Epidemiology and treatment patterns of metastatic hormone-sensitive prostate cancer in France Insights from a retrospective claims database study (EPICAP)

O. Chapet[1], L-M. Scailteux[2], L. Inchboard[3], M. Laborey[3], A. David[3], R. Dumont[4], V. Sterin[5], N. Khan[6], S. Culine[7] and S. Vincendeau[8]

[1] Department of Radiation Oncology, Lyon South Hospital Center, Pierre Benite, Lyon, France. [2] Rennes University Hospital ; Rennes University ; Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, Rennes France. [3] Horiana, Bordeaux, France. [4] Bayer HealthCare Pharmaceuticals, La Garenne-Colombes, France. [5] Bayer HealthCare Pharmaceuticals, Lille, France. [6] Bayer HealthCare Pharmaceuticals, Whippany, New Jersey, USA. [7] Department of Medical Oncology, Saint-Louis Hospital, Paris, France. [8] Department of Urology, Saint-Grégoire Private Hospital (Vivalto Santé), Saint-Grégoire, France.

Introduction

Therapeutic management at metastatic hormone-sensitive prostate cancer (mHSPC) stage has evolved from androgen-deprivation therapy (ADT) alone to combinations with Androgen Receptor Pathway Inhibitors (ARPIs) abiraterone acetate (AA), apalutamide (APA), enzalutamide (ENZ) and darolutamide (DAR), which offer significant survival benefits.
However, managing ARPIs can be challenging due to frequent patient comorbidities and polypharmacy, raising risks of drug-drug interactions (DDIs) and contraindications (CI).

The EPICAP study aims to describe real-world occurrences, in patients with mHSPC treated with ARPI in France between 2018 and 2023, of

i) dispenses of contraindicated treatment (CIT) due to pharmacokinetic characteristics according to the European Society for Medical Oncology (ESMO) 2024 guidelines (1)

ii) comorbidities specified by “special warning (SW)” or “CI” in the ARPI Summary of Production Characteristics (SmPCs).

Study population

ESND database (N=1,689,299)

Retrospective real-world longitudinal cohort conducted on a representative 2% sample of the French national insurance claims database (ESND)

Patients with active PC (N=17,866)
between 2018 and 2023

Incident patients with mHSPC (N=1,311)
between January 1st, 2018, and June 30th, 2023

ARPI-treated patients with mHSPC (N=712)

Index date is defined at the first evidence of diagnosis of metastasis.
ARPI regimen during mHSPC stage was defined from the **1st ARPI** delivered until discontinuation*, end of follow-up or switch to another ARPI.

Which ARPI regimes were identified?

Abiraterone acetate (AA) 46%	Apalutamide (APA) 23%	Enzalutamide (ENZ) 29%

Darolutamide**

Table 1: Characteristics of ARPI-treated patients with mHSPC and their ARPI

	Abiraterone acetate (N=325)	Apalutamide (N=162)	Enzalutamide (N=208)
Age at index date (years) - Median (IQR)	73.0 (66.0; 79.0)	74.0 (69.0; 81.0)	77.0 (72.0; 83.5)
Triplet regimen (i.e. docetaxel during ARPI regimen), N (%)	55 (16.9)	≤ 10	16 (7.7)
Duration of ARPI regimen (months) - Median (IQR)	13.7 (6.7; 23.3)	10.6 (5.1; 19.7)	12.1 (6.3; 20.4)
Average number of dispenses per year - Median (IQR)	11.5 (10.4; 12.4)	11.9 (9.9; 12.7)	12.38 (9.5; 13.4)
Unexplained discontinuation*, N (%)	75 (23.1)	44 (27.2)	49 (23.6)
within 3 months of ARPI initiation, N (%)	18 (24.0)	23 (52.3)	16 (32.7)
by age group			
<65 years	13 (17.3)	≤ 10	≤ 10
65-74 years	23 (30.7)	14 (31.8)	14 (28.6)
≥75 years	39 (52.0)	28 (63.6)	29 (59.2)
Identification of transition to mCRPC*, N (%)**	63 (19.4)	17 (10.5)	30 (14.4)
End of ARPI regimen due to death, N (%)	48 (14.8)	≤ 10	21 (10.1)

