



European Association of Urology

## Original Article

# Treatment Trajectories in Metastatic Hormone-sensitive Prostate Cancer: A PIONEER+ Big Data Analysis

Rossella Nicoletti<sup>a,b,c,\*\*</sup>, Alex Qinyang Liu<sup>c</sup>, Susan Evans-Axelsson<sup>d</sup>, Asieh Golozar<sup>e</sup>, Katharina Beyer<sup>f</sup>, Bertrand De Meulder<sup>g,h,i</sup>, Riccardo Campi<sup>a,b</sup>, Mauro Gacci<sup>a,b</sup>, Jeremy Yuen-Chun Teoh<sup>c,q</sup>, Carl Steinbesser<sup>j</sup>, Ayman Hijazy<sup>g,k</sup>, Artem Harbachou<sup>k</sup>, James T. Brash<sup>v</sup>, Peter-Paul M. Willemse<sup>l</sup>, Teemu Murtola<sup>m</sup>, Monique J. Roobol<sup>n</sup>, Jesus Moreno Sierra<sup>o</sup>, Anders Bjartell<sup>w</sup>, Axel S. Merseburger<sup>p</sup>, Pawel Rajwa<sup>q,r,s</sup>, Philip Cornford<sup>t</sup>, Thomas Abbott<sup>d</sup>, James Ndow<sup>u</sup>, Eleanor Davies<sup>v</sup>, Qi Feng<sup>x</sup>, Robert Snijder<sup>x</sup>, Juan Gomez Rivas<sup>o,\*</sup>, on behalf of the PIONEER + consortium

<sup>a</sup>Department of Experimental and Clinical Biomedical Science, University of Florence, Florence, Italy; <sup>b</sup>Unit of Urology and Renal Transplantation, Careggi University Hospital, Florence, Italy; <sup>c</sup>SH Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong, Hong Kong; <sup>d</sup>EAU UroEvidenceHub, Arnhem, The Netherlands; <sup>e</sup>Nemesis Health, NY USA, Northeastern University, Boston, MA, USA; <sup>f</sup>Department of Urology, Erasmus MC Cancer Institute Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands; <sup>g</sup>Association EISBM, Vourles, France; <sup>h</sup>European Association of Urology, Guidelines Office, Arnhem, The Netherlands; <sup>i</sup>BDM Consulting, Larajasse, France; <sup>j</sup>Collaborate Project Management, Munich, Germany; <sup>k</sup>Odysseus Data Services - An EPAM Company, Cambridge, MA, USA; <sup>l</sup>Department of Urology, Cancer Center, University Medical Center Utrecht, Utrecht, The Netherlands; <sup>m</sup>Department of Urology, Tampere University Hospital, Tampere, Finland; <sup>n</sup>Department of Urology, Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands; <sup>o</sup>Department of Urology, Hospital Clínico San Carlos, Madrid, Spain; <sup>p</sup>Department of Urology, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; <sup>q</sup>Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; <sup>r</sup>Second Department of Urology, Centre of Postgraduate Medical Education, Warsaw, Poland; <sup>s</sup>Division of Surgery and Interventional Science, University College London, London, UK; <sup>t</sup>Department of Urology, Liverpool University Hospitals NHS Trust, Liverpool, UK; <sup>u</sup>University of Aberdeen, Aberdeen, UK; <sup>v</sup>IQVIA, London, UK; <sup>w</sup>Department of Translational Medicine, Division of Urological Cancers, Medical Faculty, Lund University, Lund, Sweden; <sup>x</sup>Astellas

## Article info

## Article history:

Received 4 August 2025

Accepted 26 August 2025

Available online 8 October 2025

## Associate Editor:

Elena Castro

## Keywords:

Prostate cancer

Metastatic prostate cancer

Big data analysis

## Abstract

**Background and objective:** The treatment landscape for metastatic hormone-sensitive prostate cancer (mHSPC) is evolving rapidly. Real-world data (RWD) are essential to understand actual treatment use and outcomes. This study aimed to describe treatment trajectories and clinical outcomes in a large, multicenter RWD cohort under the PIONEER project.

**Methods:** Eight European and US databases (2016–2020), including electronic health records, insurance claims, primary care data, and cancer registries, were standardized to the Observational Medical Outcome Partnership Common Data Model. Patients diagnosed with mHSPC and those receiving treatment were identified. The compared and analyzed outcomes included treatment switch, symptomatic progression, adverse events, and death.

**Key findings and limitations:** In total, 107 438 patients with mHSPC were identified, and 67 909 received treatment. Most of the patients received androgen deprivation therapy

\* Corresponding author. Department of Urology, Hospital Clínico San Carlos, Madrid, Spain. Tel.: +91 704 38 60; fax: +91 704 38 62.

\*\*Corresponding author.

E-mail addresses: [rossella.nicoletti@unifi.it](mailto:rossella.nicoletti@unifi.it) (R. Nicoletti), [juangomezr@gmail.com](mailto:juangomezr@gmail.com) (J.G. Rivas).

## Real-world evidence

(ADT) monotherapy (69.4%), followed by ADT + an androgen receptor pathway inhibitor (ARPI; 15.2%), ADT + chemotherapy (14.0%), and triplet therapy (1.2%). The use of ARPIs increased over time. ADT + ARPI showed the highest persistence (53.8%) and a 5-yr switch-free survival rate of up to 72.3%. ADT monotherapy had 5-yr switch-free survival rates of 21.3–58.6% and adverse event-free survival rates of 64.7–81.2%. Addition of an ARPI improved switch-free survival (24.1–72.3%) but lowered adverse event-free survival (55.2–82.7%). Chemotherapy-based and triplet therapies showed variable results without consistent survival benefit. Limitations include residual confounding, inconsistent adverse event reporting, and possible data overlap.

**Conclusions and clinical implications:** This is the largest RWD study of systemic mHSPC treatment. Despite evidence, ADT monotherapy remains the most used first-line therapy. Increased use ADT + ARPI is associated with better persistence and improved outcomes in the real-world setting, supporting its broader adoption in clinical practice.

© 2025 The Author(s). 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/>).

