version number	Protocol section	Amendment or Update	Reason

4. Rationale and background

Prostate cancer is the second most frequently diagnosed cancer in men and the fifth leading cause of cancer-related death among men worldwide, with approximately 1.47 million new cases and nearly 400,000 deaths estimated in 2022. Despite advances in early diagnosis and treatment options, the global impact of the disease is expected to increase over the coming decades due to population ageing [1]. Following radical treatment for localized disease, biochemical recurrence, generally defined as an increase in prostate-specific antigen (PSA) levels after radical treatment, represents a frequent clinical event. It is estimated that approximately one-third of patients develop biochemical recurrence after local therapy, with rates ranging from 20% to 50% following radical prostatectomy and from 30% to 40% following radiotherapy. Although not all patients with biochemical recurrence experience clinical disease progression, this condition is associated with an increased risk of metastasis and prostate cancer-specific mortality. Longitudinal studies have shown that approximately one-third of patients with biochemical recurrence subsequently develop metastatic disease, often several years after the initial increase in PSA levels [2]. The introduction of second-

generation androgen receptor inhibitors (ARIs), apalutamide (240 mg/day), enzalutamide (160 mg/day), and darolutamide (600 mg twice daily), indicated in combination with androgen deprivation therapy (ADT), has revolutionized the treatment of high-risk non-metastatic prostate cancer (nmCRPC), metastatic hormone-sensitive prostate cancer (mHSPC, also in combination with docetaxel for darolutamide), and metastatic castration-resistant prostate cancer (mCRPC, enzalutamide in the pre- and post-chemotherapy settings). Monitoring of treated patients is intensive during the initial phase (every 4 weeks for the first 3 months to assess tolerability and treatment adherence), and subsequently every 8–12 weeks in clinically stable patients, depending on comorbidities [3–10].

In nmCRPC, the SPARTAN trial demonstrated that apalutamide in combination with ADT achieved a median metastasis-free survival (MFS) of 40.5 months compared with 16.2 months for placebo plus ADT (HR 0.28; 95% CI 0.23–0.35; p<0.001), corresponding to a 72% reduction in the risk of metastasis or death at 24 months [11]. The PROSPER trial showed that enzalutamide in combination with ADT achieved an MFS of 36.6 months compared with 14.7 months in the placebo group (HR 0.29; 95% CI 0.24–0.35; p<0.001) [12], while the ARAMIS trial demonstrated an MFS of 40.4 months for darolutamide in combination with ADT versus 18.4 months in the placebo group (HR 0.41; 95% CI 0.34–0.50; p<0.001) [13].

In mHSPC, the ARCHES trial showed that enzalutamide in combination with ADT reduced the risk of radiographic progression or death by 61% compared with placebo plus ADT (HR 0.39; 95% CI 0.30–0.50; p<0.001) [14]. Trials such as STRIVE, TERRAIN, and PREVAIL further support the efficacy of these agents compared with bicalutamide or placebo in patients with mCRPC [15–17].

From a safety perspective, fatigue, hypertension, falls, and fractures have been reported as common adverse events across all ARIs. In particular, apalutamide is associated with an increased risk of rash and hypothyroidism, enzalutamide with seizures and cardiac ischemia, whereas darolutamide may frequently cause fatigue, fractures, and hepatotoxicity.

Real-world evidence complements findings from clinical trials by extending the assessment of the safety and effectiveness of ARIs to patients with greater clinical complexity. In a study conducted in Finland including 8,369 patients between 2012 and 2023, enzalutamide was the most frequently used agent, with a total expenditure of €453 million for all ARIs during the study period. Furthermore, approximately one-third of patients (n=2,685; 32.1%) received at least two ARIs sequentially, most commonly abiraterone followed by enzalutamide (14.9%) or vice versa (14.5%) [18].

For apalutamide, several studies have documented high treatment persistence and favourable effectiveness outcomes. In particular, treatment persistence exceeding 85% at 12 months has been reported in patients with mCSPC and nmCRPC, and was associated with a one-year metastasis-free survival (MFS) rate of 89.7% [19]. In a cohort of 432 patients with mHSPC treated with apalutamide, more than 88% of patients achieved a PSA reduction of ≥90% after 12 months of treatment, while the treatment discontinuation rate was 15.6% [20]. Consistent findings also emerged from a multicentre retrospective Japanese study conducted in patients with nmCRPC, in which 58.7% of patients treated with apalutamide achieved a PSA reduction of ≥50%, with a median progression-free survival (PFS) of 13 months and a favourable safety profile, characterized by grade ≥3 adverse events in 12% of treated patients [21].

Regarding the safety profile, an analysis based on the FAERS database reported adverse events such as rash and fatigue (with an onset of approximately 2 months, of which only 24.6% resulted in hospitalization) [22].