** Discontinuation is defined as a pause between dispensing of more than 60 days, without evidence of transition to mCRPC or death. Reasons for discontinuation are not explicitly noted in the ESND.*
*** Group sizes (N= 17) were insufficient to describe treatments received by patients treated with darolutamide during the study period.*
**** Progression to mCRPC was identified by specific treatments or change of treatment regimen occuring immediately after an imaging test.*

Risk of drug-drug interaction

Methods: Identification of outpatient drug reimbursement (by ATC code) of frequent co-medications listed by ESMO (2024) during the ARPI regimen in order to identify potential risks of DDI according to:
- Increasing level of risk: C (Monitor therapy), D (Consider therapy modification) and X (Avoid combination)
- Type of potential interaction (i.e. effect on plasma concentration)

- **By risk level**

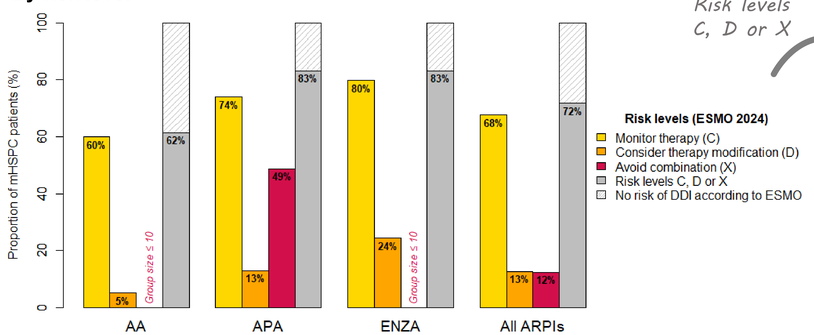

Figure 1: Proportion of ARPI-treated mHSPC patients with co-medications listed in risk levels C, D and X by ESMO (2024)

All ARPI-treated patients with mHSPC took at least 1 of the 155 co-medications listed by ESMO (all risk levels)
- 72% were exposed to co-medications with a risk-level of C or above, mostly with *Monitor therapy* drugs
- Patients treated with ENZ and APA were the most exposed (83% of each population) as they had the most potential DDIs (56 and 53 drugs listed as risk level C or above, respectively)
- APA-treated patients were the most exposed to drugs listed as *Avoid combination*, mostly due to proton pomp inhibitors and oral anti-coagulants (Table 2)
- Most of the potential DDIs cause a decrease in plasma concentration of the co-medication (Figure 2) due to either enzymatic inhibition (AA) or induction (APA, ENZA).

Table 2: Proportion of co-medicated ARPI-treated patients with mHSPC exposed to a potential DDI by risk level, ordered by frequency of drug class (including drugs with no risk of DDI). Blank cells indicate absence of risk of DDI in the corresponding drug class and empty cells indicate null values. Drug classes are restricted to those containing at least 10 patients with each ARPI.

	Abiraterone acetate (N=325)			Apalutamide (N=162)			Enzalutamide (N=208)		
Exposition to a risk of DDI, in patients treated with the following drug classes, N (%)									
Antihypertensives	19 (11.2)			48 (60.8)	≤ 10		65 (57.5)	≤ 10	
Proton pomp inhibitors - H2 blockers						61 (79.2)	27 (30.3)		
Cortisone				40 (88.9)	≤ 10		42 (85.7)	≤ 10	
Analgesics	65 (43.3)			30 (53.6)			68 (88.3)		
Drugs for coronary artery disease and heart failure		17 (12.7)			11 (20.8)		13 (13.5)	≤ 10	≤ 10
Lipid-lowering drugs	95 (91.3)			47 (83.9)			43 (53.8)		
Oral antibiotics								≤ 10	
Drugs for benign prostatic hyperplasia	45 (60.0)						13 (35.1)		
Sedatives				22 (84.6)			36 (73.5)		
Oral anticoagulants				≤ 10		25 (96.2)	≤ 10	39 (92.7)	
Oral Anti-diabetics							≤ 10		
Antiemetics	49 (37.3)			11 (52.4)		≤ 10	13 (39.4)		≤ 10
Other commonly used drugs	≤ 10			12 (57.1)	≤ 10				
Antidepressants	19 (36.5)			≤ 10			12 (48.0)		
Oral or inhaler potassium-lowering drugs									

