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Lucie-Marie Scailteux, Boris Campillo-Gimenez, Sandrine Kerbrat, Fabien Despas, Romain Mathieu, Sébastien Vincendeau, Frédéric Balusson, André Happe, Emmanuel Nowak, Emmanuel Oger

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**Overall survival among chemotherapy-naïve castration-resistant prostate cancer patients under abiraterone versus enzalutamide: a direct comparison based on a 2014-2018 French population study (the SPEAR cohort).**

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Running head: abiraterone and enzalutamide survival in CRPC patients.

**Abstract** (196/200 words)

Abiraterone acetate (ABI) and enzalutamide (ENZ) are considered as clinically relevant comparators among chemotherapy-naïve castration-resistant prostate cancer patients. No clinical trials comparing overall survival (OS) of ABI to ENZ in a head-to-head approach have been published so far. A few observational studies with lack of power suggested a potential benefit of ENZ.

Based on the French National Health Data System ('SNDS'), we built a national cohort of chemotherapy-naïve castration-resistant prostate cancer patients to compare OS of new users of ABI and ENZ in 2014-2017, followed through 2018. With an "intent-to-treat" approach, a survival analysis was performed, estimating hazard ratios (HRs) for OS with the inverse probability weighted Cox model method.

Among 10 308 new users, 64% were treated with ABI, 36% with ENZ. The crude mortality rate was 25.2 per 100 person-years, 95% CI: 24.4, 26.0 for ABI and 23.7 per 100 person-years, 95% CI: 22.6, 24.9 for ENZ. In the weighted analysis, ENZ was associated with better OS compared to ABI (HR 0.90, 95% CI: 0.85,0.96; median OS, 31.7 months for ABI and 34.2 months for ENZ). When restricting to 2015-2017 new users, the effect estimate shifted up to HR 0.93, 95% CI: 0.86, 1.01.

**Key words**

abiraterone, enzalutamide, metastatic castration-resistant prostate cancer, overall survival, population-based study, SNDS.

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**Abbreviations:**

ABI: abiraterone

ADT: androgen deprivation therapy

CRPC: castration-resistant prostate cancer

ENZ: enzalutamide

NHT: new hormonal therapies

OS: overall survival

PCa: prostate cancer

SIPTW: stabilized inverse probability of treatment weighting

SNDS: *système national des données de santé*

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Among patients with on-going androgen suppression, castration-resistant prostate cancer (CRPC) is defined as castrate levels of serum testosterone < 50 ng/dl and a biochemically observed (three consecutive increases in prostate-specific antigen) and/or a radiologically observed progression (new bone or soft tissue lesions)(1). First-line treatment includes oral treatment: abiraterone acetate [ABI] (Zytiga®, Janssen-Cilag International NV, Beerse, Belgium) enzalutamide [ENZ] (Xtandi®, Astellas Pharma Europe B.V., Leiden, Netherlands), chemotherapy (docetaxel), and radium-223. Sipuleucel-T is only authorized in the United States. Cabazitaxel is considered as a second-line chemotherapy option. ABI and ENZ efficacy and safety have been assessed in clinical trials since 2012 in two specific contexts: in patients for whom chemotherapy containing docetaxel has not worked or no longer works (COU-AA-301 and AFFIRM)(2,3), and those for whom chemotherapy is not yet needed (COU-AA-302 and PREVAIL)(4–6). ABI is the clinically relevant comparator of ENZ because of a hormonal pharmacological mechanism. They are considered as two novel hormonal therapies (NHTs): ABI is a CYP 17 enzyme inhibitor hindering androgen synthesis in the adrenal glands and testes as well as in the prostate tumor; ENZ is a second-generation anti-androgen inhibiting the nuclear translocation of the dihydrotestosterone-androgen receptor complex(7).