## ADVANCING PRACTICE

**What does this study add?**

This study provides the most comprehensive real-world analysis to date of treatment patterns and outcomes in patients with metastatic hormone-sensitive prostate cancer. It highlights that despite strong clinical evidence supporting combination therapies, androgen deprivation therapy (ADT) monotherapy remains the most common first-line treatment. This study also shows that a combination of ADT and androgen receptor pathway inhibitors is associated with better treatment persistence and improved clinical outcomes. These findings support a shift toward broader implementation of combination therapy in real-world clinical practice.

**Clinical Relevance**

The study analyzed real-world treatment patterns for metastatic hormonal sensitive prostate cancer between 2016–2020 in over 67,000 patients across Europe and the US and provides the most comprehensive real-world analysis to date. In that period, ADT monotherapy remained the most common first-line treatment. The study shows that ADT + ARPI combination is associated with improved clinical outcomes, including survival. These findings support a shift toward broader implementation of combination therapy in real-world clinical practice. Associate Editor: Elena Castro.

**Patient Summary**

We looked at real-world treatment patterns for metastatic hormone-sensitive prostate cancer in over 67 000 patients across Europe and the USA. Many patients still receive older treatments of androgen deprivation alone, although newer drug combinations are being used more often. Our findings suggest that a combination of hormone therapy and newer drugs leads to fewer drug switch and adverse events.

**1. Introduction**

Primary androgen deprivation therapy (ADT) has been the standard of care (SOC) for metastatic prostate cancer (mPCa) for over 50 yr [1–3]. Over the past two decades, the introduction of docetaxel chemotherapy and new androgen receptor pathway inhibitors (ARPIs) has transformed the treatment paradigm significantly, with “triplets” now recognized as the new SOC for mPCa [4].

In this scenario, the current European Association of Urology (EAU) prostate cancer (PCa) guidelines suggests to drive metastatic hormone-sensitive PCa (mHSPC) treatment choice by fitness for docetaxel, nature of the disease (low/

high volume as per the CHARTEED criteria [5]; synchronous/metachronous), patient preference, specific adverse event profile, treatment availability, logistics, and cost [4]. The use of treatments in practice and the actual treatment trajectories in mPCa patients remain underexplored. To date, mHSPC patients treated with systemic therapies have not been characterized thoroughly using real-world data (RWD). The analysis of such data may provide valuable insights into treatment pathways and clinical outcomes in everyday practice.

PIONEER is a project within the European network of excellence for big data in PCa. It is one of the four projects under the Innovative Medicine Initiative (IMI) that fall

within the “Big Data for Better Outcomes” initiative [6]. The main aim of PIONEER is to improve PCa care across Europe through the application of big data analytics [6]. Through a comprehensive stakeholder prioritization exercise that included input from health care professionals, pharmaceutical companies, and PCa patients, the PIONEER Consortium identified significant knowledge gaps in PCa as a priority for all stakeholders [7]. Among the ten highest-priority research questions, this study aims to address question number three: to describe the real-world treatment history, trajectories and outcomes of patients with mHSPC according to the treatment they received, utilizing an international network of RWD sources.

## 2. Patients and methods

### 2.1. Study design

A retrospective cohort study based on eight electronic health care data sources across Europe and the USA was conducted. Full details of the included data sources and study design are provided in the [Supplementary material](#) and the published protocol [8].

All the data were harmonized to the Observational Medical Outcome Partnership (OMOP) Common Data Model (CDM) [9]. Institutional review board or equivalent governance approval was obtained by all data providers prior to an analysis. Reproducibility between data partners was ensured by the development of a core analytical package used uniformly across datasets. Only aggregated, population-level (ie, not patient-level) results from each data source were shared publicly, and all data partners consented to external sharing of the result set on [data.ohdsi.org](https://data.ohdsi.org).

### 2.2. Cohort definitions

During PIONEER study-a-thon 2, two main cohorts were built. Complete cohort definitions, and the inclusion and exclusion criteria are available in the [Supplementary material](#) and the published protocol [8]. In brief, all cohorts included adult males ( $\geq 18$  yr) with no history of other primary cancers (except nonmelanoma skin cancer), and no ADT or bilateral subcapsular orchiectomy within 6 mo before the index date to ensure hormone sensitivity. Cohort 1 focused on newly diagnosed cases of mHSPC, distinguishing between synchronous (de novo) and metachronous (recurrent) presentations. Cohort 2 included patients with mHSPC who received systemic therapy (ADT  $\pm$  local treatment), with similar stratification based on disease timing. [Supplementary Fig. 1](#) summarizes the definitions of clinical cohorts.

Patients were eligible to be included in either cohort if they had at least 365 d of observation prior to a diagnosis of metastatic disease in the data source. Additionally, all cohorts were generated with a requirement of at least a 365 d of lookback period prior to the initial diagnosis date of PCa. The lookback period was selected to be sufficiently long to ensure adequate documentation of treatments received prior to inclusion, and to exclude the use of ADT as adjuvant therapy, while avoiding the exclusion of an

excessive number of patients due to insufficient historical data.

### 2.3. Data sources

We performed the analyses across a network of observational electronic health records, population-based registries, and insurance claims data. Dataset characteristics are reported in [Supplementary Table 1](#). Each data source custodian used deidentified data, and thus the analysis was determined not to be research on humans and informed consent was not deemed necessary at any site. All results were reported in an aggregated form.

### 2.4. Outcomes

Detailed information is available in the published protocol [8]. In brief, the outcomes of interest were as follows: (1) initial treatment patterns; (2) treatment switch, defined as the date when patients received a new treatment, including the addition or subtraction of treatment components; and (3) event-free survival for outcomes including adverse events, death, hospitalization and emergency department (ED) visit, and symptomatic progression defined as urinary retention, hydronephrosis, acute kidney failure, bowel obstruction, or fatigue. Outcomes were evaluated on the index date and at 1, 3, and 5 yr. Patients are followed from the index date until death, being diagnosed with another malignancy (except for nonmelanoma skin cancer), or the end of observation period.

### 2.5. Analysis

Baseline treatment characteristics and primary study outcomes were summarized using descriptive statistics, including absolute numbers and percentages to provide an overview of the study population. Kaplan-Meier survival analyses were conducted to estimate the time-to-event distributions for the prespecified outcomes. Sankey diagrams were employed to examine and visualize treatment patterns and switches [10].

