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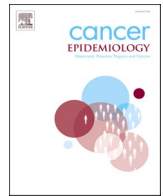
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Epidemiology of metastatic castration-resistant prostate cancer: A first estimate of incidence and prevalence using the French nationwide healthcare database

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ABSTRACT

Background: There is a lack of information about the burden of metastatic castration-resistant prostate cancer (mCRPC). The present work aims to estimate the incidence and prevalence of mCRPC in 2014 using the French nationwide healthcare database (SNDS).

Methods: Prevalence and incidence were estimated based on an SNDS extraction of men covered by the general healthcare insurance (86 % of the French population), and aged ≥ 40 . Patients with mCRPC were identified amongst prostate cancer cases using an algorithm estimating a date of first metastasis management and a date of castration resistance. This algorithm was validated by clinical experts through a blind review of 200 anonymized medical charts from SNDS data. Prevalence and incidence were standardized on the European Standard Population (2013 edition).

Results: Prevalence and incidence of mCRPC were estimated as, respectively, 62 and 21 cases per 100 000 men in 2014. Less than one mCRPC case per 100 000 was observed in men aged 40–49. Maximum mCRPC incidence was in men aged 80–89 (175 per 100 000). The algorithm used for mCRPC identification had 97 % positive and 99 % negative predictive values.

Conclusion: The good performances of the algorithm for mCRPC identification and the consistency of the generated results with the existing data highlight the robustness of these first estimates of mCRPC prevalence and incidence. Future updates will call for algorithm adjustment as practices evolve over time. These first real-life data will serve for future follow-up of the impact of changes in the management of prostate cancer.

1. Introduction

Prostate cancer (PC) is the most common cancer in men [1]. The management of PC depends on the stage of the disease. Locally limited disease usually receives active surveillance or local treatment such as surgery, radiotherapy, brachytherapy, or high-intensity focused

ultrasound (HIFU) [2–5]. In advanced PC, androgen deprivation therapy (ADT)—relying on gonadotropin-releasing hormone (GnRH) analogs or antagonists, anti-androgens or estrogens—is added to the local treatment [2–5]. However, after varying lengths of time, many patients develop resistance to ADT (castration-resistant PC, CRPC) [6]. Patients diagnosed at localized and locally advanced stages develop metastases

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within 5 years in 20 % and 40 % of cases respectively [7]. Thus, patients progress gradually from non-metastatic hormone-sensitive PC to metastatic castration-resistant PC (mCRPC), requiring specific treatments such as androgen-receptor-targeted therapies (abiraterone acetate or enzalutamide) or chemotherapy (docetaxel, cabazitaxel), most of the time with prednisone or prednisolone [3,8,9].

The French National Cancer Institute (Institut National du Cancer, INCa) and the French Network of Cancer Registries (Francim) estimated the total prevalence of PC in 2008 in France at 508 699, with 53 913 new cases in 2011 and 50 430 cases in 2015 [1,10,11]. Many studies have been limited to local registries, estimating national incidences using mortality as a correlate [10,12]. More recent estimations can be found in studies that used the French nationwide healthcare database (Système National des Données de Santé, SNDS) [13,14]. However, no data are available on metastatic, resistant or mCRPC stages. The CAMERRA study—Therapeutic strategy in Metastatic castration-Resistant prostate cAnCER: target population and changes between 2012 and 2014—was launched to address the lack of real-world data about this specific stage of PC, identifying mCRPC patient in the SNDS database, describing their characteristics, and assessing the evolution of their management. The objective of this paper is to introduce and discuss the first stage of the study, the identification of the mCRPC patients (including the estimation of the mCRPC incidence and prevalence in 2014), to provide rational for forthcoming CAMERRA results.

2. Methods

2.1. Study design

The incidence and prevalence of PC and mCRPC were estimated for the year 2014 through a cross-sectional study using the SNDS database over the period 2009–2014. Access to data was approved by the national data protection agency (CNIL) after the review of the protocol by a specific committee in health data research (CERES) [15].