To date, no clinical trials comparing patient overall survival (OS) under ABI and ENZ in a head-to-head approach have been published. Two small phase-III clinical trials (200 and 50 patients included respectively) have been designed to assess OS as a secondary outcome in chemotherapy-naïve CRPC patients; results are expected by 2020(8,9). Several meta-analyses involving the same core clinical trials have indirectly compared ABI and ENZ in a pre- and post-chemotherapy setting(10–16): in a pre-chemotherapy setting, authors suggested a potential (but non-significant) benefit consistently around 10% with ENZ in terms of OS(10,13,16). Presented at the American Urological Association 2019 Annual Meeting, using the US military veterans database involving 3174 metastatic CRPC patients

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between 2013 and 2018, a population-based study suggested a significantly longer OS for patients initiating ENZ compared to those starting ABI (HR 0.87, 95%CI: 0.78,0.96)(17).

Because a powerful clinical trial is costly and time-consuming, and because the patients enrolled are often not representative of real-world practice, an observational study using a healthcare database seems appropriate and provides additional information. The aim of our study was to compare OS among metastatic chemotherapy-naïve CRPC patients under ABI and ENZ using a direct approach.

## METHODS

*Study design and data sources.* This cohort study (named 'SPEAR') was designed using the pseudo-anonymous individual French National Health Data System ('SNDS', *système national des données de santé*). 'SNDS' links the healthcare reimbursement database to the French hospital discharge database. The healthcare reimbursement database collects since 2009 all claims covered at least partly by the universal French Health insurance system which shelter 99% of the French population, through several insurance plans. The healthcare reimbursement database database contains data on all reimbursements of health expenditure (biological, radiological, pathology examinations as well as clinicians' consultations), the drugs involved, and vital status. The hospital discharge database provides diagnoses through the International Statistical Classification of Diseases, 10<sup>th</sup> revision [ICD-10] codes, details on medical acts as well as on some expensive drugs(18).

*Study population and exposure.* The target population was metastatic CRPC (mCRPC). We identified all adult men who were new users of ABI or ENZ in 2014-2017, as a proxy for PCa progression towards the mCRPC stage. ABI and ENZ were identified through Anatomical Therapeutic Chemical codes in the healthcare reimbursement database (Web Table 1). The date of the first ABI or ENZ reimbursement in 2014-2017 was considered as the start (T0) of

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the follow-up and exposure was based on the first received. New users were defined as having had no previous ABI or ENZ reimbursement in the 3 years before T0 (Web Figure 1). We excluded patients with female gender, without data in the 'SNDS' in the 2 years preceding T0 as well as patients with a cancer in addition to PCa before T0, based on ICD-10 codes (Web Table 1) for hospitalization or registration for long-term disease status which authorizes 100% reimbursement of all disease-related claims. In 'SNDS', the code name of the chemotherapy or radiotherapy sessions do not specify the type of cancer concerned. By excluding other cancers, we were reassured that the chemotherapy or radiotherapy sessions were performed only for PCa. We focused the analysis on patients who did not require chemotherapy by excluding patients for whom chemotherapy sessions (docetaxel, cabazitaxel) were identified, through the hospital discharge database, using all patient history data with a look back up to 01/01/2009, if available (90% of the study population had data history prior to T0 as far as 2009 and 98% prior to T0 as far as 2012). Patients with some comorbidities listed as contraindications or precaution for use in the summary of product characteristics of ABI (Zytiga®) or ENZ (Xtandi®)(Figure 1) were also excluded.

*Outcome.* The primary outcome was overall survival (OS), defined as the time from the first NHT reimbursement to death from any cause. Patients were censored on December 31<sup>st</sup>, 2018 if they were still alive.

*Covariates.* Several chronic comorbidities were identified (see details on ICD-10 codes, medical acts and drugs in Web Table 1) in the 3 years before T0: chronic renal failure, hypertension, diabetes, atrial fibrillation, cardiac failure, arterial ischemic disease (stroke, myocardial infarction and other coronary disorders). In the year before T0, we identified variables included in the modified Charlson comorbidity index according to Bannay et al.(19) We also identified specific treatments (antidiabetics, anticoagulants, platelet inhibitors, opiates, bisphosphonates, and bone metastasis treatment), and prostate-specific antigen

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titration. Previous PCa treatments were identified from January 1<sup>st</sup>, 2009 (androgen deprivation therapy [ADT], radical prostatectomy, radiotherapy (palliative or not), brachytherapy). Regarding ADT, we took into account the first date of ADT reimbursement in the absence of a gap of at-least 6 months after the last day of exposure of the last ADT reimbursed. If a gap was identified, we considered the ADT to begin from the first date of the more recent ADT session prior the ADT or ENZ introduction.