Cohorts were developed systematically and defined using the Observational Health Data Sciences and Informatics (OHDSI) ATLAS software, hosted on the PIONEER data analytics platform. To ensure transparency and reproducibility, the defined cohorts were incorporated into an R package, which is publicly accessible along with detailed cohort definitions at <https://github.com/bdemeulder/PIO NEERmetastaticTreatment>. This R package was distributed across the data network to facilitate a consistent analysis. The results of the study were compiled and made publicly available for exploration via an interactive platform: <https://pioneer-shiny.hzdr.de/app/PioneerMetastaticTreatmentExplorer2>.

## 3. Results

### 3.1. Initial treatment distribution overview

From a sample of >100 000 000 adult individuals, 107 438 mHSPC patients were identified in cohort 1, assuming no

**Table 1 – Overall counts of the included cohorts according to database**

| Database        | Cohort 1 (mHSPC) | Cohort 1.1 (synchronous mHSPC) | Cohort 1.2 (metachronous) | Cohort 2 (mHSPC treated) | Cohort 2.1 (synchronous mHSPC treated) | Cohort 2.2 (metachronous mHSPC) |
|-----------------|------------------|--------------------------------|---------------------------|--------------------------|----------------------------------------|---------------------------------|
| AMBEMR          | 1358             | 1169                           | 44                        | 1545                     | 792                                    | 18                              |
| CPRD            | 317              | 238                            | 13                        | 703                      | 583                                    | 9                               |
| MarketScan      | 3959             | 2791                           | 376                       | 2485                     | 1602                                   | 94                              |
| NCR             | 10 521           | 9712                           | 54                        | 9095                     | 9054                                   | –                               |
| ONCO            | 2436             | 1859                           | –                         | 1593                     | 767                                    | –                               |
| OPENCLAIMS      | 69 383           | 51 652                         | 5                         | 38 915                   | 24 637                                 | 1145                            |
| OPTUM           | 8595             | 6408                           | 442                       | 6119                     | 3411                                   | 139                             |
| PharmetricsPlus | 10 869           | 8108                           | 546                       | 7454                     | 4813                                   | 192                             |
| Total           | 107 438          | 81 937                         | 1480                      | 67 909                   | 45 659                                 | 1597                            |

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; mHSPC = metastatic hormone-sensitive prostate cancer.

**Table 2 – Treatment distribution across databases in cohort 2**

| Database        | ADT    | ADT + ARPI | ADT + chemotherapy | ADT + ARPI + chemotherapy | Total  |
|-----------------|--------|------------|--------------------|---------------------------|--------|
| AMBEMR          | 1067   | 437        | 0                  | 0                         | 1504   |
| CPRD            | 678    | 0          | 0                  | 0                         | 678    |
| MarketScan      | 1511   | 488        | 339                | 32                        | 2370   |
| NCR             | 4900   | 254        | 3756               | 25                        | 8935   |
| ONCO            | 766    | 443        | 189                | 0                         | 1398   |
| OPENCLAIMS      | 29 716 | 6028       | 3715               | 408                       | 39 867 |
| OPTUM           | 4381   | 1217       | 486                | 40                        | 6124   |
| PharmetricsPlus | 5681   | 1800       | 1423               | 346                       | 9250   |
| Total           | 48 700 | 10 667     | 9908               | 851                       | 70 126 |

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor.

overlap between databases. Among these patients, 67 909 fulfilled cohort 2 definition, that is, mHSPC with treatment initiated. [Table 1](#) summarizes the overall cohort numbers and [Table 2](#) the treatment distribution within cohort 2, across the different databases. The majority of mHSPC patients received ADT monotherapy as the first-line treatment (69.4%), followed by ADT + ARPI doublet (15.2%), ADT + chemotherapy doublet (14.1%), and ADT + chemotherapy + ARPI triplet (1.2%) therapies.

### 3.2. Change in treatment distribution over time

The analysis of treatment patterns from 2016 to 2020 demonstrates a consistent notable shift in the first-line management of mHSPC, despite small variations observed across different cohorts. [Supplementary Fig. 2](#) summarizes the treatment combination distribution across the study period in the different cohorts.

There is a consistent increase in the use of ADT + ARPI doublet therapy seen in the analyzed RWD, for instance, in the OPTUM cohort, the proportion of patients receiving ADT and ARPIs increased steadily from 5.33% in 2016 to 30.34% in 2020. Similar trends were evident across other datasets, such as MarketScan (from 5.04% in 2016 to 37.58% in 2020) and PharmetricsPlus (from 5.11% in 2016 to 22.71% in 2020), among others. This upward trajectory highlights the growing adoption of ARPI-based regimens as a preferred treatment option over the study period. In contrast, the use of ADT in combination with chemotherapy showed a consistent decline. The MarketScan cohort, for instance, reported a decrease in ADT and chemotherapy use from 20.15% in 2016 to 9.94% in 2020. Similar reductions were observed in other datasets, such as ONCO (from 14.29% in 2016 to 7.55% in 2020) and OPENCLAIMS (from 13.88% in 2016 to 6.52% in 2020). This decline reflects the

diminishing reliance on chemotherapy-based approaches in PCa treatment as newer, more targeted therapies gain prominence.