2.2. Data source

The SNDS covers almost the whole French population (98.8 %) from birth (or immigration) to death (or emigration) [16]. Captured data include (among others): (a) gender, year of birth, location, date of death, (b) outpatient reimbursed healthcare expenditures such as medical visits, laboratory tests (without results), drugs dispensed with date and quantity supplied (but not the indication), etc., (c) inpatient hospital discharge summaries with medical and imaging procedures performed, International Classification of Diseases (ICD10) codes for diagnoses, etc., and (d) registration for long-term diseases (*affections de longue durée* in French) allowing the full coverage of the expenses related to the registered disease, including ICD10 codes (C61 for PC).

2.3. Study population

To be included, men had to be alive on January 1st 2014, aged ≥ 40 years, and with no gap > 1 year in their data history. This threshold was chosen because PC is extremely rare in men under 40 [11]. In addition, to join the study population, men also had to be covered by the general health insurance scheme—corresponding to 86 % of the French population—because until 2010 not all the specific French insurance schemes (independent professions, farmers, etc.) were loading their whole data into the SNDS.

2.4. Identification of PC

Patients with PC were identified in the study population by the presence of at least one of the following criteria in 2014: (a) registration for PC as a long-term disease declared prior to December 31st 2014, (b) reimbursements for drugs corresponding to at least 2 months of ADT, (c)

at least one reimbursement of estramustine or mCRPC-specific treatments (abiraterone acetate, enzalutamide or cabazitaxel), and (d) a hospital stay for PC, including notably chemotherapy (docetaxel) or radiotherapy, and a PC-specific procedure or treatment observed in the 5-year history period (e.g. radical prostatectomy, orchiectomy, HIFU, brachytherapy, cryotherapy). In order to be more specific, patients presumed chemically castrated for a reason other than PC, especially paraphilia, were excluded (see [Supplementary data, Appendix A](#)). For the remaining patients, a date of diagnosis was estimated using the first PC-specific event recorded.

2.5. Identification of mCRPC

To be considered as having mCRPC, a patient with PC had to complete two conditions: to be identified as both metastatic and castration-resistant. The construction of these two complex indicators relies on several proxies, which have been developed by a multidisciplinary team composed of oncologists, urologists, radiation therapists, pharmacists and epidemiologists.

2.5.1. Estimation of the date of first metastasis management

The first hospital stay with ICD10 discharge diagnosis code for ‘secondary malignant neoplasm’ (C77, C78, C79) was used to set the first metastasis diagnosis date for patients with PC, if no other cancer was mentioned in the diagnosis. Denosumab or zoledronic acid dispensing (excluding Aclasta®) as well as targeted β or α particle therapy and hepatic radiofrequency ablations were also used to estimate the date of metastases. Dispensings of specific mCRPC treatment, including docetaxel (see [Supplementary data, Appendix B](#)), were considered as metastasis indicators if preceded by a medical imaging procedure and at least 3 months of continuous ADT. In the particular case of the youngest patients (< 70 years old) who directly started ADT after PC diagnosis until the dispensing of an mCRPC-specific treatment without any previous local treatment, the first metastasis diagnosis date corresponded to the first GnRH analog dispensing unless the patient died in the first ADT year. The last way used to identify the date of metastases was through radiotherapy (see [Supplementary data, Appendix C](#)). Three types of radiotherapy were distinguished: (a) non-intensity modulated radiotherapy, (b) intensity-modulated radiotherapy, and (c) stereotactic radiotherapy. Duration, number of sessions and previous patient history were then used to differentiate between prostate-targeted and metastases-targeted radiotherapy.

Metastases diagnosed within 4 months following the initial PC diagnosis were considered as synchronous.

2.5.2. Estimation of castration resistance diagnosis date

Detection of castration resistance relies mainly on switching between different ADTs. A patient with a GnRH analog or surgical castration (orchidectomy, pulpectomy) was considered as resistant to castration at the initiation of an anti-androgen, diethylstilbestrol or degarelix for at least 2 months. The first dispensing of a CRPC-/mCRPC-specific treatment was also set as a resistance indicator, unless this dispensing took place during the first 3 months following the date of diagnosis (hormone-sensitive period).