For darolutamide, a study conducted in China in patients with mHSPC showed that 93.5% of treated patients achieved a PSA reduction of ≥50% within three months of treatment initiation, while adverse events were reported in 5.9% of patients [23]. Furthermore, in a comparative study between darolutamide and abiraterone, treatment with darolutamide in combination with ADT was associated with a significantly lower risk of PSA progression, corresponding to a 58% reduction in risk compared with abiraterone in combination with ADT ($p=0.006$) [24].

Additional real-world evidence has further contributed to the characterization of the safety profile of ARIs. In the European observational PREMISE study, treatment-emergent adverse events with enzalutamide were reported in 51.0% of chemotherapy- and abiraterone-naïve patients and in 62.2% of patients previously treated with chemotherapy; fatigue was the most frequently reported adverse event, with an incidence of 14.5% and 14.4% in the two groups, respectively [25]. A French observational study showed that, compared with enzalutamide, abiraterone was associated with a significantly increased risk of acute kidney injury, laboratory abnormalities suggestive of liver injury, and atrial fibrillation (IRR 1.42 [95% CI 1.01–2.00], 3.06 [95% CI 2.66–3.53], and 1.12 [95% CI 1.05–1.19], respectively) [26]. Other real-world data on enzalutamide have suggested that the use of reduced doses may maintain clinical effectiveness comparable to the standard dose while being associated with less worsening of fatigue [27]. Pharmacovigilance analyses based on the FAERS database

identified, for darolutamide, an unexpected cluster of neurological disorders not reported in the drug prescribing information, including peripheral neuropathy (ROR 10.56), brain fog (ROR 4.16), difficulty standing (ROR 4.15), ageusia (ROR 3.83), and hypoesthesia (ROR 2.98) [28]. Finally, a meta-analysis of randomized clinical trials showed that enzalutamide was associated with an increased risk of cardiovascular adverse events, particularly acute myocardial infarction (OR 3.11; 95% CI 1.17–8.28; p=0.02), coronary artery disease (OR 8.33; 95% CI 1.54–44.95; p=0.01), and severe hypertension (OR 4.94; 95% CI 1.11–22.06; p=0.04). Overall, ARIs were also associated with an increased risk of hypertension of any grade, angina pectoris, and myocardial infarction, although differences were observed among individual agents [29].

In this context, the analysis of Tuscan administrative healthcare databases provides the opportunity to describe the use of the main oral therapies for prostate cancer in the region, with particular focus on the introduction of second-generation androgen receptor inhibitors compared with abiraterone. In particular, the descriptive comparison between abiraterone and second-generation androgen receptor inhibitors may provide useful insights into how the introduction of new therapeutic options has changed the management of prostate cancer in Tuscany and whether this has occurred uniformly or differently across the various regional areas.

5. Research question and objectives

Research question

How have the utilization patterns of oral therapies for prostate cancer evolved over time in Tuscany following the introduction of second-generation androgen receptor inhibitors (apalutamide, enzalutamide, and darolutamide) compared with the previously most widely used therapy (abiraterone)? What are the clinical characteristics of users of these therapies? Are there differences across the Tuscan regional healthcare areas? What are the clinically relevant adverse events occurring during treatment with these therapies that resulted in hospitalization?

Primary endpoints:

- Description of the use of the main oral therapies for prostate cancer in routine clinical practice in Tuscany, with particular focus on the use of abiraterone, apalutamide, enzalutamide, and darolutamide during the study period (2016–2025).

- Description of the distribution of patient categories (first-line users, new users beyond first-line therapy, and prevalent users) for each study drug by calendar year and Regional Healthcare Area (Area Vasta) of Tuscany.
- Description of the demographic (age, sex, and area of residence) and clinical (comorbidities and concomitant treatments) characteristics of patients treated with the oral therapies of interest for prostate cancer during the study period (2016–2025).

- Description of the frequency of treatment discontinuation and treatment switching among patients treated with abiraterone, apalutamide, enzalutamide, and darolutamide.

Secondary endpoint

- Description of the occurrence of major cardiovascular events and other clinically relevant events during the follow-up period.