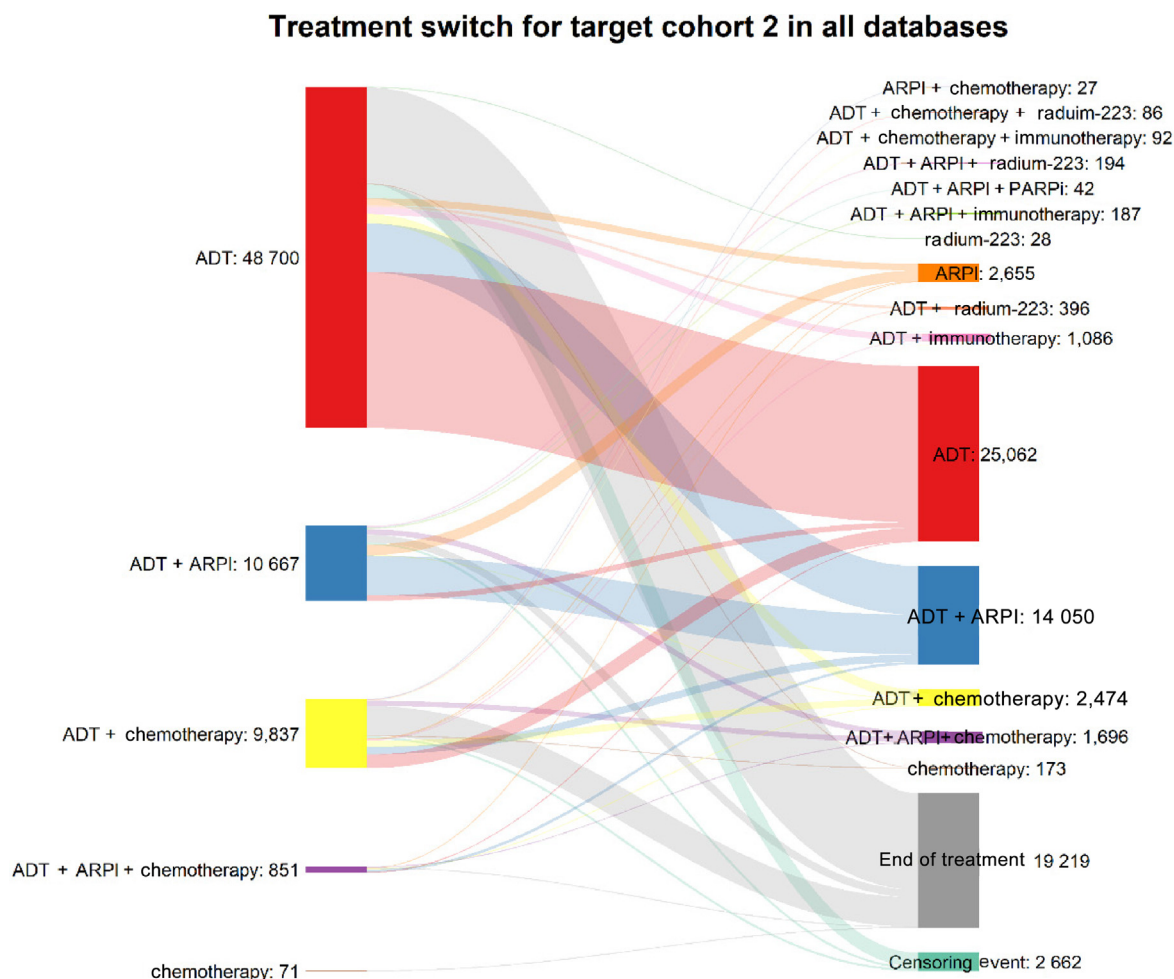
The use of intensified combination therapies, such as triplet therapy with ADT + ARPI + chemotherapy, has remained relatively stable over the years, with only minor fluctuations across cohorts. ADT monotherapy remained relatively stable over the study period, and there are no noticeable patterns regarding baseline patient characteristics across different treatment groups.

### 3.3. Treatment switch patterns

A comprehensive visual summary of the treatment trajectories for all patients is provided in the Sankey diagram shown in [Fig. 1](#). This graphical representation depicts the distribution of initial treatments at baseline and illustrates the subsequent transitions between therapeutic strategies throughout the study period, allowing for a clear visualization of treatment patterns and changes over time.

RWD show that the majority of patients began their treatment with ADT monotherapy, as indicated by the large proportion of patients in the ADT-only category at the start of treatment. Specifically, 48 700 of 70 126 (69.4%) patients initiated treatment with ADT alone, representing the dominant starting point for PCa therapy. The most prominent initial combination therapy was ADT combined with ARPIs, accounting for 10 667 (15.2%) patients, followed by treatment with ADT combined with chemotherapy in 9837 (14.0%) patients. The proportions of patients who started on other treatment options were even smaller; for instance, 851 (1.2%) patients started on triplet therapy.

Regarding treatment persistence, patients who started on ADT plus ARPI combination demonstrated the highest persistence rate, with 5999 patients (56.2%) continuing



**Fig. 1 – Plotted Sankey diagram illustrating treatment trajectories for patients with prostate cancer. The diagram visualizes the distribution of initial therapies and subsequent treatment transitions over time. ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; PARPi = PARP inhibitor.**

treatment. Among patients on ADT monotherapy, 23 060 (47.4%) remained on ADT alone. The persistence rate reduces for treatment combinations containing chemotherapy; 138 patients (16.2%) remained in the triplet therapy group of ADT + ARPI + chemotherapy, and 990 patients (10.1%) remained in the doublet therapy group of ADT + chemotherapy.

Among patients who started on ADT monotherapy, 7166 (14.7%) switched to ADT + ARPI and 1357 (2.8%) switched to ADT + chemotherapy. Among patients who started on ADT + chemotherapy, 2056 (20.9%) transitioned to ADT alone, 1121 (11.4%) switched to ADT + ARPI, and 801 (8.1%) switched to ADT + ARPI + chemotherapy triplet. Among patients who started on ADT + ARPI, 1562 (14.6%) transitioned to ARPI monotherapy, 803 (7.5%) switched to ADT alone, and 834 (7.8%) added chemotherapy as part of triplet therapy. The detailed treatment switch patterns and the respective Sankey diagrams of each database can be found in the [Supplementary material](#).

### 3.4. Event-free survival with different treatments

**Table 3** summarizes the 5-yr event-free survival of mHSPC patients, stratified for treatment pattern, across different

databases for the predefined outcomes of interest, namely, adverse events, death, hospitalization and ED visit, symptomatic progression, and treatment switch. These findings are represented graphically in the combined survival curves in [Fig. 2](#).

