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Abiraterone in metastatic castration-resistant prostate cancer: Efficacy and safety in unselected patients☆

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ABSTRACT

Background: Abiraterone acetate (AA), an androgen biosynthesis inhibitor, is now a standard of care for men with metastatic, castration-sensitive and castration-resistant prostate cancer (mCRPC). Data exploring real-world toxicity and outcomes are scarce.

Methods: Retrospective study on unselected patients with mCRPC on AA plus steroids.

Results: 93 patients were included in the study. Median duration of treatment by AA was 7.5 months (95% CI 5.7–12) among the 58 patients pretreated with chemotherapy, versus 12.7 months (95% CI 8.2–35.9) among the 33 chemo-naive patients. Median survivals would reach 13.4 months (95% CI 10.2–19.1) and 36.4 months (95% CI 24.7–41.5) respectively. Rates of hypokalemia, peripheral edema, hypertension, cardiac failure, and overall survival assessments in patients with and without prior chemotherapy were similar to that previously reported in phase 3 randomized trials. The median survival time without adverse event of special interest was 7.5 months for hypokalemia and hypertension, and 5.3 months for liver-function test abnormalities (it was not reached for cardiac disorders).

Conclusion: Our findings provide further evidence for the survival benefits of AA with a low frequency of additional adverse events among unselected patients. In patients who have not developed hypokalemia or a transaminase increase within 7.5 and 5.3 months respectively, a lighter systematic monitoring may be considered.

Introduction

Prostate cancer is the third cause of death by cancer in Western countries [1]. *De novo* metastatic prostate cancer is involved in more than 50% of deaths despite a 40% decrease in the incidence of metastases on diagnosis since the 1970s, whereas the other half are due to a metastatic progression of a cancer that was originally localized [2].

Castration is the cornerstone of treatment of advanced prostate cancer [3–5], though modifications in the underlying biology of the cancer unavoidably lead to the maintaining of an androgen receptor-dependent transcriptional program, despite androgen deprivation through standard hormonotherapy [6]. Castration-refractory prostate cancer (CRPC) is the stage of the disease that is characterized by a tumor progression in spite of castration-level testosterone in serum (< 0.50 nd/ml) [7].

Abiraterone acetate (AA) is an inhibitor of CYP17A1 (a key enzyme in steroidogenesis), that allows both blocking of extra tumor and intra tumor biosynthesis of androgens and lowering of testosterone serum levels down to about 1–2 ng/dl [8]. Additionally AA is metabolized into delta-4 AA (D4A)—an androgen receptor antagonist [9].

AA combined with low doses of prednisone improves overall survival of patients treated for metastatic CRPC (mCRPC) before and after docetaxel [10,11]. Recently, AA proved its efficacy in treating *de novo* metastatic castration-sensitive prostate cancer [12,13]. Adverse mineralocorticoid effects (hypokalemia, peripheral edema, hypertension, cardiac failure) and transaminase increase have been reported in

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pivotal trials. The survival improvement and tolerance data were reported for a clinical-trial selected population, one non necessarily-representative of real-life patients.

This retrospective study evaluated efficacy and tolerance of AA in a routine clinical practice population with patients with mCRPC both pretreated by chemotherapy and chemo-naive. The routine clinical practice group was compared for tolerance to a group of selective patients treated as part of the pivotal studies of AA before and after docetaxel treatment. Distribution over time of the main adverse events was also reported.

Material and method

Population

The patients must have had undergone or be undergoing treatment by AA for a mCRPC. The patients were followed at an expert university hospital center in uro-oncology (Hôpital Saint Louis, Pr. Stéphane Culine's team, Paris), in the medical oncology department. The treatment by AA could not be conditioned by patient eligibility to a therapeutic phase, and initiating, monitoring and continuing of treatment were at the discretion of the clinician, beyond protocols. The characteristics of the Saint Louis patient group represented the real conditions of use of AA in a routine clinical practice.

A second group of patients followed at the Gustave Roussy and formerly treated with AA as part of the COU-AA-301 and 302 trials was studied [10,14]. The patients were selected based on stringent criteria when starting AA such as defined by inclusion protocols.

Intervention

The study consisted in a retrospective collecting of clinical variables—biological and radiological—based on computerized or manuscript medical records in two international expert centers in genito-urinary tumors.

The tumor characteristics (Gleason score, spreading of the disease to the lymph nodes, viscera, bones; pre-treatment by chemotherapy and number of lines), prognoses (hemoglobin, lactate dehydrogenases, alkaline phosphatases and PSA levels in serum), demographics (age) and overall life quality and condition (ECOG performance scale; analgesic level) were collected when getting on AA. The specific side effects (peripheral edemas, hypertension, emergence or aggravation of cardiac failure, hypokalemia, increase of SGPT and SGOT transaminases) were collected with every consultation under treatment, at a given date. The date, the reasons and the modalities of stopping AA (progression/toxicity; suspension/permanent discontinuation) were recorded. The collected data compiled the results of iterative radiological evaluations on AA as well as the dates of progression and demise, all causes included for each patient.