6. Methods

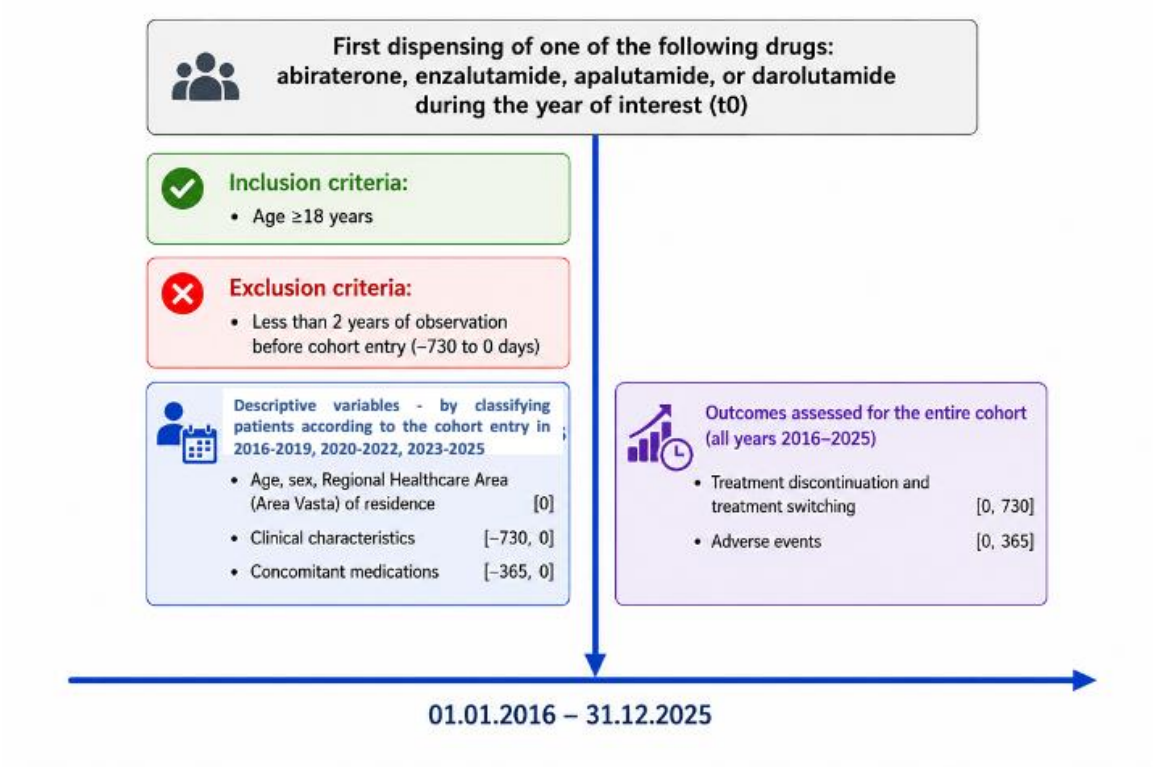
6.1 Study design

This study will be a retrospective, descriptive observational study based on the identification of a cohort of patients treated with abiraterone, apalutamide, enzalutamide, or darolutamide in each year of the study period, using data extracted from the integrated administrative healthcare databases of the Tuscany Region.

Rationale: Since the primary objective of the study is to describe the utilization patterns of oral therapies for prostate cancer in routine clinical practice in Tuscany, a retrospective descriptive observational study design was selected. The use of regional administrative healthcare databases allows the identification of a large, unselected population, providing a more accurate representation of routine clinical practice than clinical trials, which typically include selected patients who may not be representative of the real-world population.

The use of a retrospective design based on routinely collected administrative healthcare data offers several practical and methodological advantages. It allows the analysis of an adequately long study period, reduces study time and costs, and is particularly suitable for describing the use of high-cost therapies in a real-world population. Furthermore, for therapies characterized by rapidly evolving prescribing patterns and regional variations in use, the analysis of administrative healthcare databases allows the systematic description of utilization patterns over time and may support regional healthcare planning.

6.2 Study flow diagram



6.3 Study population

All individuals residing in Tuscany, registered with the Regional Healthcare Service, aged ≥18 years, and with at least one dispensing of one of the drugs of interest (Table A) between 1 January 2016 and 31 December 2025 (i.e., the index drug) will be included. The cohort entry date (index date) will correspond to the dispensing date of the index drug. Individuals aged <18 years at the index date will be excluded to avoid including patients who received these treatments for indications other than prostate cancer. In addition, individuals with less than 24 months of available observation in the regional healthcare registry before the index date will be excluded. Three categories of users will be identified:

1) First-line users: patients with a dispensing of the index drug and no dispensing of any other drug of interest during the 24 months preceding the index date;
2) New users beyond first-line therapy: patients with at least one dispensing of the index drug and at least one previous dispensing of another drug of interest, excluding the index drug, during the 24 months preceding the index date;

3) Prevalent users: patients with at least one dispensing of one of the drugs of interest and at least one dispensing of the same drug during the 24 months preceding the index date.

Patients will be identified based on the first dispensing of the study drugs recorded in the regional administrative FED and SPF databases using Anatomical Therapeutic Chemical (ATC) codes (Table A). Follow-up for each patient will begin on the index date and will end

on 31 December 2025, or on the date of death, transfer outside the Tuscany Region, loss to follow-up, discontinuation of the index drug, or switching to another antineoplastic drug other than the index drug, whichever occurs first. Treatment discontinuation and treatment switching will be defined according to the criteria described in the "Variables" section. Treatment discontinuation and switching events will be assessed during the 12 months following the index date.