*Statistical analysis.* Patient characteristics, treatment received and outcome were compared between patients who were prescribed ABI (reference) and ENZ. We reported mortality during the study period, median follow-up (1<sup>st</sup> and 3<sup>rd</sup> quartile, Q1, Q3), and estimated the crude mortality rate per 100 person-years with 95 % confidence interval (95% CI). In an “intent-to-treat” approach (treatment group was based on the first ABI or ENZ reimbursement in 2014-2017), a survival analysis was performed. We generated the probability of treatment (ABI versus ENZ) using logistic regression model using specified variables (all variables of the modified Charlson comorbidity index (19), other comorbidities, and previous PCa treatment, especially ADT duration, listed in [Web Table 2](#) along with standardized differences). We then used the stabilized inverse probability of treatment weighting (‘SIPTW’) based on the propensity score(20) as weights in Cox proportional hazard regression model.

Regarding the propensity score, due to a history limited to data available since 2009, it was not possible to determine the total duration of ADT for some patients because the starting for ADT was not observable. ADT duration was categorized as follows: < 2 years of ADT, between 2 years and 3 years of ADT, > 3 years of ADT. In addition, a binary variable (yes or no) expressed a potential gap of ADT exposure in the 6 months before ABI or ENZ started. Variables identified in fewer than 2% of patients and not significantly associated with OS were not considered in the propensity score.



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Weighted (SIPTW) Kaplan-Meier cumulated incidence plots were generated to characterize overall survival.

Sensitivity analyses were planned as follows. Firstly, the propensity score weights were truncated by resetting the extreme value of weights above (or below) the 99<sup>th</sup> (1<sup>st</sup>) percentile to the value of the 99<sup>th</sup> (1<sup>st</sup>) percentile(21). Secondly, because potential channeling (due to different market authorization dates for NHT) and selection biases (publication in July 2017 of the LATITUDE trial showing a increased overall survival with ABI in men newly diagnosed metastatic castration-sensitive prostate(22)), we performed an analysis restricted to NHT new users between July 1<sup>st</sup>, 2015 and and June 30<sup>th</sup>, 2017 (Web Figure 2).

The 'SNDS' database does not include clinical information: residual confounding might occur since we can not identify *performans status* and fatigue for example (23,24). We reported an E-value, calculated through a straightforward formula using the HR(25), to estimate how strongly an unmeasured confounder would have to be associated with the treatment and outcome for the treatment–outcome association not to be causal(25,26).

## RESULTS

Over the 2014-2017 period, 10 308 new NHT users were identified: 6 585 (64 %) were prescribed ABI, and 3723 (36 %) ENZ (Figure 1). Patients characteristics are provided in Table 1.

The mean age was close, 77.3 years in the ABI group and 78.6 years in the ENZ group. Using the available history of PCa treatment from 2009, all patients had a minimum of 3 prostate-specific antigen titrations in the year before NHT instatement. The ADT initiation date was identified for 77 % of ABI patients and 81 % of ENZ patients: around 42 % had more than 3

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years of ADT, 23 % between 1 and 2 years, and 16 % had less of 1 year (Web Table 3). Less than 9 % of patients had at least one session of radiotherapy in their history (since 2009).

The distribution of comorbidities and the modified Charlson comorbidity index were broadly similar. Web Table 2 shows the absolute standardized differences in covariates included in the propensity score: after weighting, it varied from 0.000 to 0.003 indicating a good balance between the treatment groups (see Web Figure 3 for propensity score curves).

Table 2 describes the number of deaths and the incidence rates. With a median follow-up of 23.2 months for ABI and 20.8 months for ENZ, the mortality rate (95%CI) was 25.2 (24.4, 26.0) per 100 person-years for ABI and 23.7 (22.6,24.9) per 100 person-years for ENZ.

In the weighted Cox model analysis, ENZ was associated with a better OS compared to ABI (HR 0.90, 95% CI: 0.85, 0.96). Weighted Kaplan-Meier cumulated incidence plots are shown in Figure 2: SIPTW median OS was 31.7 months for ABI and 34.2 months for ENZ (Web Table 4).