Across the databases, ADT monotherapy yielded 5-yr treatment switch-free survival rates ranging from 21.3% to 58.6%. When an ARPI was added to ADT, consistently higher treatment switch-free survival rates were seen, ranging from 24.1% to 72.3%. No consistent pattern was observed for chemotherapy-containing doublet or triplet therapy for treatment switch. The ADT monotherapy group reported 5-yr adverse event-free survival rates in the range of 64.7–81.2% across the different databases. Generally lower adverse event-free survival rates were observed in the intensified combination treatment groups, ranging from 55.2% to 82.7% for ADT + ARPI, even lower rates ranging from 49.8% to 74.2% for ADT + chemotherapy, and rates ranging from 60.8% to 74.4% for triplet therapy. Similar patterns could be observed for hospitalization and ED visits, with smaller differences between ADT monotherapy and the combination groups. ADT monotherapy yielded slightly higher but statistically significant 5-yr hospitalization-free

**Table 3 – Five-year event-free survival (95% CI) across databases stratified by initial treatments**

| Database                            | ADT                 | ADT + ARPI         | ADT + Chemo        | ADT + Chemo + ARPI |
|-------------------------------------|---------------------|--------------------|--------------------|--------------------|
| <i>Adverse events</i>               |                     |                    |                    |                    |
| AMBEMR                              | 71.5 (67.8; 75.5)   | 69.7 (62.7; 77.4)  | NR                 | NR                 |
| CPRD                                | 71.0 (64.0; 78.9)   | NR                 | NR                 | NR                 |
| MarketScan                          | 77.5 (72.4; 82.9)   | 74.2 (65.4; 84.1)  | 74.2 (68.9; 79.8)  | NR                 |
| NCR                                 | NR                  | NR                 | NR                 | NR                 |
| ONCO                                | 64.8 (59.6; 70.3)   | 55.2 (48.5; 62.9)  | 49.8 (40.9; 60.7)  | NR                 |
| OPENCLAIMS                          | 81.2 (80.6; 81.8)   | 80.2 (78.8; 81.7)  | 74.0 (72.3; 75.8)  | 74.4 (69.9; 79.2)  |
| OPTUM                               | 79.3 (77.5; 81.2)   | 82.7 (79.8; 85.7)  | 73.2 (68.4; 78.3)  | NR                 |
| PharmetricsPlus                     | 64.7 (62.4; 67.1)   | 55.7 (41.1; 75.5)  | 60.2 (55.2; 65.6)  | 60.8 (50.0; 74.0)  |
| <i>Death</i>                        |                     |                    |                    |                    |
| AMBEMR                              | 87.5 (84.9; 90.13)  | 85.6 (79.4; 92.3)  | NR                 | NR                 |
| CPRD                                | 33.5 (26.91; 41.59) | NR                 | NR                 | NR                 |
| MarketScan                          | 99.8 (99.48; 100)   | NR                 | NR                 | NR                 |
| NCR                                 | 36.1 (34.36; 37.94) | 37.4 (28.4; 49.1)  | 45.7 (43.8; 47.7)  | NR                 |
| ONCO                                | 99.7 (99.04; 100)   | NR                 | NR                 | NR                 |
| OPENCLAIMS                          | NR                  | NR                 | NR                 | NR                 |
| OPTUM                               | 62.9 (60.33; 65.65) | 58.5 (52.3; 65.4)  | 66.8 (59.2; 75.6)  | 70.5 (57.5; 86.5)  |
| PharmetricsPlus                     | NR                  | NR                 | NR                 | NR                 |
| <i>Hospitalization and ED visit</i> |                     |                    |                    |                    |
| AMBEMR                              | 99.8 (99.5; 100.0)  | 99.8 (99.4; 100.0) | NR                 | NR                 |
| CPRD                                | 65.5 (56.0; 76.5)   | NR                 | NR                 | NR                 |
| MarketScan                          | 78.3 (72.3; 85.0)   | 72.2 (56.7; 92.0)  | 72.2 (62.7; 83.2)  | NR                 |
| NCR                                 | NR                  | NR                 | NR                 | NR                 |
| ONCO                                | 99.9 (99.7; 100.0)  | NR                 | 99.5 (98.6; 100.0) | NR                 |
| OPENCLAIMS                          | 80.0 (79.4; 80.6)   | 77.4 (75.7; 79.1)  | 74.5 (72.6; 76.5)  | 74.5 (69.1; 80.4)  |
| OPTUM                               | 68.7 (66.2; 71.2)   | 68.0 (62.4; 74.1)  | 63.0 (55.5; 71.5)  | NR                 |
| PharmetricsPlus                     | 66.9 (64.5; 69.3)   | 62.9 (51.2; 77.1)  | 63.5 (59.1; 68.2)  | 65.1 (57.1; 74.2)  |
| <i>Symptomatic progression</i>      |                     |                    |                    |                    |
| AMBEMR                              | 75.5 (72.2; 79.0)   | 71.5 (65.3; 78.3)  | NR                 | NR                 |
| CPRD                                | 45.0 (37.3; 54.3)   | NR                 | NR                 | NR                 |
| MarketScan                          | 71.2 (67.3; 75.4)   | 63.9 (55.1; 74.2)  | 68.0 (59.4; 77.9)  | NR                 |
| NCR                                 | 36.1 (34.4; 37.9)   | 37.4 (28.4; 49.1)  | 45.7 (43.8; 47.7)  | NR                 |
| ONCO                                | 66.0 (58.4; 74.6)   | 36.7 (17.7; 76.2)  | 61.6 (50.0; 75.9)  | 55.5 (34.0; 90.4)  |
| OPENCLAIMS                          | 69.7 (69.0; 70.4)   | 66.4 (64.5; 69.4)  | 62.1 (60.0; 64.3)  | 63.1 (57.2; 69.7)  |
| OPTUM                               | 60.2 (57.4; 63.1)   | 64.7 (59.7; 70.0)  | 52.6 (43.4; 63.7)  | NR                 |
| PharmetricsPlus                     | 56.8 (54.0; 59.7)   | 54.5 (46.4; 63.9)  | 53.5 (48.4; 59.2)  | 64.3 (54.4; 76.1)  |
| <i>Treatment switch</i>             |                     |                    |                    |                    |
| AMBEMR                              | 44.9 (41.0; 49.2)   | 70.0 (61.7; 79.5)  | NR                 | NR                 |
| CPRD                                | 26.7 (21.0; 33.9)   | NR                 | NR                 | NR                 |
| MarketScan                          | 56.9 (51.6; 62.8)   | 68.8 (62.5; 75.6)  | 19.6 (10.9; 35.4)  | 54.9 (36.2; 83.4)  |
| NCR                                 | 21.3 (19.8; 22.9)   | 33.1 (24.5; 44.6)  | 30.8 (28.9; 32.8)  | NR                 |
| ONCO                                | 45.5 (37.3; 55.5)   | 61.0 (52.1; 71.6)  | 27.1 (17.5; 41.8)  | NR                 |
| OPENCLAIMS                          | 58.6 (57.8; 59.4)   | 72.3 (70.7; 73.9)  | 37.1 (35.0; 39.2)  | 70.1 (65.5; 75.0)  |
| OPTUM                               | 22.9 (20.9; 25.1)   | 24.1 (19.4; 30.0)  | 16.2 (12.1; 21.6)  | 13.7 (3.2; 58.7)   |
| PharmetricsPlus                     | 52.7 (49.5; 56.2)   | 58.8 (52.8; 65.4)  | 31.9 (26.2; 38.9)  | 60.6 (51.1; 72.0)  |