Among patients receiving one of the drugs of interest, selected clinically relevant events (cardiovascular events, renal impairment, hepatic impairment, and fractures) will also be identified according to diagnoses recorded in the Hospital Discharge Records (HDR) and Emergency Department (ED) databases during the 12 months following the index date (Table B).

Table A

Study drugs	ATC code
Abiraterone	L02BX03
Apalutamide	L02BB05
Enzalutamide	L02BB04
Darolutamide	L02BB06

6.4 Studi variables

The drugs of interest will include apalutamide, enzalutamide, darolutamide, and abiraterone, identified using Anatomical Therapeutic Chemical (ATC) codes (Table A).

Demographic characteristics (age, sex, and Local Health Authority of residence, categorized according to one of the three Regional Healthcare Areas of Tuscany) and clinical characteristics at the index date will be identified for first-line users and new users beyond first-line therapy receiving one of the drugs of interest during the period 2016–2025, by classifying patients on the basis of the cohort entry year in 2016-2019, 2020-2022, 2023-2025 in order to provide an overview of prescribing patterns.

Concomitant diseases described in Tables 1a–d will be identified using algorithms based on information recorded in one or more administrative healthcare databases, including Hospital Discharge Records (HDR), Emergency Department (ED), exemption registries, FED, and SPF, using ICD-9-CM diagnosis codes and ATC codes for drugs used as proxies for specific diseases.

Concomitant treatments recorded during the 12 months preceding the index date (at least two dispensings) will also be identified, with particular attention to the concomitant use of corticosteroids, antianginal drugs, antithrombotic agents, lipid-lowering drugs, antidiabetic drugs, and bisphosphonates.

Treatment discontinuation and switching from the index drug to another drug of interest will be identified during a 12-month follow-up period (primary analysis) and a 24-month follow-

up period (sensitivity analysis), respectively. A patient will be classified as having discontinued the index drug if no new dispensing of the index drug is recorded within a time interval corresponding to the theoretical duration of coverage of one drug package (e.g., abiraterone: theoretical package coverage of 28 days) plus a grace period of the same duration (28 days). Switchers will be defined as patients receiving a drug other than the index drug among abiraterone, apalutamide, enzalutamide, and darolutamide during follow up.

Among patients who discontinue the index drug, switchers will be identified as those receiving a different drug of interest before the date of treatment discontinuation (i.e., a subset of discontinuers).

In addition, re-starters will be identified as patients who restart treatment with any drug of interest within 90 days after the date of discontinuation of the index drug.

Cardiovascular safety will be described through the occurrence of acute myocardial infarction, stroke, heart failure, angina, and arrhythmias during the 12 months following the index date. Acute kidney injury, acute liver injury, and fractures identifiable within the administrative healthcare databases will also be identified using ICD-9-CM codes recorded in the Hospital Discharge Records (HDR) and Emergency Department (ED) databases and, where necessary, specialist outpatient databases, with analysis of their distribution across the different treatment groups.

A detailed description of the identification algorithms, the administrative healthcare databases used, the coding lists, and the corresponding observation windows is provided in the methodological appendix (Table B).

6.5 Data analysis

The analyses will be primarily descriptive. Categorical variables will be summarized as absolute frequencies and percentages, while continuous variables will be described using the mean and standard deviation or the median and interquartile range, according to the distribution of the data.

The following will be described:

A. The percentage of first-line users, new users beyond first-line therapy, and prevalent users among all users of each drug of interest, by calendar year (2016–2025) and Local Health Authority of residence (Figures 1a–d);
B. The percentage of first-line users receiving each of the four drugs of interest among all first-line users, by Local Health Authority of residence and calendar year (2016–2025) (Figure 2);
C. The demographic and clinical profile (comorbidities and concomitant pharmacological treatments) of first-line users and new users beyond first-line therapy during the periods 2016-2019, 2020-2022, 2023-2025, on the basis of the

patients' cohort entry, by drug of interest and Local Health Authority of residence (Tables 1a–d);

D. The frequency of treatment discontinuation and switching from the index drug to one of the other drugs of interest among first-line users and new users beyond first-line therapy during the 12 months following the index date, by drug of interest and Local Health Authority of residence (Tables 1a–d)

E. The frequency of safety events of interest across the different treatment groups classified according to treatment line (first-line users and new users beyond first-line therapy) (Table 2). Specifically, the adverse events listed in Table 2 will be evaluated among patients receiving the drug of interest, who will be followed for up to 12 months from the dispensing date of the index drug or until death, treatment discontinuation, treatment switching, or loss to follow-up (removal from the regional healthcare registry), whichever occurs first.

Sensitivity analysis

- Treatment discontinuation and switching from the index drug to one of the other drugs of interest among first-line users and new users beyond first-line therapy will also be assessed using a follow-up period of 24 months instead of 12 months.