Regarding the sensitivity analyses, consistent result were observed when using truncated weights (Table 3). When restricting to new NHT users between July 2015 and June 2017 (Web Table 5, Table 3), the effect estimate shifted up and toward and including the null: HR 0.93 (95% CI, 0.86, 1.01).

The respective treatment durations are provided in Web Table 6. A subsequent PCa treatment was observed for 53.8 % patients in the ABI group and 35.3 % in the ENZ group (Web Table 7): the first subsequent therapy was NHT in both groups (ABI to ENZ in 59 %, and ENZ to ABI in 52%); chemotherapy with docetaxel concerned 40 % of the ABI group and 47 % of the ENZ group. Based on the available follow-up, approximately 29% and 25% of patients in the ABI and ENZ groups, respectively, discontinued their NHS treatment without any further treatment being introduced.

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Regarding residual confounding, the observed hazard ratio of 0.90 could be explained away by an unmeasured confounder that was associated with both treatment and outcome with a risk ratio of at least 1.47 for each, but a weaker association for the unmeasured confounder could not do so (Web Figure 4).

## DISCUSSION

According to the European guidelines, ABI and ENZ are equivalent first-line treatment options in mCRPC(1). On the basis of this population-based study including 10 308 new users of NHT in a chemotherapy-naïve setting, our analysis suggested a 10 % better OS with ENZ compared to ABI (SIPTW median OS, 31.7 months for ABI and 34.2 months for ENZ). However, after restricting to NHT new users between July 2015 and June 2017, the effect estimate shifted up to HR 0.93 (95% CI, 0.86, 1.01).

Our result is in line with those consistently observed but non-significant in indirect meta-analyses(10,13,16). It is also similar to that observed in the US military veteran database (HR 0.87, 95 % CI: 0.78, 0.96)(17). Cautious comparison has to be made considering that their statistical analysis involved a propensity score matching between ABI and ENZ treated patients, their patients were younger (73 and 74 years), median OS was slightly lower compared to us (26.0 months for ABI and 29.3 months for ENZ), and finally their cohort probably involved more African-American patients than our French cohort.

Possibly due to a lack of power, two cohorts did not detect any significant difference on OS in chemotherapy-naïve CRPC patients: respectively, HR 0.60, 95% CI: 0.27, 1.36 (median OS, 31.6 months for ABI and not reached for ENZ) when ENZ was compared to ABI in a cohort of 120 Brazilian patients(27), and HR 1.20, 95% CI: 0.89,1.63 (median OS, 13.2 months for ABI and 18.7 for ENZ) when ABI was compared to ENZ in a cohort of 210 Canadian patients of the British Columbia Cancer Agency(28).

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Unfortunately, we were unable to compare the characteristics of our patients with those of the patients of US, Brazilian and Canadian observational studies as only brief information of the 2018 and 2019 annual meetings of the American Urological Association and American Society of Clinical Oncology was available(17,27,28).

Two clinical trials (not referenced on [www.clinicaltrials.gov](http://www.clinicaltrials.gov)) are currently recruiting (final results expected after 2020) to include respectively 200 and 50 japanese chemotherapy-naïve CRPC men (8,9). OS was the secondary endpoint in both trials. Several studies compared OS between ABI to ENZ through sequential therapies(29–34). The main limitations were the retrospective design, the low number of patients included and, contrary to our intent-to-treat design, analysis involved only specific treatments sequences. Looking more in depth on the optimal sequence in our study could be interesting to challenge the literature.

Compared to our study, median OS in the core clinical trials were slightly higher: 34.7 months (95% CI: 32.7, 36.8) in COU-AA-302(4), and 32.4 months in the interim analysis and 35.3 months (95% CI: 32.2, not yet reached) in the extended analysis of PREVAIL(5,6), respectively. This may be due to the fact that patients treated in daily practice are older and have more comorbidities than patients included in clinical trials(35,36). A systematic review of ‘real-life’ studies involving ABI in chemotherapy-naïve CRPC patients (8 studies; 11 to 204 patients included), revealed that median OS ranged from 14 to 36.4 months(37). Among 457 Austrian chemotherapy-naïve CRPC patients receiving at least one prescription of ABI and/or ENZ between 2013 and 2016, the median OS was 18 months for ABI and 17 months for ENZ(38).

