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Assessment of bone mineral density in men with de novo metastatic castration-sensitive prostate cancer treated with or without abiraterone acetate plus prednisone in the PEACE-1 phase 3 trial

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ABSTRACT

Aim: Addition of abiraterone acetate plus prednisone (AAP) to androgen deprivation therapy (ADT) with or without docetaxel (D) improved overall survival in patients with de novo metastatic castration sensitive prostate cancer in the PEACE-1 trial. The protocol was amended during the course of the study to assess whether addition of AAP increases bone loss.

Methods: Patients were randomized to receive either ADT + D with or without AAP. Bone mineral density (BMD) of the lumbar spine, femoral neck, and total hip were measured by dual X-ray absorptiometry at baseline, 6, 12, and 24 months (M). T-Scores and mean percent change in BMD values were assessed.

Results: With 97 patients treated with AAP and 98 without, the median age was 65 years and 69 patients were ECOG 0 in each arm. Median baseline body mass index was 25.6 and 26.5 kg/m^2 in patients treated with or without AAP, respectively. Ten and 30 % presented with baseline osteoporosis and osteopenia, respectively. Mean T scores and mean percent changes in BMD measured on three anatomic sites decreased during the first year of treatment in both arms, without difference between arms. At M24, a numerical two-fold increase in patients with osteoporosis was observed in the AAP arm.

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Conclusions: This is the first prospective assessment of BMD in a randomized trial with an experimental treatment using AAP. Bone loss occurred rapidly in both arms, and addition of AAP did not increase bone loss significantly although a numerically higher rate of osteoporosis was observed at 2 years.
Trial registration: NCT01957436.

1. Introduction

Despite a decrease in mortality rate, prostate cancer remains the fifth leading cause of cancer death worldwide [1], highlighting persistent challenges in patients with advanced disease [2]. Androgen deprivation therapy (ADT) remains the cornerstone of advanced prostate cancer treatment [3]; however, ADT is associated with bone loss and fracture [4,5] due to imbalance of bone homeostasis toward bone resorption induced by testosterone and estrogen decreases. This process mostly impacts trabecular bone [6,7]. Bone loss can occur early, within the first year of exposure to ADT, and affects all commonly assessed sites of bone mineral density (BMD) [8]. Among androgen receptor pathway inhibitors (ARPI) commonly used with ADT, abiraterone acetate plus prednisone (AAP) may not only increase bone loss by decreasing testosterone level [9], but also by the concomitant use of low dose steroids with abiraterone acetate (i.e. prednisone 5–10 mg/d). More generally, ARPIs may also be involved in bone morbidity, through falls and fractures favored by sarcopenia and potential central nervous system side effects [10,11]. In a population of older patients with prostate cancer, more likely affected by physiologic bone loss, falls and fractures can impact on quality of life, autonomy, and even survival.

Patients with metastatic castration sensitive prostate cancer (mCSPC) form an heterogeneous group with significant variations in age and comorbidities [12]. Over the past decade, standard treatment has been revolutionized by combining systemic treatment to ADT, and nowadays, triplet or doublet systemic treatments with or without radiotherapy to the prostate are standard [2,13–15]. For instance, a consistent survival benefit was established with AAP by the LATITUDE, STAMPEDE, and PEACE-1 trials [16–18].

The improving survival of patients with mCSPC (from a median of about 4 years with ADT alone to a median of about 6 years with intensified systemic treatment) resulting in longer exposure to ADT increases bone health concerns. We prospectively assessed BMD changes in the PEACE-1 phase 3 trial to better understand this important side effect and to assess whether addition of AAP may increase its occurrence and intensity.

2. Material and methods

Participants were enrolled in PEACE-1 trial, an open-label, randomized, phase 3 study with a 2 × 2 factorial design evaluating the efficacy of AAP and prostate radiotherapy. The study was conducted across seven European countries. Initial and amended protocols were approved by ethics committees as previously described [18], the bone mineral density assessment was introduced in the protocol by the amendment of March 2018. Details of the study design and participants have previously been published [18]. Briefly, eligible patients were 18 years or older with newly diagnosed metastatic prostate adenocarcinoma, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1 (or 2 in case of bone pain). From March 2018 to the end of accrual, patients were randomized to either ADT +/- prostate radiation therapy + docetaxel (standard arm) or ADT +/- prostate radiation therapy + docetaxel + AAP (experimental arm).