6.5.1 Figures and shell tables

Figure 1a. Percentage of first-line users, new users beyond first-line therapy, and prevalent users of abiraterone among all abiraterone users, by calendar year (2016–2025) and Local Health Authority of residence.

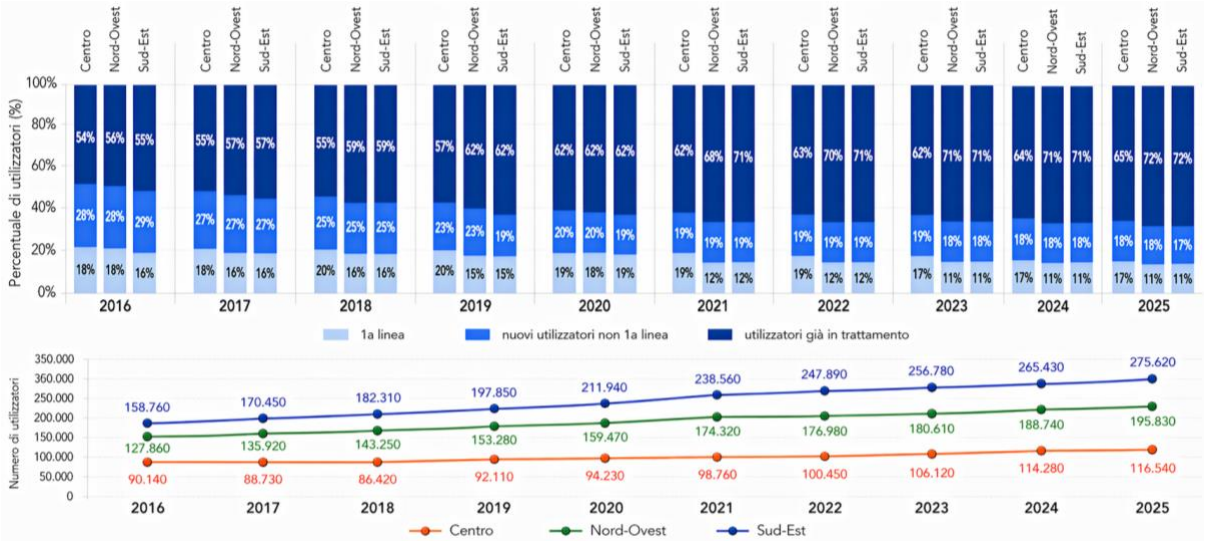


Figure 1b. Percentage of first-line users, new users beyond first-line therapy, and prevalent users of apalutamide among all apalutamide users, by calendar year (2016–2025) and Local Health Authority of residence.

Figure 1c. Percentage of first-line users, new users beyond first-line therapy, and prevalent users of enzalutamide among all enzalutamide users, by calendar year (2016–2025) and Local Health Authority of residence.

Figure 1d. Percentage of first-line users, new users beyond first-line therapy, and prevalent users of darolutamide among all darolutamide users, by calendar year (2016–2025) and Local Health Authority of residence.

Figure 2. Percentage of first-line users receiving each of the four drugs of interest among all first-line users, by Local Health Authority of residence and calendar year (2016–2025).

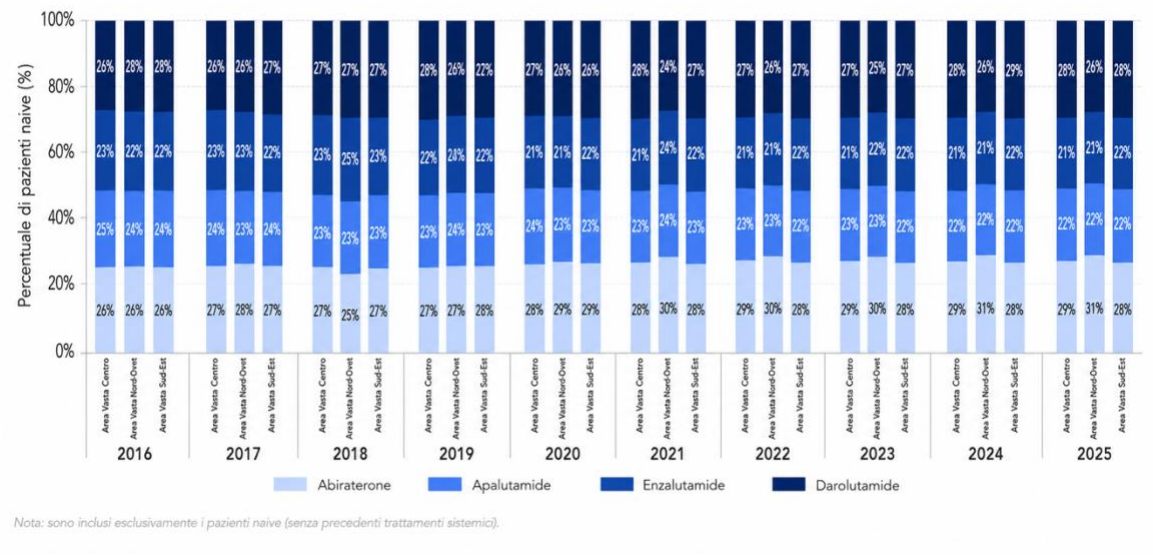


Table 1a. Demographic and clinical profile of first-line users and new users beyond first-line therapy receiving abiraterone during the period 2016–2025, by Local Health Authority of residence