As a proxy measure of PCa progression toward CRPC, we observed that in the year before the initiation of NHT, all patients had a minimum of 3 prostate-specific antigen titrations, which is compliant with the European guidelines defining CRPC(1). Regarding PCa treatment,

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using data from 2009, all patients were previously exposed to ADT, which is consistent with the European guidelines(1). We had no information on the PCa diagnosis date or the initial PCa treatment but we were able to estimate the duration of ADT before NHT initiation: in a similar proportion between groups, around 42% were long-term ADT users (> 36 months) while 16% had rapid disease progression with less than 12 months of ADT. In the clinical trials, the median time from initial diagnosis or first PCa treatment was 63 months (5.25 years) in the ENZ group (PREVAIL)(5); the median time from initial diagnosis to the first ABI dose was 5.5 years (COU-AA-302)(39). We observed a smaller proportion of patients with previous PCa cancer treatments (especially surgery and radiotherapy) compared to the clinical trials involving ABI or ENZ (COU-AA-302(4) and PREVAIL(5)).

## Strengths

Our large comprehensive study using 'SNDS' database is unique by its ability to include all men eligible for treatment for mCRPC, and more specifically those for whom NHT treatment was initiated in a chemotherapy-naïve setting. Conducting a well-designed and powerful clinical trial comparing NHT for OS would be complex and costly. Our study directly compared different NHTs in the same indication (chemotherapy-naïve setting). The use of the PS minimized the indication bias, conditional on all factors being measured. Data exhaustiveness minimized any potential selection or recall biases, which can be a problem in observational studies. Although we selected patients who survived up to the mCRPC stage, focusing on new NHT users minimized the immortal time bias. Another strength concerns the use of OS as the main outcome: considered as the reference outcome in clinical trials, especially in oncological studies(40,41), it is not subject to a classification bias unlike specific survival or progression-free survival for instance. More easily transferred to the context of observational studies and easily determined from the French administrative database, OS

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enables a comparison of results across clinical trials(42). Given the kinetics of cancer progression, especially at the mCRPC stage, and given that our study period lasts 5 years, death is an event liable to be detected.

Regarding subsequent PCa treatment, in our study, clinicians tended to use NHT alternative (ABI in ENZ group and vice-versa), and docetaxel was used as second-line treatment. This is not in line with clinical trials(4,5) nor the European guidelines(1) where docetaxel should be offered next, if patients remain clinically suitable. This recommendation is supported by several studies suggesting cross-resistance between hormonal therapies(43–46). To limit bias and misinterpretation, keeping in mind we aimed to assess effectiveness, we used an “intent-to-treat” like analysis which is a more conservative approach.

#### Limitations

‘SNDS’ database did not provide data regarding cancer staging, especially grading the metastases extension. However, we performed a head-to-head comparison between two drugs which have the same indication. Previous PCa treatments were also carefully taken into account, for instance the duration of ADT. As an attempt to assess frailty status, we used all variables included in the Charlson comorbidity index (which was correlated with overall mortality in France(19)), as well as other comorbidities. For all those comorbidities, the two groups seemed to be similar owing to SIPTW with very low standardized differences. Lastly, we could not rule out a differential prescription of ABI or ENZ. As residual confounding is a concern, we calculated an E-value which is also a matter of debate (26,47,48).

## **Conclusion**

Without taking account of subsequent PCa therapy, our French population-based study including new NHT users among chemotherapy-naïve mCRPC men suggested that first-line ENZ is associated with better OS compared to ABI, keeping in mind that the strength of association could be weak.

## **Acknowledgments**

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### Author contributions:

Scailteux, Oger, Kerbrat and Nowak had full access to all of the data that was used to generate the study population. The database extracted was stored in a dedicated space on the CNAMTS portal. Kerbrat carried out the data management (cleaning, table design and choice of variables for statistical analyses). They take responsibility for the integrity of the data and the accuracy of the data analysis. They performed the statistical analysis.