Baseline characteristics collected were as follows: age, ECOG PS, body mass index, steroid intake, median total testosterone, bone resorptive agents including bisphosphonate or denosumab, bone mineral density (BMD) and T score (number of standard deviation from a young adult mean; an osteopenia is defined by a T score between − 1 and − 2.5; an osteoporosis is defined as a T score less than − 2.5), and fracture (reported on dual-energy X-ray absorptiometry [DXA]).

BMD was assessed using DXA, performed on 3 sites (lumbar spine, total hip, and femoral neck), at baseline and repeated before progression at 6, 12, and 24 months, following the initiation of systemic treatment (e. g. docetaxel or docetaxel + AAP) to ADT. BMD data were considered for a specific timepoint if at least one variable out of the date of BMD, value of BMD, T score, and presence of fracture was available in the Case Report Form (CRF), whatever the location, and after exclusion of bone metastasis on the measurement site. DXA were performed locally and were not centrally reviewed.

Statistical analyses were performed with SAS (version 9.4). Continuous variables were summarized using mean, SD, median, interquartile range, range and number of missing values. Categorical variables were summarized with frequency counts and percentages. Evolution of BMD was reported using T score and mean percent change in BMD in g/cm^2 from baseline, according to the following formula: Percent change from baseline at time X = 100 × (Value at time X - Value at baseline)/Value at baseline. This study is ongoing and is registered with ClinicalTrials.gov, NCT01957436.

3. Results

Among the 210 patients randomized after the amendment introducing the BMD assessments, 195 provided BMD data over their follow-up: 182 (87 %) had available BMD data at baseline, 109 (52 %) at M6, 94 (45 %) at M12, and 109 (52 %) at M24.

3.1. Baseline characteristics (Table 1)

Ninety-seven and 98 patients were treated by ADT + D with or without AAP, respectively. Median age was 65 years in each arm. Sixty-nine patients were ECOG PS 0 in each arm. Median body mass index was 25.6 and 26.5 kg/m^2 in patients treated with or without AAP, respectively. In both arms, 4 % of patients were using corticosteroids less than 10 mg/day at baseline. Bone resorptive agents were used by 4 % of patients in the experimental arm and 1 % in the standard arm. Median total testosterone level was 0.2 ng/mL in both arms. Median BMD values for lumbar spine, femoral neck, and hip were 1.2, 0.9, 1.0 g/cm^2 and 1.2, 0.9, 1.0 g/cm^2 in patients treated with and without AAP, respectively. Median T scores in lumbar spine, femoral neck, and hip were 0.3, − 0.8, − 0.7 and 0.4, − 0.4, − 0.5, in patients treated with and without AAP, respectively. Fifty-seven percent and 56 % of the patients had normal BMD, 33 % and 35 % had osteopenia, and 10 % and 9 % had osteoporosis in the experimental and the standard arm, respectively. Of the 5 fractures reported, 3 occurred in the femoral neck in the standard arm and 2 in the lumbar spine (1 in each arm). All baseline characteristics are summarized in Table 1.

3.2. Evolution of mean T scores

A decrease in mean T score in lumbar spine is observed between M12 (-0.3; − 0.1) and M24 (-0.6; − 0.3) in experimental and standard arm, respectively (Fig. 1a). All the confidence intervals are overlapping between the two arms. Data related to the evolution of T score for femoral neck are more heterogeneous and are shown in Fig. 1b. Regarding total hip, the baseline T score is lower than lumbar spine and the subsequent values relatively constant over time (Fig. 1c). All the confidence intervals are also overlapping.

At M24, 35 % and 30 % of patients had osteopenia and 21 % and

Table 1
Baseline characteristics of population included in bone mineral density (BMD) analysis from PEACE-1 trial.