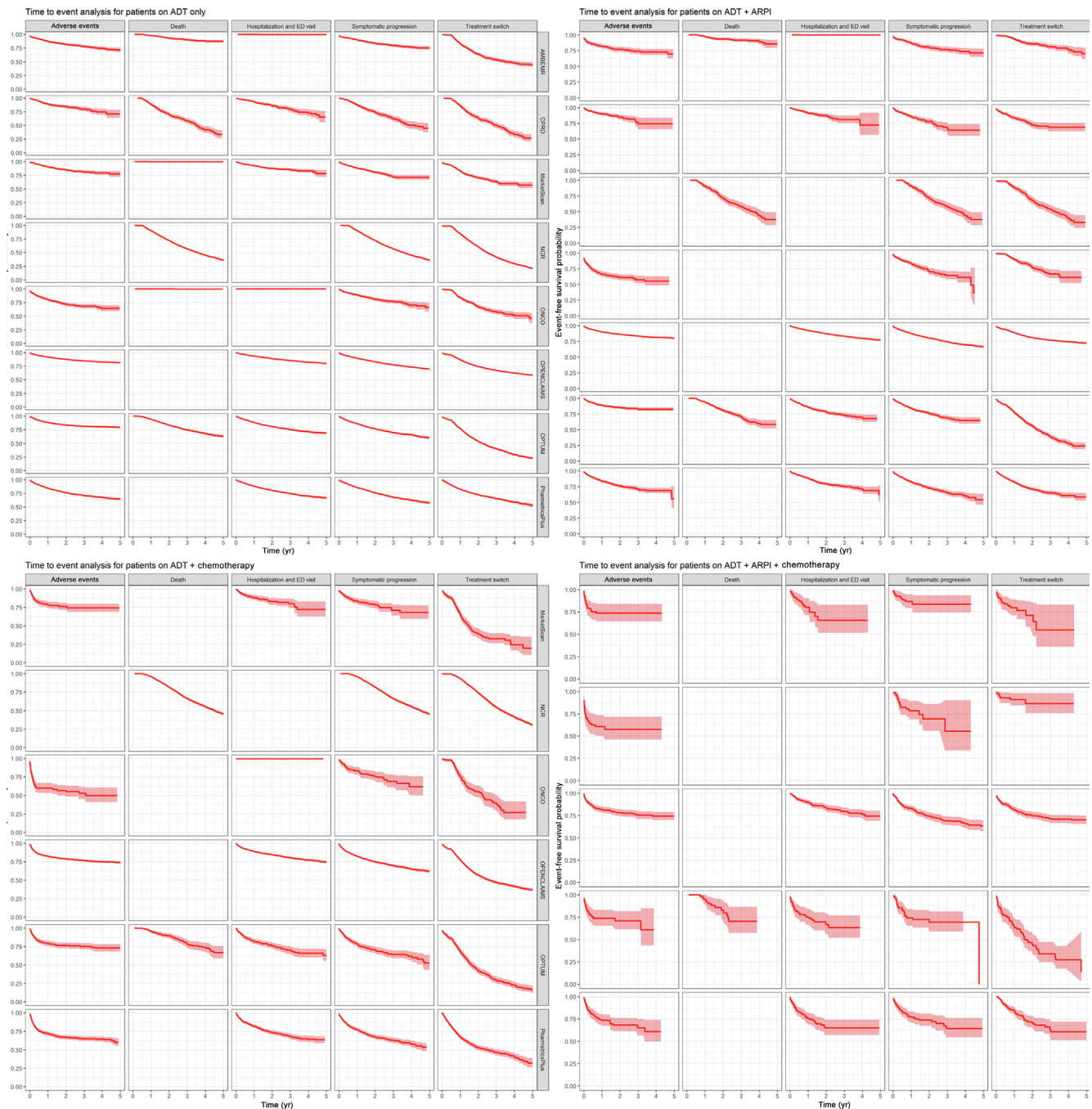
ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; Chemo = chemotherapy; CI = confidence interval; ED = emergency department; NR = not reported.

survival rates ranging from 65.5% to 99.9%, compared with ADT + ARPI (from 62.9% to 99.8%), ADT + chemotherapy (from 63.0% to 99.5%), and triplet therapy (from 65.1% to 74.5%). No consistent patterns can be identified across the treatment groups in terms of mortality and symptomatic progression.

#### 4. Discussion

This large-scale, multinational observational study offers a comprehensive evaluation of real-world treatment patterns and outcomes in patients with mHSPC. Leveraging the federated infrastructure of the OHDSI network and the standardized OMOP CDM, the study successfully harmonized disparate data environments to analyze treatment distribution, changes over time, treatment switch behavior, and event-free survival in over 111 000 mHSPC patients. The findings contribute valuable real-world insights into how mHSPC is managed globally and how treatment choices may influence long-term outcomes. With the largest avail-

able patient-level cohort of men with mPCa undergoing systemic treatment, our study provides one of the first resources of real-world evidence to improve our understanding of the current landscape of the treatment pattern in this setting. In addition, it represents the first major attempt for in-depth treatment characterization and a treatment pattern analysis of men with mPCa at the largest scale to date. A central observation is that ADT monotherapy continues to dominate as the initial treatment strategy for mHSPC, accounting for nearly 68.9% of patients, despite the enormous strides in the last 10 yr in the metastatic armamentarium. Despite clear clinical guideline recommendations promoting treatment intensification with ARPIs or chemotherapy based on randomized clinical trials [4], uptake of combination therapies remains moderate. Only 15.2% of patients received ADT + ARPI as their initial regimen, and even fewer began with ADT + chemotherapy (14.1%) or triplet therapy (1.2%). This finding confirms, at a larger scale, the real-world results from a previous systematic review and a smaller retrospective study [11,12].