Scailteux, Oger, Campillo-Gimenez, Despas : conception and design.

Scailteux: drafting of the manuscript.

Scailteux, Oger: obtained funding.

Oger: supervision, administrative, technical, or material support.

Campillo-Gimenez, Despas, Mathieu, Vincendeau: critique of completed data analysis and interpretation in the manuscript.

All authors: acquisition, analysis and interpretation of the data; critical revision of the manuscript for important intellectual content.



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**Table 1. Baseline Characteristics of Chemotherapy-naïve mCPRC patients, France, 2014-2017.**

	Source population				Weighted pseudo-population <sup>i</sup>	
	ABI <sup>h</sup> n = 6585		ENZ <sup>h</sup> n = 3723		ABI	ENZ
Age in years <sup>a</sup>	77.3 (8.9)		78.6 (8.9)		77.7 (8.9)	77.7 (8.9)
Characteristics	n	%	n	%	%	%
Prostate cancer treatment and management <sup>b</sup>						
ADT exposure with an ADT start date identified <sup>c</sup>	5052	76.7	3007	80.8	76.9	80.5
Duration <sup>d</sup> of ADT (when ADT start date was identified), in months	23.9 (13.6, 38.3)		24.1 (13.4, 40.2)		j	j
Brachytherapy	5	0.1	5	0.1	0.1	0.1
Prostatectomy	88	1.3	57	1.5	1.3	1.6
Radiotherapy <sup>e</sup>	538	8.2	327	8.8	8.6	8.1
Curative Radiotherapy	447	6.8	300	8.1	7.3	7.3
PSA titration 1 year before inclusion						
Number <sup>c</sup> of PSA titrations	4 (3-5)		4 (3-5)		4 (3-5)	4 (3-5)
Number <sup>a</sup> of PSA titrations	4.5 (2)		4.4 (2)		4.5 (2)	4.4 (2)
Comorbidities <sup>f</sup>						
Hypertension	4235	64.3	2453	65.9	64.9	64.9
Chronic renal insufficiency	234	3.6	166	4.5	3.8	3.8
Diabetes (with or without organ damage)	1204	18.3	824	22.1	19.7	19.7
Atrial fibrillation	525	8.0	402	10.8	9.0	9.0
Heart disease (including cardiomyopathy)	205	3.1	142	3.8	3.4	3.3
Ischemic stroke	107	1.6	71	1.9	1.7	1.8
Atherosclerosis and peripheral embolism	148	2.2	110	3.0	2.4	2.5
Use of anticoagulants in the year before T0	797	12.1	526	14.1	12.9	12.9
Use of antiplatelet inhibitors in the year before T0	1979	30.0	1241	33.3	31.2	31.1
Use of dyslipidemia drugs in the year before T0	2702	41.0	1607	43.2	41.8	41.8
Ischemic heart disease and/or coronary revascularisation	841	12.8	573	15.4	13.7	13.7
Carotid and peripheral angioplasty	40	0.6	35	0.9	0.7	0.8
Smoking disorders or chronic obstructive pneumopathy	518	7.9	365	9.8	8.2	9.1
Alcohol use disorders	94	1.4	47	1.3	1.4	1.3
Obesity	285	4.3	234	6.3	5.1	5.1
Use of drugs affecting bone structure and mineralisation in the year before T0	174	2.6	82	2.2	2.5	2.5
Use of drug preventing tumor bone complications in the year before T0	810	12.3	359	9.6	11.4	11.1
Use of opioids and derivatives in the year before T0	1297	19.7	710	19.1	19.5	19.5
Modified CCI (according to Bannay et al.) <sup>g</sup>						
0	439	6.7	287	7.7	6.7	7.7
1	85	1.3	47	1.3	1.4	1.2
2	4869	73.9	2626	70.5	72.9	72.3
≥ 3	1192	18.1	763	20.5	19.0	18.8
Component of the Modified CCI identified in the year before ABI / ENZ initiation						
Ischemic heart disease	724	11.0	494	13.3	11.8	11.8
Peripheral vascular disease	322	4.9	225	6.0	5.3	5.3
Cerebrovascular disease	252	3.8	165	4.5	4.1	4.1
Dementia	131	2.0	81	2.2	2.1	2.0
Chronic pulmonary disease	605	9.2	387	10.4	9.7	9.7
Rheumatic disease, connective tissue disease	50	0.8	35	0.9	0.8	0.9
Peptic ulcer disease, ulcer disease	10	0.2	9	0.2	0.2	0.2
Diabetes without complications	1108	16.8	764	20.5	18.0	18.3
Diabetes with end-organ damage	49	0.7	30	0.8	0.9	0.7
Hemiplegia	33	0.5	25	0.7	0.5	0.6
Moderate or severe renal disease	161	2.5	102	2.7	2.6	2.3
AIDS/HIV	11	0.2	3	0.1	0.2	0.1