Abiraterone																		
	2016-1019						2020-2022						2023-2025					
	Area Vasta Centro		Area Vasta Nord-Ovest		Area Vasta Sud-Est		Area Vasta Centro		Area Vasta Nord-Ovest		Area Vasta Sud-Est		Area Vasta Centro		Area Vasta Nord-Ovest		Area Vasta Sud-Est	
	First-line users, n (%)	New users beyond first-line therapy, n (%)	First-line users, n (%)	New users beyond first-line therapy, n (%)	First-line users, n (%)	New users beyond first-line therapy, n (%)	First-line users, n (%)	New users beyond first-line therapy, n (%)	First-line users, n (%)	New users beyond first-line therapy, n (%)	First-line users, n (%)	New users beyond first-line therapy, n (%)	First-line users, n (%)	New users beyond first-line therapy, n (%)	First-line users, n (%)	New users beyond first-line therapy, n (%)	First-line users, n (%)	New users beyond first-line therapy, n (%)
Age at index date, median (IQR)																		
Sex at index date																		
Comorbidities																		
Hypertension																		
Ischemic heart disease																		
Acute myocardial infarction																		
Arrhythmias																		

Angina																		
Ischaemic or haemorrhagic stroke																		
Transient ischaemic attack (TIA)																		
Heart failure																		
Dislipidaemia																		
Diabetes mellitus																		
Chronic kidney disease																		
Concomitant treatments, mean (SD)																		
Concomitant medications																		
Systemic corticosteroids																		
Antianginal drugs																		
Antithrombotic agents																		
Lipid-lowering drugs																		

Antidiabetic drugs																		
Bisphosphonates																		
Treatment discontinuation																		
Treatment Switching																		
Vs apalutamide																		
Vs enzalutamide																		
Vs darolutamide																		
Vs other antineoplastic drugs (ATC L01)																		

Table 1b. Demographic and clinical profile of first-line users and new users beyond first-line therapy receiving apalutamide during the period 2016–2025, by Local Health Authority of residence.

Table 1c. Demographic and clinical profile of first-line users and new users beyond first-line therapy receiving enzalutamide during the period 2016–2025, by Local Health Authority of residence.

Table 1d. Demographic and clinical profile of first-line users and new users beyond first-line therapy receiving darolutamide during the period 2016–2025, by Local Health Authority of residence

Table 2. Adverse events observed within 12 months among patients receiving abiraterone, apalutamide, enzalutamide, or darolutamide, by treatment line (first-line users and new users beyond first-line therapy).

	Abiraterone		Apalutamide		Enzalutamide		Darolutamide	
	First-line users, n (%)	New users beyond first-line therapy, n (%)	First-line users, n (%)	New users beyond first-line therapy, n (%)	First-line users, n (%)	New users beyond first-line therapy, n (%)	First-line users, n (%)	New users beyond first-line therapy, n (%)
Death								
Treatment discontinuation								
Treatment switching								
Loss to follow-up								
Cardiovascular events, n (%)								
Acute myocardial infarction, n (%)								
Ischemic heart disease, n (5)								
Ischaemic or haemorrhagic stroke, n (%)								
Heart failure, n (%)								
Angina, n (%)								
Arrhythmias, n (%)								
Acute kidney injury, n (%)								
Acute liver injury, n (%)								
Fractures, n (%)								

6.6 Data sources

The study will exclusively use the regional administrative healthcare databases of Tuscany, whose data are routinely collected for administrative purposes and allow the identification of healthcare services provided to individuals covered by the Tuscan Regional Healthcare Service. Specifically, the following databases will be used: the Regional Healthcare Registry, to identify the eligible population; the Territorial Pharmaceutical Database, to identify dispensing reimbursed through the territorial pharmaceutical service; the FED (Directly Dispensed Drugs) database, for drugs directly dispensed by public healthcare facilities, through distribution on behalf of the Regional Healthcare Service, in outpatient settings, and in day hospitals; the Hospital Discharge Records (HDR) database, to identify comorbidities and safety events of interest; the Exemptions database, to identify relevant chronic conditions; and the Emergency Department (ED) database, to describe emergency department visits and acute events of interest.