	ADT + /- RT + D n = 98	ADT + /-RT + D + AAP n = 97
Age; median (interquartile range)	65 (58; 70)	65 (61; 70)
ECOG PS; n (%)		
0	69 (70)	69 (71)
1	29 (30)	26 (27)
2	0	2 (2)
BMI in kg/m^2; median (interquartile range)	26.5 (23.5; 29.4)	25.6 (23.8; 28.7)
Corticosteroid (≤ 10 mg/d); n (%)		
No	89 (91)	88 (91)
Yes	4 (4)	4 (4)
Missing	5 (5)	5 (5)
Bone resorptive agent*; n (%)		
No	92 (94)	88 (91)
Yes	1 (1)	4 (4)
Missing	5 (5)	5 (5)
Total testosterone in ng/mL; median (interquartile range)	0.2 (0.1; 0.6)	0.2 (0.1; 0.6)
BMD in g/cm^2; median (interquartile range)		
Lumbar spine	1.2 (1.0; 1.4)	1.2 (1.0; 1.3)
Femoral neck	0.9 (0.8; 1.0)	0.9 (0.8; 1.0)
Total hip	1.0 (0.9; 1.1)	1.0 (0.9; 1.1)
T Score; median (interquartile range)		
Lumbar spine	0.4 (− 1.1; 1.4)	0.3 (− 1.2; 1.5)
Femoral neck	− 0.4 (− 1.2; 0.2)	− 0.8 (− 1.7; 0.3)
Total hip	− 0.5 (− 1.1; 0.2)	− 0.7 (− 1.2; 0.6)
BMD status (WHO definition); n (%)		
Normal	45 (56)	46 (57)
Osteopenia	28 (35)	27 (33)
Osteoporosis	7 (9)	8 (10)
Fractures; n (%)	1 (1.3)	1 (1.3)
Lumbar spine	3 (4.6)	0
Femoral neck	0	0
Total hip		

ADT: Androgen Deprivation Therapy; D: docetaxel; AAP: abiraterone prednisone; BMI: Body Mass Index; BMD: bone mineral density; RT: prostate radiation therapy; WHO: World Health Organization.
* Bisphosphonate or denosumab.

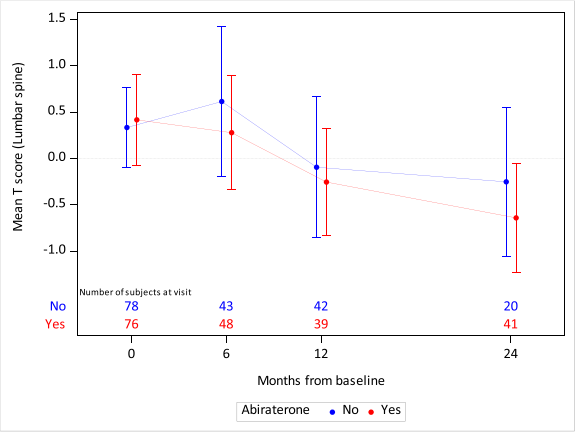

Fig. 1a. Evolution of mean T scores over the first 2 years in lumbar spine.

15 % of patients had osteoporosis with and without AAP, respectively.

3.3. Mean percent changes in bone mineral density

In the lumbar spine, a decrease of mean percent changes in BMD was observed as soon as M6 for the experimental arm (-3.1) and M12 in the standard arm (-3.4), (Fig. 2a). The curves crossed at a later point with a mean percent change of at least 5 % at M24 (-5.9 for patients with vs − 10 without AAP). In femoral neck, bone loss was observed at M6 (-2.1 in both groups) and M12 (-4.1 in experimental arm vs − 2.9 in standard arm). At M24, there was no further decrease in BMD in the experimental arm compared to the standard arm (-3.9 vs − 8), (Fig. 2b). In total hip, bone loss was also observed from M6 in the experimental arm (-3.7) and

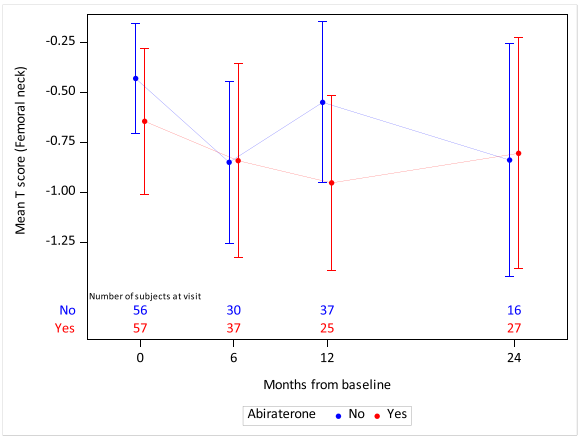

Fig. 1b. Evolution of mean T scores over the first 2 years in femoral neck.