ABI: abiraterone; ADT: androgen deprivation therapy; ENZ: enzalutamide; mCPRC: metastatic castration-resistant prostate cancer.

a Values are expressed as mean (standard deviation).

b Prostate cancer treatment history used data from January 2009.

c Patients for whom an ADT start date was identified because sufficient history was available before ABI or ENZ start.

d Values are expressed as median (1<sup>st</sup> quartile value, 3<sup>rd</sup> quartile value).

e Radiotherapy sessions, at least one session identified in the entire history (from January 2009).

f Comorbidities were identified in the 3 years before T0 except if specifically mentioned.

g According to the Bannay et al. definition (19), components of the modified Charlson comorbidity index were identified in the year before T0;

h New users of ABI/ENZ and based on the first drug received.

i Weights are based on the stabilized inverse probability of treatment.

j The ADT duration was not considered as a continuous variable since patients could have more than 3 years of treatment (open category). The ADT duration was therefore considered in 3 categories (<1y; 1-2 y; >3y).

**Table 2. Number of Deaths and Crude Mortality Incidence Rate of mCPRC Patients (new users of ABI and ENZ in 2014-2017, followed through 2018) in the Weighted Pseudo-population<sup>a</sup>, France, 2014- 2018.**

Treatment	Median follow-up in months (Q1, Q3)	Number of deaths	Person-years	Crude mortality incidence rate per 100 person-years	95% CI
ABI	23.2 (14.4, 37.4)	3543	14073.4	25.2	24.4, 26.0
ENZ	20.8 (14.0, 29.6)	1580	6665.0	23.7	22.6, 24.9

ABI: abiraterone; CI: confidence interval; ENZ: enzalutamide; mCPRC: metastatic castration-resistant prostate cancer; Q1, Q3: Q1 stands for 1<sup>st</sup> quartile value and Q3 for 3<sup>rd</sup> quartile value.

<sup>a</sup> Weights are based on the stabilized inverse probability of treatment.

**Table 3. Survival Analysis using Propensity Score Weighted Cox Model in mCRPC patients, France, 2014-2018.**

Treatment	Main analysis with SIPTW		Sensitivity analysis with truncated weights at the 1 <sup>st</sup> and 99 <sup>th</sup> percentiles		Sensitivity analysis restricted to new users between July 2015 and June 2017	
	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI
ABI	1.0	Referent	1.0	Referent	1.0	Referent
ENZ	0.90	0.85, 0.96	0.90	0.85, 0.96	0.93	0.86, 1.01