The data will be pseudonymized and linked through a unique regional identifier, enabling longitudinal analyses without access to directly identifiable information. All data will be processed in accordance with the applicable data protection legislation.

6.7 Data management and Quality control

A dedicated public repository for the study will be created within the GitHub organization of the Tuscan Regional Centre for Pharmacovigilance (https://github.com/CentroRegionaleFVToscana). The data analysis workflow will be conceptually divided into a series of intermediate steps, starting from the original administrative healthcare data in TheShinISS format through to the final tables and figures. Each intermediate step will be documented in a codebook. For each step, simulated datasets will be developed to allow the analytical procedures to be implemented and tested. At the end of this process, a complete simulated dataset in TheShinISS format will be generated, and the entire analytical workflow will be executed to verify its correct implementation. The analytical procedures, together with the simulated datasets, will remain publicly available to ensure transparency and reproducibility in accordance with the principles of Open Science.

A simple set of data extraction criteria will be defined for the identification of the study population in the ARS Oracle database. The extracted dataset will include the study population together with all corresponding data from the administrative healthcare databases relevant to the study. This dataset will be stored on the ARS file server and converted into the TheShinISS data model. The analytical workflow described above will then be applied to the converted dataset. The final tables and figures will be sent by email to the Principal Investigator and the study team.

6.8 Study size

Not applicable due to the descriptive nature of the study.

7. Limitation of the research methods

The main methodological limitation of the study is the potential misclassification of exposure, as exposure will be ascertained from drug dispensing data, which do not necessarily reflect the actual medication use by patients. Furthermore, due to the nature of administrative healthcare databases, only drugs reimbursed by the Italian National Health Service (NHS) will be captured. Consequently, medications purchased privately by patients, whether prescription-only or over-the-counter, cannot be captured through the data sources used in this study. Similarly, drugs administered during inpatient hospitalizations cannot be captured at the individual patient level. This may result in an underestimation of the actual medication burden, particularly among patients with prostate cancer, who may experience frequent and/or prolonged hospitalizations.

8. Protection of Study Subjects and Data Processing

This study is a retrospective observational study conducted using healthcare data routinely collected as part of the institutional activities of the Tuscan Regional Healthcare Service. No additional clinical or diagnostic procedures will be performed, and no direct contact with data subjects is envisaged. Therefore, the study does not entail any physical risk for the individuals included. The only residual risk relates to the potential breach of personal data confidentiality, which will be minimized through the implementation of appropriate technical and organizational safeguards.

The processing of personal data for the purposes of this study is based on the performance of a task carried out in the public interest, in accordance with Article 6(1)(e) of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation, GDPR). The processing of special categories of personal data is carried out pursuant to Article 9(2)(g) of the same Regulation and Article 2-sexies, paragraph 2, letter (v), of Italian Legislative Decree No. 196 of 30 June 2003 (Personal Data Protection Code), as amended, concerning activities related to the planning, management, monitoring, and evaluation of healthcare services.

Data processing will be carried out in accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 (General Data Protection Regulation, GDPR), Italian Legislative Decree No. 196 of 30 June 2003 (Personal Data Protection Code), as amended, the Rules of Conduct for the Processing of Personal Data for Statistical or Scientific Research Purposes, and all other applicable data protection legislation.

Only data that are relevant and necessary for achieving the objectives of the study will be processed, in accordance with the principles of lawfulness, fairness, transparency, data minimization, purpose limitation, and data protection by design and by default.

Data management and statistical analyses will be performed using pseudonymized data from which direct identifiers have been removed, in accordance with the applicable regional legislation and organizational procedures. Appropriate technical and organizational measures will be implemented to ensure the confidentiality, integrity, and availability of the data and to prevent unauthorized access or processing inconsistent with the purposes of the study.

The results of the study will be reported only in aggregated form or otherwise in a manner that precludes the direct identification of study subjects.

Any required approvals, authorizations, or other regulatory requirements applicable to the study will be obtained before the start of the study.

9. Adverse events

In accordance with Module VI, Section VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (GVP), adverse event reporting is not applicable to this study, as the study is based exclusively on secondary healthcare data.

10. Plans for disseminating and communicating study results

The results of this study will be published in the 2026 edition of the "*Rapporto sui farmaci in Toscana"* and disseminated at the regional level through a presentation during the official presentation of the Report. Subsequently, the possibility of further presentations and publication in peer-reviewed journals will be evaluated.