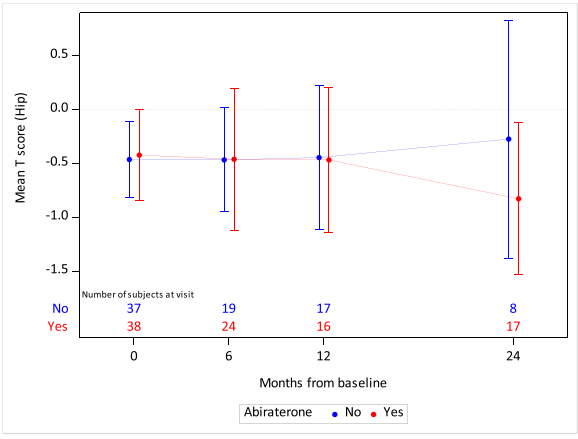

Fig. 1c. Evolution of mean T scores over the first 2 years in total hip.

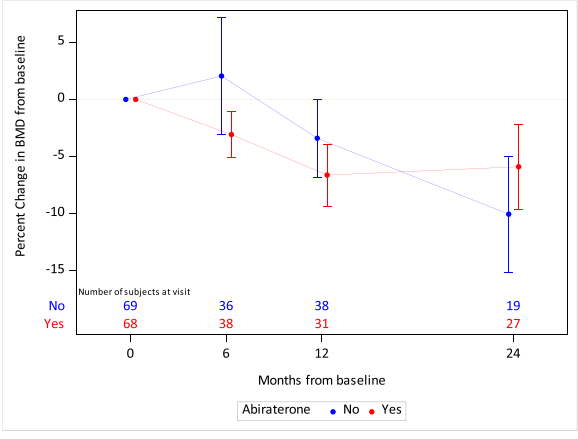

Fig. 2a. Evolution of mean percent changes in BMD over the first 2 years in lumbar spine.

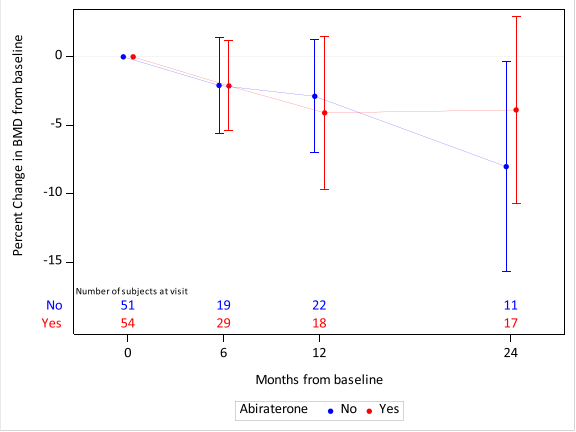

Fig. 2b. Evolution of mean percent changes in BMD over the first 2 years in femoral neck.

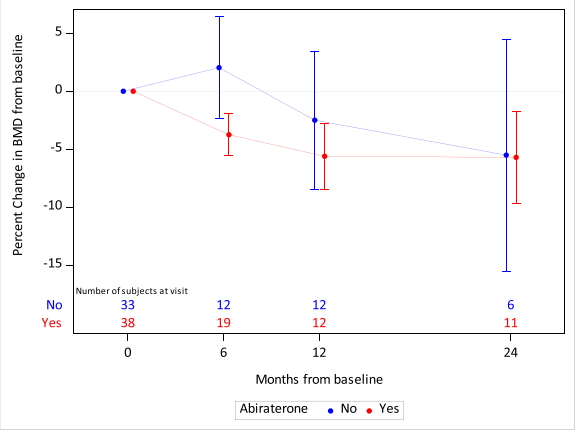

Fig. 2c. Evolution of mean percent changes in BMD over the first 2 years in total hip.

at M12 (-2.5) in the standard arm with a mean percent change of at least 5 % at M24 (-5.7 for patients treated with and − 5.5 without AAP), (Fig. 2c). For each point of assessment, all confidence intervals were overlapping. Four fractures were reported during treatment (1 in femoral neck and 1 in lumbar spine at M6, 2 in lumbar spine at M24), all in the experimental arm.

All the raw data regarding the evolution of BMD, T score and Mean Percent Changes in BMD are presented in Table 2.