**Fig. 2 – Combined 5-yr survival curves for the outcomes of interest (adverse event, death, hospitalization and ED visit, symptomatic progression, and treatment switch), per database, stratified by treatment. ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; ED = emergency department.**

However, temporal trends between 2016 and 2020 indicate a meaningful shift in treatment practice. The proportion of patients initiating therapy with ADT + ARPI increased steadily, tripling or more across nearly all databases. In contrast, the use of ADT + chemotherapy declined during the same period. This may reflect increasing clinician confidence in the efficacy of ARPIs, their favorable toxicity profiles compared with chemotherapy, and most importantly the updated evidence around 2017 supporting their use as the SOC. This pattern is especially evident in selected databases, such as OPTUM, MarketScan, and PharmetricsPlus, suggest-

ing that the integration of clinical trial evidence into practice is ongoing but uneven. The adoption of triplet therapy (ADT + ARPI + chemotherapy) remained low and relatively stable across the study period, with some surprising early uptake observed even before definitive trial results were available widely. This suggests variability in early-adopter behavior across health care systems or possibly off-label use based on evolving clinical experience.

The above patterns of first-line treatments reflect the paradigm shift in mHSPC treatment over the years. The increasing adoption of ADT + ARPI combination in the late

2010s coincides, naturally, with the maturation of clinical evidence supporting its efficacy. Abiraterone, for instance, was initially approved by the Food and Drug Administration for metastatic castration-resistant PCa in 2011 and had its indication expanded to mHSPC in 2017 after the LATITUDE trial [13,14]. ADT + ARPI was subsequently recommended as a first-line treatment in the 2018 update of the EAU guidelines. However, another main driving force in real-life adoption of combination therapy, or the lack thereof given the high prevalence of ADT monotherapy, has been the financial factors. Cost barriers and reimbursement issues were identified previously as qualitative factors influencing whether ARPI-based intensification is used [12]. Reimbursement policies can also explain the uneven adoption of this SOC across different databases, as different health systems have been shown to have different drug approval status, treatment funding, and out-of-pocket costs for patients [15]. The low rate of chemotherapy-containing regimen usage may also be driven by patient-related factors such as tolerability, age, comorbidity burden, and socioeconomic factors. Treatment switch patterns further highlighted real-world treatment dynamics. Sankey diagram visualizations and switch metrics revealed that patients who initiated on ADT + ARPI had the highest persistence rate of 53.8%, compared with the 46.3% persistence rate for ADT monotherapy and substantially lower persistence for chemotherapy-containing regimens. These findings reinforced the notion that ARPI-containing regimens may be more tolerable and sustainable in the long term. Furthermore, patients on ADT monotherapy were those most likely to escalate treatment, with 14.4% switching to ADT + ARPI and smaller proportions escalating to chemotherapy-containing combinations. These switches may reflect delayed treatment intensification in response to progression, patient preference, or clinician hesitation to initiate combination therapy upfront. Notably, some patients de-escalated therapy or cycled between treatment strategies, suggesting variability in treatment goals and possibly side-effect management. For instance, among patients starting with ADT + ARPI, some switched to an ARPI alone or even back to ADT alone, indicating clinical scenarios that required treatment modification. Patients initially on ADT + chemotherapy also switched in diverse directions, including to ADT alone or triplet therapy, revealing a complex interplay between treatment efficacy, toxicity, and disease progression.

Event-free survival outcomes stratified by treatment type provided important insights into the comparative effectiveness of different regimens in routine care. For treatment switch-free survival at 5 yr, ADT + ARPI outperformed ADT monotherapy and ADT + chemotherapy consistently across multiple databases. Assuming treatment failure is a major driving force of treatment switch, these findings suggested external validity of ADT + ARPI trials in the real-world setting. In contrast, ADT + chemotherapy and triplet therapy showed less consistent and more variable outcomes. The heterogeneity across databases suggests differences in case mix, data capture, and health care system factors influencing survival estimates. Interestingly, in terms of adverse event-free survival, hospitalization, and ED visit-free survival, ADT monotherapy reported consis-

tently higher rates than or comparable rates with combination regimens. This may reflect lower baseline severity among patients selected for ADT alone, as well as a reduced toxicity burden of monotherapy. Conversely, intensified therapies, while more effective in disease control, may be associated with higher short-term toxicity, especially in frailer patients. For example, adverse event-free survival for ADT + chemotherapy ranged from 49.8% to 74.2%, consistently lower than monotherapy, underscoring the clinical tradeoffs between efficacy and tolerability outside the ideal trial patient population. Mortality and symptomatic progression outcomes did not show consistent patterns favoring any single treatment group. This might be due to multiple confounding variables, such as differential follow-up time, competing risks, or underlying patient health status, which were not fully adjusted for in this descriptive analysis.

The strengths of this study include its large sample size, broad geographic coverage, and methodological rigor via the use of the OMOP CDM and a federated analytic approach. The study-a-thon framework also illustrates the power of collaborative research networks to generate real-world evidence with clinical relevance. Importantly, the use of a common analytical pipeline ensured reproducibility and transparency across the participating sites, enhancing the validity of comparisons. This study harnesses the power of big data, which can be defined as “an information asset characterized by such a high volume, velocity and variety to require specific technology and analytical methods for its transformation into value” [16]. PIONEER+ was able to create a multidisciplinary environment of technologies, methods, and support where clinicians may overcome the technological barriers of big data analyses in PCa. Indeed, our findings, aligning with previous experiences, confirm the unique opportunity offered by the PIONEER+ project to provide real-world evidence on PCa treatment [17].