11. References

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12. Appendix

Table B. Identification algorithms for concomitant pharmacological treatments, comorbidities, and adverse events using administrative healthcare databases, ICD-9-CM codes, and ATC codes

	Administrative healthcare databases		
	Hospital Discharge Records (HDR)	**Exemptions Registry (EXE)**	**Drug Registry (DRUG)[1]**
	ICD9CM	**ICD9CM**	**ATC**
Concomitant pharmacological treatments			
Systemic corticosteroids ≥2 dispensings recorded in [DRUG] during the 12 months preceding the index date			H02AB H02B
Antianginal drugs ≥2 dispensings recorded in [DRUG] during the 12 months preceding the index date			C01DA
Antithrombotic agents ≥2 dispensings recorded in [DRUG] during the 12 months preceding the index date			B01A
Lipid-lowering drugs ≥2 dispensings recorded in [DRUG] during the 12 months preceding the index date			C10
Antidiabetic drugs ≥2 dispensings recorded in [DRUG] during the 12 months preceding the index date			A10
Bisphosphonates ≥2 dispensings recorded in [DRUG] during the 12 months preceding the index date			M05BA M05BB
Comorbidities			

Hypertension ≥1 diagnosis in [HDR] (any diagnosis position), OR recorded in [EXE], OR ≥2 dispensings in [DRUG] during the 2 years preceding the index date.	401* 402* 403* 404* 405* 36211	401 402 403 404 405	C09 C02 C07 C08C
Ischemic heart disease ≥1 diagnosis in [HDR] (any diagnosis position), OR recorded in [EXE], OR ≥2 dispensings in [DRUG] during the 2 years preceding the index date.	410* 414*	414	C01DA
Acute myocardial infarction ≥1 diagnosis recorded in [HDR] (any diagnosis position) during the 2 years preceding the index date	410*		
Arrhythmias ≥1 diagnosis recorded in [HDR] (any diagnosis position) during the 2 years preceding the index date	427*		
Angina ≥1 diagnosis in [HDR] (any diagnosis position), OR recorded in [EXE], OR ≥2 dispensings in [DRUG] during the 2 years preceding the index date	413*		C01DA
Ischaemic or haemorrhagic stroke ≥1 diagnosis recorded in [HDR] (any diagnosis position) during the 2 years preceding the index date	430* 431* 432* 434* 436*		
Transient ischaemic attack (TIA) ≥1 diagnosis recorded in [HDR] (any diagnosis position) during the 2 years preceding the index date	435*		
Heart failure ≥1 diagnosis recorded in [HDR] (any diagnosis position) OR recorded in [EXE], during the 2 years preceding the index date	428* 398.1x 40201 40211 40291	428	

	40401 40403 40411 40413 40491 40493		
Dyslipidaemia ≥1 diagnosis in [HDR] (any diagnosis position), OR recorded in [EXE], OR ≥2 dispensings in [DRUG] during the 2 years preceding the index date	272.0x 272.1x 272.3x 272.4x		C10*
Diabetes mellitus ≥1 diagnosis in [HDR] (any diagnosis position), OR recorded in [EXE], OR ≥2 dispensings in [DRUG] during the 2 years preceding the index date	250*	250	A10*
Chronic kidney disease (CKD) ≥1 diagnosis in [HDR] (any diagnosis position), OR recorded in [EXE], OR ≥2 dispensings in [DRUG] during the 2 years preceding the index date	5820* 5821* 5822* 5823* 5824* 5825* 5826* 5827* 5828* 5829* 581* 7531* 59000 59001 5890* 585* 586*	585	DRUG1: C09C* AND C09B* AND M04AA01 DRUG2 B03XA01 OR V03AE03 OR V03AE02 OR V03AE01 OR H05BX02 OR B03XA02 OR H05BX01
Adverse events			
Acute myocardial infarction ≥1 diagnosis recorded in [HDR] (primary diagnosis) within 12 months following the index date	410*		
Ischemic heart disease ≥1 diagnosis in [HDR] (primary diagnosis), OR ≥2 dispensings in [DRUG] within 12 months following the index date	410* 414*	414	C01DA

Ischaemic or haemorrhagic stroke ≥1 diagnosis recorded in [HDR] (primary diagnosis) within 12 months following the index date	430* 431* 432* 434* 436*		
Heart failure ≥1 diagnosis recorded in [HDR] (primary diagnosis) within 12 months following the index date	428* 398.1x 40201 40211 40291 40401 40403 40411 40413 40491 40493	428	
Angina ≥1 diagnosis in [HDR] (primary diagnosis), OR ≥2 dispensings in [DRUG] within 12 months following the index date	413*		C01DA
Arrhythmias ≥1 diagnosis recorded in [HDR] (primary diagnosis) within 12 months following the index date	427*		
Acute renal failure ≥1 diagnosis recorded in [HDR] (primary diagnosis) within 12 months following the index date	580* 584*		
Acute hepatic failure ≥1 diagnosis recorded in [HDR] (primary diagnosis) within 12 months following the index date	570* 572.2x 572.4x		
Fractures ≥1 diagnosis recorded in [HDR] (primary diagnosis) within 12 months following the index date	800–829, 733.1x		

[1] DRUG includes data from the regional drug dispensing databases SPF and FED.