2.5.3. mCRPC status

Patients were classified as prevalent mCRPC when both the date of first management of metastases and the date of castration resistance were identified in their medical history. The date of mCRPC status was set to the most recent of the two previous dates. Incident mCRPC cases corresponded to patients for whom mCRPC status was identified in 2014.

2.6. Validation of the algorithm

A validation study was set up in the final stages of the algorithm

conception. A sample of 200 patients was randomly created by selecting 100 mCRPC cases identified by the algorithm and 100 non-mCRPC PC cases. So as to ensure the presence of all categories of non-mCRPC patients, three groups of non-mCRPC patients were identified: 34 with non-metastatic hormone-sensitive PC, 33 with metastatic hormone-sensitive PC, and 33 with non-metastatic castration-resistant PC. For each of these 200 patients a medical chart was reconstituted and anonymized, based on the medical history available in the SNDS during 2009–2014: long-term disease registration, drug dispensings, procedure codes including surgery and imaging, hospitalizations with all diagnosis codes, and lab tests (without results). These 200 cases were randomly divided into two groups of 100 cases. Two pairs of experts—including a urologist and an oncologist—each blindly adjudicated the mCRPC status of 100 cases. In case of disagreement within a pair, the case was assessed by all four experts to reach consensus. False-negative cases were weighed according to the distribution of non-mCRPC patient classes. Positive predictive values (PPVs) and negative predictive values (NPVs) of the algorithm for mCRPC identification were then calculated.

Based on expert feedback, following the validation study, slight adjustments of indicator settings were implemented in the algorithm. Note that the final settings are those described in the present publication. PPVs and NPVs were then updated and used to estimate the sensitivity and specificity (see [Supplementary data, Appendix D](#)) [17].

2.7. Analyses

All analyses were performed using SAS® 9.4 software. Extrapolation of the total number of cases in the overall French population was standardized on the 2014 French age distribution provided by the National

Institute of Statistics and Economic Studies (Insee) [18]. Extrapolation of the incidence and the prevalence per 100 000 men was standardized on the 2013 European Standard Population [19]. Given the power of the SNDS confidence intervals generated are very narrow and not presented here.

3. Results

In 2014, among the population of men aged ≥ 40 covered by the general health insurance scheme (86 % of the French population) 386 127 PC cases were counted ([Fig. 1](#)), including 26 470 new ones. Amongst the PC population, 28 845 were classified as metastatic and 18 973 as castration-resistant (7.5 % and 4.9 % respectively), giving a total of 12 951 mCRPC patients (3.4 %). By extrapolation, the age-standardized prevalence of PC using the European Standard Population was estimated at 1842 per 100 000 men, with an annual incidence of 121 per 100 000, assuming the rate of PC as negligible for men under the age of 40. Considering mCRPC, the age-standardized prevalence was 62 cases per 100 000 men, with an annual incidence of 21 cases per 100 000 men ([Table 1](#)). Incidence and prevalence according to age classes are presented in [Fig. 2](#). Prevalence of prostate cancer increased with age: 14 cases per 100 000 were observed in men 40–49 years of age versus 14 900 in men aged ≥ 90 , whereas the corresponding incidence remained stable after 70 years of age (522, 450 and 500 cases per 100 000 in men aged 70–79, 80–89 and ≥ 90 , respectively). Less than one mCRPC case per 100 000 was observed in men aged 40–49 versus 500 and 400 in men aged 80–89 and ≥ 90 respectively. Incidence was <1 in men aged 40–49 and reached 175 cases per 100 000 in the 80–89-year age group, decreasing to 100 in men aged ≥ 90 . Estimates were supported by a blind