4. Discussion

This study aimed to evaluate bone loss in patients with de novo mCSPC. To our knowledge, this is the first prospective assessment of BMD in a population treated with AAP compared to a control arm. Baseline characteristics of the population were well balanced for risk factors of bone loss between the two arms. While bone loss was rapidly observed in both arms, addition of AAP to ADT + docetaxel was not associated with a significant increase in bone loss over the first 2 years. ADT + docetaxel was associated with bone loss predominantly affecting trabecular bone (which is more prevalent in the lumbar spine), however, no marked decrease was observed at the other 2 anatomic sites where BMD was assessed.

Only few fractures were reported, likely due to, at least in part, the short follow up of this sub-study (i.e. 24 months) of PEACE-1, fractures typically occurring later on ADT [19]. Also, as only fractures described on the X-ray performed during DXA were reported, this may have led to under-estimation of the real incidence. Still, it is noteworthy that all fractures were reported in the experimental arm. Symptomatic skeletal events (SSE) experienced by all patients who participated to PEACE-1 will be reported later. The ERA-223 phase 3 trial, which enrolled men with mCRPC and bone metastases, reported an excess of fractures in patients treated with ADT + AAP + Radium-223 compared with placebo on top of ADT + AAP. Most fractures were due to bone loss and typically occurred outside of bone metastatic sites [20]. Performed in a similar population, the PEACE-3, an open label phase 3 trial (enzalutamide + Radium-223 vs enzalutamide) reported an unexpected high frequency of early fractures at the beginning of the study, triggering an amendment for mandatory administration of bone protective agents for all patients [21]. While corticosteroids were used for a longer period in patients treated with AAP, it is not possible to explore their relative impact. A previous post hoc study performed in patients with mCRPC treated with AAP suggested that the cumulative side effects related to the addition of low dose of corticosteroids was modest [22].

This study had some limitations. While it is the first prospective assessment of bone loss in this setting, the number of patients is quite low. Also, patients were treated until disease progression and the BMD assessment performed during treatment. Thus, the higher number of missing BMD data in the standard arm, can mostly be explained by earlier cancer progression in patients not treated with AAP. While bone loss occurs early [8], a follow up of 24 months remains short for collecting later events such as fractures, which are typically reported later [19]. Finally, results from DXA may be influenced by osteoblastic bone metastases representing a challenge to reliably assess BMD even if sites without metastases were preferentially selected. Furthermore, some asymptomatic vertebral compression fractures might have been underdiagnosed using DXA, as previously reported [7].

These results, together with previous data, emphasize the importance of early BMD monitoring in men with mCSPC [23]. mCSPC typically occurs after the age of 60, and roughly 10 % and 30 % of patients in our study presented with baseline osteoporosis and osteopenia, respectively. Moreover, bone loss was observed early while on systemic treatment and previous studies have shown that duration of ADT is a risk factor [4,5,8]. Importantly, patients in our study were treated using intensified treatments, as recommended by current guidelines [3,13]. Finally, regarding the use of bone protecting agents in prostate cancer, they are indicated (together with physical activity and calcium/vitamin D supplementation) in patients with mCSPC at schedule and doses used for osteoporosis [23], but not using a monthly schedule of zoledronic acid or denosumab, as recommended for mCRPC to prevent SSEs [24,25].

4.1. Conclusion

Addition of AAP to ADT + docetaxel was associated with no or only modest increase in bone loss over the first 2 years in PEACE-1. Results from this study emphasize the importance of BMD monitoring in men with mCSPC.

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CRediT authorship contribution statement

Ronchin Philippe: Investigation, Writing – review & editing. **Foulon Stephanie:** Data curation, Formal analysis, Methodology, Validation, Writing – original draft. **Berthold Dominik R:** Investigation, Writing – review & editing. **Bossi Alberto:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. **Flechon Aude:** Investigation, Writing – review & editing. **Ribault**

Table 2
Evolution of bone mineral density, mean T score, and mean percent changes from baseline to 6, 12, and 24 months in patients treated without (standard arm) and with AAP (experimental arm).