Risk-level according to ESMO 2024: *Monitor therapy (C)* *Consider therapy modification (D)* *Avoid combination (X)*

- **By type of potential DDI**

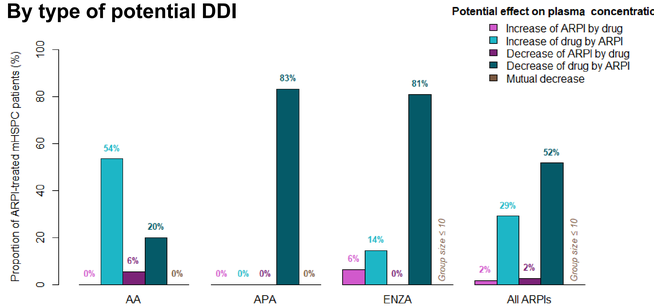

Figure 2: Proportion of ARPI-treated patients with co-medications listed as C, D or X by type of interaction

Contra-indications

Methods: Identification of comorbidities listed in the ARPI SmPCs based on healthcare consumption and reimbursements prior to and during ARPI regimen

Table 3: Proportion of ARPI-treated mHSPC patients with contra-indications and special warnings listed in the SmPCs

	Abiraterone acetate (N=325)	Apalutamide (N=162)	Enzalutamide (N=208)
Presence at baseline of contra-indications or special warning listed in the SmPCs, N (%)			
Treatment for high blood pressure	177 (54.5)	104 (64.2)	131 (63.0)
Cardio-neurovascular diseases	115 (35.4)	64 (39.5)	87 (41.8)
Cardiac rhythm or conduction disorders	72 (22.2)	39 (24.1)	50 (24.0)
Chronic respiratory diseases, excluding cystic fibrosis	38 (11.7)	18 (11.1)	35 (16.8)
Other cancer	11 (3.4)	≤ 10	13 (6.3)
Stroke sequelae	14 (4.3)	≤ 10	14 (6.7)
Osteoporosis	15 (4.6)	≤ 10	≤ 10
Chronic heart failure	≤ 10	≤ 10	11 (5.3)
Epilepsy	≤ 10	≤ 10	≤ 10
Liver disease	**≤ 10**	≤ 10	≤ 10
Chronic renal disease	0 (0.0)	0 (0.0)	0 (0.0)
Serious cutaneous adverse event	0 (0.0)	0 (0.0)	0 (0.0)
Co-medication with oral corticosteroid (OCS), N (%)			
Absence of corticosteroids dispensing	≤ 10	112 (69.1)	146 (70.2)
Withdrawal *(Delay between dispensing > 60 days)*	186 (57.2)	-	-

Legend: ***Special warning***; ***contra-indication.***

- At ARPI initiation, 54.5% of AA users were under treatment for hypertension (Table 3).
- 39.5% of APA users had evidence of cardio-neurovascular disease and 24.1% had cardiac rhythm or conduction disorders.
- 41.8% of ENZ users had cardiac rhythm or conduction disorders.
- Practically all AA-treated patients receive corticosteroids but 57.2% have at least one suspected pause during their AA regimen, for which the cause is missing.

Take home message

This study highlights that over 70% of patients with mHSPC are exposed to a risk of DDIs when treated with ARPIs in real-world settings in France. These findings underscore the complexity of managing of polypharmacy in patients with prostate cancer. Moreover, differences exist between ARPIs regarding their metabolic profiles and interaction potential, highlighting the need to carefully consider DDIs when selecting the most appropriate therapy.

(1) Bolek H, Yazgan SC, Yekedüz E, Kaymakcalan MD, McKay RR, Gillessen S, Ürün Y. Androgen receptor pathway inhibitors and drug-drug interactions in prostate cancer. ESMO Open. 2024 Nov;9(11):103736. doi: 10.1016/j.esmoop.2024.103736. Epub 2024 Oct 18. PMID: 39426080; PMCID: PMC11533040.