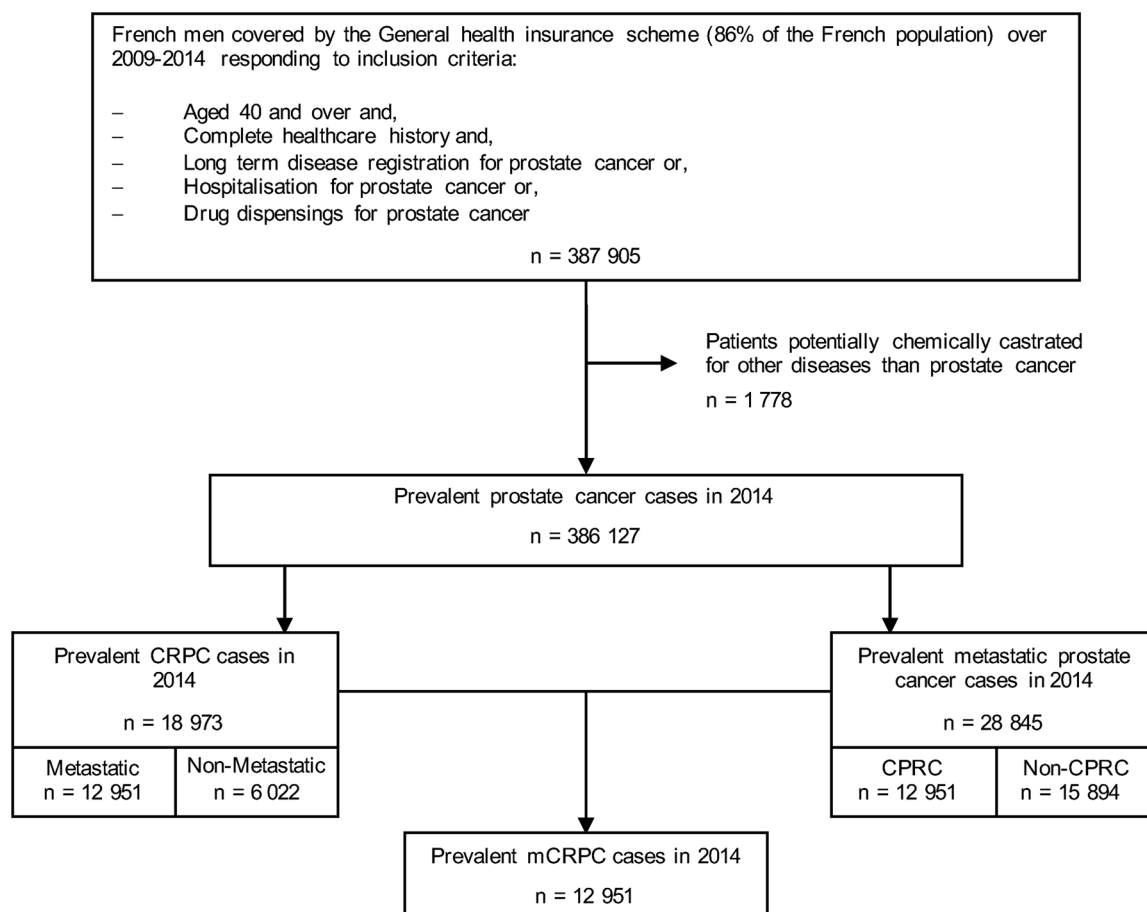


Fig. 1. Flowchart for the identification of prevalent prostate cancer, metastatic prostate cancer, castration-resistant prostate cancer (CRPC), and metastatic castration-resistant prostate cancer (mCRPC) cases in men covered by the general health insurance scheme, in the French national healthcare database in 2014.

Table 1

Prevalence and incidence of prostate cancer and metastatic castration-resistant prostate cancer (mCRPC) in France in 2014.

	General scheme n	French population	
		N ^a	per 100 000 men ^b (standardized, Europe)
Prevalent prostate cancer	386 127	488 618	1 842
Incident prostate cancer	26 470	33 364	121
Prevalent mCRPC	12 951	16 423	62
Incident mCRPC	4 384	5 561	21

^a Standardized on the French men age distribution (Insee), assuming the rate of prostate cancer as negligible in men aged <40.