	Baseline		M6		M12		M24	
AAP	No	Yes	No	Yes	No	Yes	No	Yes
BMD in g/cm^2 mean (SD)								
Lumbar spine	1.2 (0.2)	1.2 (0.2)	1.2 (0.3)	1.2 (0.3)	1.1 (0.3)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)
Femoral neck	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)
Total hip	1.0 (0.2)	1.0 (0.2)	1.0 (0.1)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	0.9 (0.2)
T score mean (SD)								
Lumbar spine	0.3 (1.9)	0.4 (2.1)	0.6 (2.6)	0.3 (2.1)	− 0.1 (2.4)	− 0.3 (1.8)	− 0.3 (1.7)	− 0.6 (1.9)
Femoral neck	− 0.4 (1.0)	− 0.6 (1.4)	− 0.8 (1.1)	− 0.8 (1.5)	− 0.5 (1.2)	− 1.0 (1.1)	− 0.8 (1.1)	− 0.8 (1.5)
Total hip	− 0.5 (1.1)	− 0.4 (1.3)	− 0.5 (1.0)	− 0.5 (1.6)	− 0.4 (1.3)	− 0.5 (1.3)	− 0.3 (1.3)	− 0.8 (1.4)
BMD status (WHO definition); n (%)								
Normal	45 (56)	46 (57)	24 (53)	26 (51)	22 (49)	20 (49)	11 (55)	19 (44)
Osteopenia	28 (35)	27 (33)	18 (40)	20 (39)	17 (38)	16 (39)	6 (30)	15 (35)
Osteoporosis	7 (9)	8 (10)	3 (7)	5 (10)	6 (13)	5 (12)	3 (15)	9 (21)
Fractures n (%)								
Lumbar spine	1 (1.3)	1 (1.3)	0	1 (2)	0	0	0	2 (5.3)
Femoral neck	3 (4.5)	0	0	1 (2.3)	0	0	0	0
Total hip	0	0	0	0	0	0	0	0
Mean percent changes in BMD (95 %CI)								
Lumbar spine	0	0	2 (− 3.1; 7.2)	− 3.1 (− 5.1;− 1.1)	− 3.4 (− 6.8; 0.0)	− 6.6 (− 9.3;− 3.9)	− 10 (− 15.1;− 5.0)	− 5.9 (− 9.6;− 2.2)
Femoral neck	0	0	− 2.1 (− 5.6; 1.4)	− 2.1 (− 5.4; 1.2)	− 2.9 (− 7.0; 1.2)	− 4.1 (− 9.7; 1.5)	− 8.0 (− 15.7;− 0.4)	− 3.9 (− 10.7; 2.9)
Total hip	0	0	2.0 (− 2.4; 6.4)	− 3.7 (− 5.5;− 2.0)	− 2.5 (− 8.4; 3.4)	− 5.6 (− 8.5;− 2.8)	− 5.5 (− 15.5; 4.5)	− 5.7 (− 9.7;− 1.7)

AAP: abiraterone prednisone; BMD: bone mineral density; SD: Standard Deviation; WHO: World Health Organization. Mean percent changes were calculated as follows: Percent change from baseline at time X = 100 × (Value at time X - Value at baseline)/Value at baseline. 95 %CI: 95 % confidence interval.

Helene: Project administration, Resources. **Silva Marlon:** Investigation, Writing – review & editing. **Climent Miguel Angel:** Investigation, Writing – review & editing. **Maldonado Xavier:** Investigation, Writing – review & editing. **Maurina Tristan:** Investigation, Writing – review & editing. **Bernard-Tessier Alice:** Conceptualization, Methodology, Writing – review & editing. **Abadie-Lacourtoisie Sophie:** Investigation, Writing – review & editing. **McDermott Raymond S:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Escande Anne:** Investigation, Writing – review & editing. **Kostine Marie:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Gravis Gwenaelle:** Investigation, Writing – review & editing. **Roubaud Guilhem:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Mourey Loic:** Investigation, Writing – review & editing. **Tombal Bertrand F:** Investigation, Writing – review & editing. **Fizazi Karim:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – original draft.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. **GR** reports Advisory Boards: Astellas, Astra Zeneca, Bayer, Pfizer. Consulting: AAA Novartis, Astra Zeneca, Janssen, Merck, Pfizer; Funding research: Bayer; Travel accomodations expenses: AAA Novartis, Astra Zeneca, Bayer, Janssen, and has served on a data safety monitoring board paid to his institution for Gilead,

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