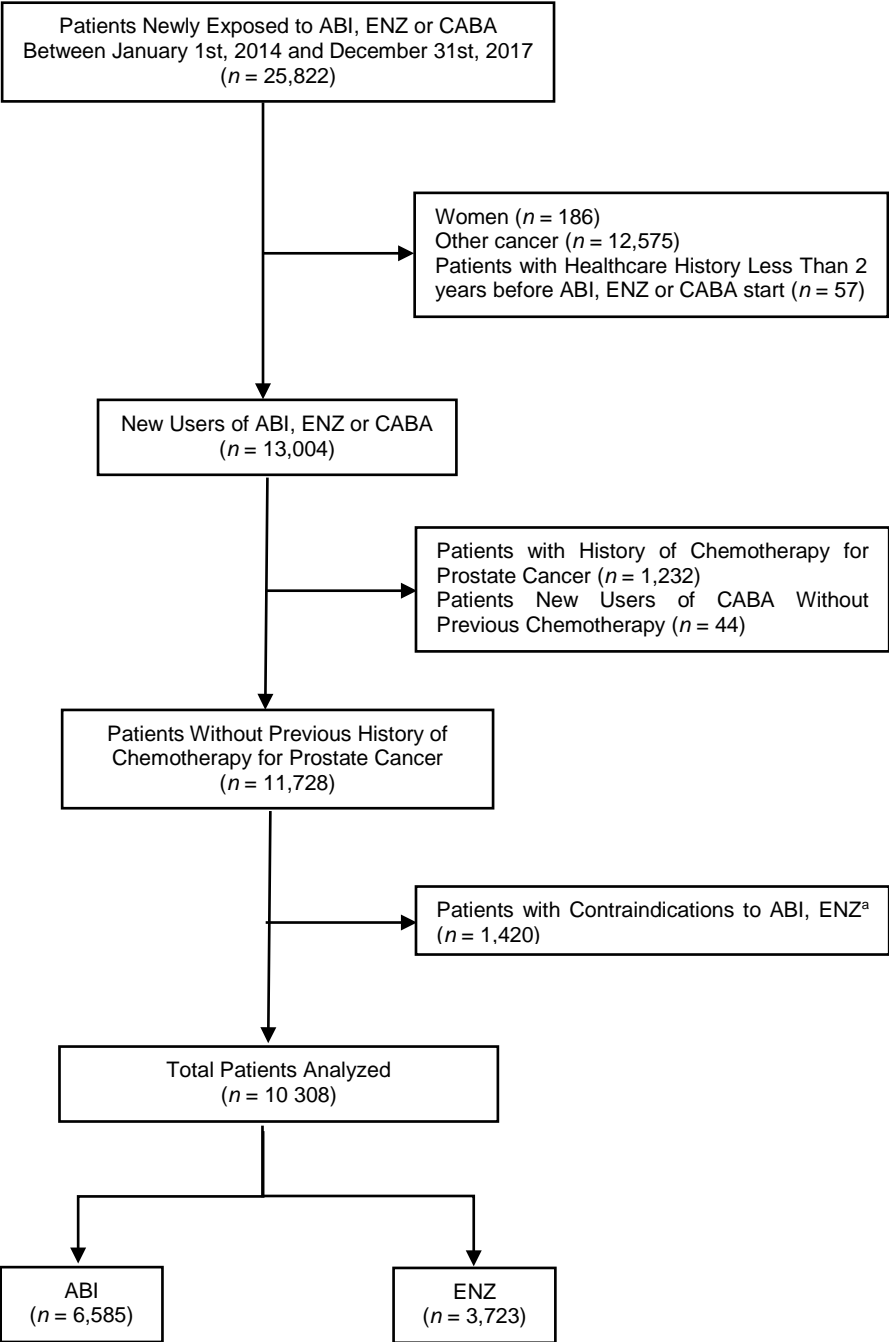
ABI: abiraterone; CI: confidence interval; ENZ: enzalutamide; mCRPC: metastatic castration-resistant prostate cancer; SIPTW: stabilized inverse probability of treatment weighting.

FIGURE LEGENDS

Figure 1. Flow-chart of the mCRPC Population, France, 2014-2017.

Figure 2. Weighted Kaplan-Meier Curve of Overall Survival in mCRPC patients, France, 2014-2018.

Figure 1. ABI: abiraterone; CABA: cabazitaxel; ENZ: enzalutamide. a: Patients with at least one of the following drug contraindications were excluded: recent myocardial infarction (in the year before drug start), cardiac failure, liver failure, antiepileptic drugs (in the year before drug start).





**Figure 2.** Kaplan-Meier curve with number of subjects at risk (solid line, abiraterone; dotted line, enzalutamide). Efficiency analyses were done in the intention-to-treat weighted pseudo-populations (i.e., all patients assigned to abiraterone or enzalutamide), irrespective of subsequent crossover. Weights are based on the stabilized inverse probability of treatment. The median overall survival is 31.7 months for abiraterone and 34.2 months for enzalutamide.