^b Standardized on the European Standard Population (2013 edition), assuming the rate of prostate cancer as negligible in men aged <40.

review of the cases by experts, underlining the good performance of the method. Before the final adjustment of the algorithm, out of the 100 mCRPC cases and 100 non-mCRPC cases identified by the algorithm, the experts agreed in 92 and 93 respectively. In total, the experts identified 99 mCRPC and 101 non-mCRPC cases in the randomly selected pool of patients. At this stage, the algorithm PPV and NPV were respectively 92 % and 99 %, after weighting. Following the final adjustment based on expert feedback, the updated algorithm identified 93 mCRPC and 107 non-mCRPC cases from the same pool of patients (Table 2). Out of these, three were false positives (*i.e.* cases classified as mCRPC by the algorithm and as non-mCRPC by the experts) and nine were false negatives (*i.e.* cases classified as non-mCRPC by the algorithm and as mCRPC by the experts). All the false-negative cases proceeded from metastatic hormone-sensitive patients and non-metastatic castration-resistant patients (seven and two cases respectively), although these two categories counted for <6% of the overall non-mCRPC cases (see [Supplementary data, Appendix E](#)). The resulting PPV and NPV were 97 % and 99 % respectively after weighting (Table 2). Based on these results, the sensitivity of the final algorithm was estimated as 77 % and the specificity as 100 %.

For prevalent mCRPC patients, the initial date of diagnosis of PC occurred before 2010 in 70 % of the cases, although 95 % of them reached mCRPC status after 2010. Castration resistance and metastases appeared over a 4-month period in 43 % of the cases. More details about mCRPC patient characteristics are shown in [Supplementary data](#),

Appendix F.

4. Discussion

The present works allowed identification of mCRPC cases in the prostate cancer population in a large nationwide data source (the SNDS) through the development and validation of an *ad-hoc* algorithm. The good performances shown by the algorithm support the accuracy of the prevalence and incidence that we estimated for mCRPC: respectively 62 and 21 cases per 100 000 men per year.

The French National health insurance system (Caisse National d'Assurance Maladie, CNAM) estimates every year the prevalence and the cost associated with the main diseases supported by the general health insurance scheme (86 % of the French population) [13]. In 2014 it counted 396 600 PC cases, which seems to be consistent with our current observation of 386 127 cases in the same population. The restrictive criteria used in our work (*e.g.* exclusion of patients potentially treated for paraphilia, minimum number of consecutive dispensings) could explain this small observed discrepancy. CAMERRA allowed the identification of nearly 26 500 new PC cases in 86 % of the French population in 2014, or approximately 33 400 at the national level. This number is lower than that provided in 2015 by the French network of cancer registries (50 430), where patients either actively treated for their cancer or not are tracked [11]. That may result from the non-inclusion of some patients having exclusively received active

Table 2

Positive predictive values (PPV) and negative (NPV) predictive values of the final algorithm for the identification of metastatic castration-resistant prostate cancer (mCRPC) in the CAMERRA study.

Algo- rithm	Validation committee			PPV = 97% NPV = 99%
		mCRPC +	mCRPC –	
	mCRPC +	90	3	93
	mCRPC –	1.23*	105.77*	107
Total		91.23	108.77	200

*After weighting

^aAfter weighting.