Nonetheless, this study has limitations. The use of observational data introduces potential biases, including unmeasured confounding and incomplete information on relevant clinical factors such as performance status, socioeconomic background, prostate-specific antigen (PSA) levels, serum testosterone levels, or metastatic burden, thus limiting our ability to analyze disease volume, individual risk, and castration resistance status. The lack of patient stratification into low- versus high-volume or low- versus high-risk groups may certainly introduce an additional bias, as it prevents meaningful subgroup analyses. This limitation stems from the fragmented nature of the available data, which does not allow for consistent stratification. Moreover, the substantial proportion, albeit not overwhelmingly dominant, of claims data may also have implications on data quality. Nonetheless, the data presented still offer a meaningful snapshot of the current clinical practice. It is also important to highlight that the clinical reasons underlying treatment switches cannot be determined from the available data. Potential factors may include economic considerations, such as changes in reimbursement criteria, treatment-related adverse events and drug tolerability, disease progression not captured in the databases due to the lack of biomarkers such as PSA levels or imaging data, as

well as patient preferences. The reliance on administrative codes to define metastasis and symptomatic progression may affect accuracy, and variations in coding practices across databases can influence the observed estimates. For instance, this could have led to an underestimation as the absence of relevant coding was considered to indicate the absence of a disease. The highly varied nature of data sources also created heterogeneity in the data, for instance, chemotherapy combinations were more prevalent in NCR, a European registry, than in US claims-based databases, reflecting differences in either regional practice or coding behaviors. Some treatment regimens, particularly triplet therapy, had small sample sizes in certain databases, reducing statistical power. Moreover, the lack of information on supportive care measures, such as the use of bone-protective agents or the management of treatment-related side effects, should be acknowledged as it may have played a role in the outcomes results, specifically adverse events and access to ED. As a result, we were unable to determine what proportion of patients receiving ADT + ARPI also received a bone agent, or whether these rates varied by country. Finally, due to the nature of the RWD, we were unable to describe the follow-up duration for patients without an event.

## 5. Conclusions

Despite the current evidence supporting doublet or triplet therapy as the SOC, the majority of mHSPC patients were still treated with ADT monotherapy in real life, according to big data. The increasing adoption of ADT + ARPI and the declining use of chemotherapy reflect broader shifts in clinical practice favoring more targeted therapies. Persistence and event-free survival outcomes suggest potential advantages of ARPI-containing regimens, although further adjustment for confounding is necessary. This study provides a comprehensive, international snapshot of real-world treatment trajectories in mHSPC, illuminating how the disease is managed across diverse health care systems and how therapeutic approaches are evolving in response to emerging clinical evidence. Our findings may provide meaningful guidance for clinicians, policymakers, and researchers working to optimize mHSPC care and support the development of future clinical guidelines. Further studies are needed to better understand the underlying drivers of treatment choices and treatment switches.

**Author contributions:** Rossella Nicoletti and Juan Gomez Rivas had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Gomez Rivas, Nicoletti, Golozar.

*Acquisition of data:* None.

*Analysis and interpretation of data:* De Meulder, Hijazy, Harbachou, Golozar.

*Drafting of the manuscript:* Nicoletti, Liu, Gomez Rivas.

*Critical revision of the manuscript for important intellectual content:* Rajwa, Gacci, Campi, Teoh, Axelsson, Brash, Willemse, Murtola, Robool, Bjartell, Sierra, Merseburger, Beyer, Cornford, Abbott, Ndow.

*Statistical analysis:* None.

*Obtaining funding:* PIONEER Consortium.

*Administrative, technical, or material support:* Steinbesser.

*Supervision:* None.

*Other:* None.

**Financial disclosures:** Rossella Nicoletti and Juan Gomez Rivas certify 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: None.

**Funding/Support and role of the sponsor:** PIONEER is funded through the IMI2 Joint Undertaking and is listed under grant agreement 777492. This joint undertaking receives support from the European Union Horizon 2020 Research and Innovation Programme and EFPIA. The views communicated within are those of PIONEER. Neither of the IMI, European Union, EFPIA, or any associated partners are responsible for any use that may be made of the information contained herein.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euo.2025.08.007>.

## References

- [1] Riaz BI et al.. First-line systemic treatment options for metastatic castration-sensitive prostate cancer: a living systematic review and network meta-analysis. *JAMA Oncol* 2023;9:635–45.
- [2] Roy S et al.. Addition of docetaxel to androgen receptor axis-targeted therapy and androgen deprivation therapy in metastatic hormone-sensitive prostate cancer: a network meta-analysis. *Eur Urol Oncol* 2022;5:494–502.
- [3] Wang L et al.. Comparison of doublet and triplet therapies for metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis. *Front Oncol* 2023;13:1104242.
- [4] Cornford P et al.. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer—2024 update. Part I: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2024;86:148–63.
- [5] Sweeney CJ et al.. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015;373:737–46.
- [6] Omar MI et al.. Introducing PIONEER: a project to harness big data in prostate cancer research. *Nat Rev Urol* 2020;17:351–61.
- [7] Omar MI et al.. Unanswered questions in prostate cancer—findings of an international multi-stakeholder consensus by the PIONEER consortium. *Nat Rev Urol* 2023;20:494–501.
- [8] Gomez Rivas J et al.. Research protocol to identify progression and death amongst patients with metastatic hormone-sensitive prostate cancer treated with available treatments: PIONEER IMI's "big data for better outcomes" program. *Int J Surg Protoc* 2023;27:122–9.
- [9] Jean-Baptiste L, Mouazer A, Sedki K, Tsopra R. Translating the Observational Medical Outcomes Partnership - Common Data Model (OMOP-CDM) electronic health records to an OWL ontology. *Stud Health Technol Inform* 2022;290:76–80.
- [10] Daniel D, West-Mitchell K. The Sankey diagram: an exploratory application of a data visualization tool. *Transfusion (Paris)* 2024;64:967–8.
- [11] Yang X et al.. Far from the truth: real-world treatment patterns among newly diagnosed metastatic prostate cancer in the era of treatment intensification. *Int J Urol* 2023;30:991–9.

- 
- [12] Raval AD, Chen S, Littleton N, Constantinovici N, Goebell PJ. Real-world use of androgen-deprivation therapy intensification for metastatic hormone-sensitive prostate cancer: a systematic review. *BJU Int* 2025;135:408–21.
  - [13] de Bono JS et al.. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364:1995–2005.
  - [14] Fizazi K et al.. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2017;377:352–60.
  - [15] Goebell PJ et al.. Real-world treatment of metastatic hormone-sensitive prostate cancer in the USA, Europe and Asia. *Future Oncol* 2024;20:903–18.
  - [16] De Mauro A, Greco M, Grimaldi M. A formal definition of big data based on its essential features. *Library Rev* 2016;65:122–35.
  - [17] Gandaglia G et al.. Clinical characterization of patients diagnosed with prostate cancer and undergoing conservative management: a PIONEER analysis based on big data. *Eur Urol* 2024;85:457–65.