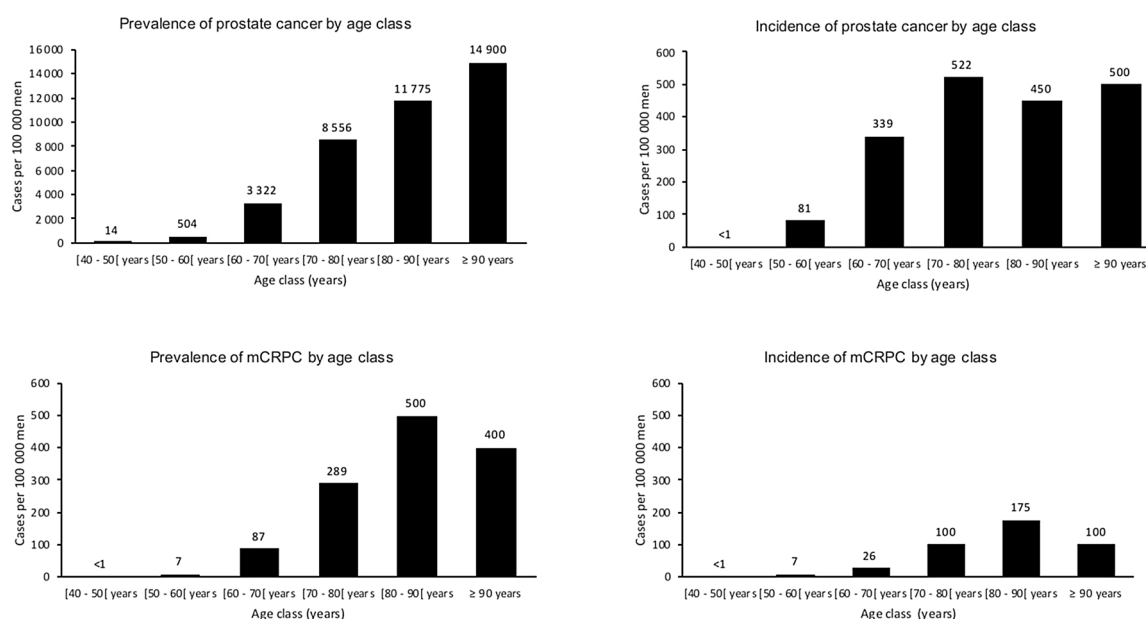


Fig. 2. Prevalence and incidence of prostate cancer and metastatic castration-resistant prostate cancer (mCRPC) according to age classes in 2014 and standardized on the European age distribution (2013 edition).

surveillance (watchful waiting) as management of their prostate cancer over the study period, especially those without related long-term disease registration. However, since patients at the mCRPC stage have received active treatments, they should all have been included in the initial study population.

At the time of the study, the general health insurance scheme covered wage earners in the private industrial, trade, and service sectors [20]. Hence included patients may present disparities in terms of occupation compared to the general French population. However, from all the ascertained risk factors for PC [21], age is the most likely to bias extrapolated incidence and prevalence by a differential distribution between the studied population and the French population. To address this potential issue, the number of cases at the national level were standardized on the 2014 French age distribution provided by the Insee. To facilitate potential comparisons, rates per 100 000 men per year were standardized on the European Standard Population (2013 edition).

Very few data are available on mCRPC epidemiology, and to our knowledge no estimate relying on a large nationwide data source has ever been published. In 2014 Marteau et al. estimated the number of new mCRPC cases across eight European countries and Australia—based on cancer registries, literature review and medical chart review—to be 76 201. Among these, a similar number to that observed in CAMERRA was approximated for France: 16 451 (versus 16 423) [22]. Furthermore, Scher et al., using a dynamic model in 2015, estimated the prevalence of PC and mCRPC in the US in 2009 (2.8 %) and found a ratio of mCRPC/PC of the same order of magnitude as that observed in CAMERRA (3.4 %) [23].

The wealth of data available in the SNDS allowed the experts to conduct a comprehensive blind review of cases and to reliably assess and validate the algorithm. Even if some medical elements are still missing, as in most claims databases (e.g. lab test values, imaging results, tumor, nodes and metastasis classification), SNDS includes exhaustive data about reimbursed healthcare expenditures and hospital discharge summaries (drug dispensing, radiotherapy sessions, hospitalizations, procedures performed, etc.), quality of coding being ensured at the hospital level by specialized medical teams [24]. Data available remain rich enough to reconstitute electronic health records for patients, proving more detailed than what would usually be recorded in a standard medical chart. However, ruling on some cases regarding the presence or absence of metastases (or castration resistance) was sometimes intricate and open to interpretation. As highlighted by the proportion of patients presenting metastases and castration resistance within 4 months, the two stages of the disease are sometimes very close in time or even indistinguishable. This complexity could partially explain the sensitivity of the algorithm (77 %), which may induce a slight underestimation of the actual prevalence of mCRPC in the population. An alternative explanation for this imperfect sensitivity could be the absence of patient data prior to 2009. The limited 5-year lookback period could make the detection of the onset of castration resistance or metastasis management impossible by the algorithm, especially for patients with a very long prostate cancer history. Furthermore, the excellent estimated specificity (100 %) ensures that patients identified as positive by the algorithm are highly likely to be true mCRPC cases and will provide a reliable study population for further investigation around mCRPC management. However, it is important to remember that as practices have substantially evolved since 2016, with the introduction of new androgen-receptor-targeted therapies and new indications for existing therapies, the generation of updated results relying on SNDS data will require an adjustment of the algorithm [5,9,25].

5. Conclusion

The good performances of the algorithm used to identify mCRPC cases in the SNDS, and the consistency of the generated results with the existing data, highlight the robustness of these first estimates of mCRPC prevalence and incidence in real-life settings. The accurate

identification of this particular stage of PC in a large healthcare database is a first step in the evaluation of the mCRPC burden and in the assessment of the evolutions of mCRPC management.

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CRediT authorship contribution statement

Nicolas H. Thurin: Conceptualization, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **Magali Rouyer:** Conceptualization, Investigation, Methodology, Validation, Project administration, Visualization, Writing - review & editing. **Marine Gross-Goupil:** Conceptualization, Investigation, Validation, Writing - review & editing. **Xavier Rebillard:** Conceptualization, Investigation, Visualization, Writing - review & editing. **Michel Soulié:** Conceptualization, Investigation, Validation, Writing - review & editing. **Thibaud Haaser:** Conceptualization, Investigation, Writing - review & editing. **Mathieu Roumigué:** Investigation, Validation, Writing - review & editing. **Sylvestre Le Moulec:** Investigation, Validation, Writing - review & editing. **Camille Capone:** Conceptualization, Investigation, Writing - review & editing. **Marie Pierrès:** Investigation, Writing - review & editing. **Stéphanie Lamarque:** Investigation, Validation, Project administration, Visualization, Writing - review & editing. **Jérémy Jové:** Conceptualization, Software, Methodology, Formal analysis, Data curation, Investigation, Validation, Visualization, Writing - review & editing. **Emmanuelle Bignon:** Investigation, Validation, Project administration, Visualization, Writing - review & editing. **Cécile Droz-Perroteau:** Conceptualization, Methodology, Supervision, Funding acquisition, Writing - review & editing. **Nicholas Moore:** Funding acquisition, Supervision, Writing - review & editing. **Patrick Blin:** Conceptualization, Investigation, Methodology, Validation, Visualization, Supervision, Funding acquisition, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

M. Gross-Goupil declares personal fees and non-financial support from Janssen, Sanofi, Astellas, Ipsen, Amgen and Pfizer. M. Soulié and M. Roumigué declare personal fees and non-financial support from Janssen, Sanofi, Astellas, Ipsen, Amgen, Ferring, and Astra-Zeneca. X. Rebillard declares honoraria from IPSEN, Ferring, GSK, Astellas, Janssen, Mylan, Bristol-Myers Squibb and Sanofi; consulting or advisory roles with Janssen, Astellas and Sanofi; travel, accommodation, expenses from Bouchara-Recordati, IPSEN, Ferring, GSK, Astellas, Janssen Mylan, Bristol-Myers Squibb and Sanofi. C. Capone and M. Pierrès are employees of Janssen-Cilag France. All remaining authors have declared no conflicts of interest.

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Appendix A–F. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.canep.2020.101833>.

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