Clinical and biological adverse events expected on AA (mineralocorticoids and hepatic) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE v4.03). The radiological progression was only actually recorded when it conformed to the RECIST (Response Evaluation Criteria in Solid Tumors) evaluation criteria [15,16]. The overall state of the patient, his quality of life and his everyday activity were measured using the scale of ECOG Performance Status (ECOG PS) [17].

Statistic analysis

The quantitative variables were analyzed using proportions. The distribution of continued variables was appreciated according to the median. The Kaplan–Meier method was used to assess the survival functions. The analyses were done in the intention to treat population (ITT). The proportions were compared thanks to the chi-squared parametric test and Fisher's exact test for smaller samples.

Table 1
Demographics, tumor, clinical and prognosis characteristics at diagnosis of prostate cancer and when starting AA among the patients of the Saint Louis group.

Characteristic	Saint Louis, $N = 93$
Age	
No. of patients[a]	93
Median (range), years	70 (43–88)
≥75 years	35 (37.6%)
Gleason score	
No. of patients[a]	88
≤7	47 (53.4%)
≥8	41 (46.6%)
Prostate-specific antigen	
No. of patients[a]	59
Median (range), ng/ml	328 (0.19–6000)
No. of previous chemotherapy regimens	
No. of patients[a]	91
0	33 (36.3%)
1	58 (63.7%)
≥2	9 (9.9%)
Disease location	
No. of patients[a]	89
Bone	87 (97.7%)
Visceral and node	2 (2.3%)
Characteristic	Saint Louis, $N = 93$
Analgesic grade	
No. of patients[a]	88
0	34 (38.6%)
1	9 (10.2%)
2	19 (21.6%)
3	26 (29.5%)
ECOG performance status	
No. of patients[a]	85
0	26 (30.6%)
1	36 (42.4%)
2	20 (23.5%)
3	3 (3.5%)
4	0
Prostate-specific antigen	
No. of patients[a]	90
Median (range), ng/ml	240.2 (1.11–2750)
Hb	
No. of patients[a]	84
Median (range), g/dl	11.97 (7.8–17)
LDH	
No. of patients[a]	42
Median (range)	305.88 (106–704)
ALK-P	
No. of patients[a]	74
Median (range)	256.12 (41–1702)

Abbreviations: LDH, lactate deshydrogenase; ALK-P, alkaline phosphatase.
[a] Number of assessable patients for the study characteristic.

Values of $p < 0.05$ were considered as statistically significant. The analyses were carried out using the software R Studio® v0.98.501.

Results

Population

The Saint Louis patient group included 93 mCRPC patients. 9 were lost-to-follow-up and 1 had not undergone AA. Treatment started between January 2011 and August 2015, and the median duration of treatment was 9.3 months (95% CI 7.02–13.3).

Among the 91 assessable patients on prior lines of chemotherapy 64% ($N = 58$) received at least one line of treatment. The patients were for the majority symptomatic when starting on AA: 21.6% ($N = 19$) used level-2 analgesics, whereas 29.5% ($N = 26$) used class 3 analgesic with opioids. Additionally 23.5% ($N = 20$) and 3.5% ($N = 3$) of

Table 2
Demographics, tumor, clinical and prognosis characteristics at diagnosis of prostate cancer and when starting AA among the patients of the Gustave Roussy group.

Characteristic	IGR (COU-AA-301), *N* = 11	IGR (COU-AA-302), *N* = 12
Age		
No. of patients[a]	11	12
Median (range), years	70 (50–83)	72 (60–85)
≥75 years	4 (36.4%)	4 (33.3%)
Gleason score		
No. of patients[a]	8	8
≤7	4 (50%)	4 (50%)
≥8	4 (50%)	4 (50%)
Prostate-specific antigen		
No. of patients[a]	10	12
Median (range), ng/ml	497 (17.2–4000)	96 (305–750)
No. of previous chemotherapy regimens		
No. of patients[a]	11	12
0	0	12
1	3 (27.3%)	0
≥2	8 (72.7%)	0
Disease location		
No. of patients[a]	11	10
Bone	8 (72.7%)	10
Visceral and node	3 (27.3%)	0
Analgesic grade		
No. of patients[a]	11	12
0	6 (54.6%)	8 (66.7%)
1	1 (9.1%)	3 (25%)
2	2 (18.2%)	0
3	2 (18.2%)	1 (8.3%)
ECOG performance status		
No. of patients[a]	11	12
0	6 (54.5%)	8 (66.7%)
1	5 (45.5%)	4 (33.3%)
2	0	0
3	0	0
4	0	0
Prostate-specific antigen		
No. of patients[a]	11	12
Median (range), ng/ml	306 (31–859)	39.8 (2.5–138)
Hb		
No. of patients[a]	11	12
Median (range), g/dl	11.48 (9.6–13.1)	13.64 (12.4–15.7)
LDH		
No. of patients[a]	11	12
Median (range)	248.9 (135–400)	197.33 (139–266)
ALK-P		
No. of patients[a]	11	11
Median (range)	214.72 (63–811)	92.36 (50–206)

Abbreviations: IGR: Institut Gustave Roussy; LDH, lactate deshydrogenase; ALK-P, alkaline phosphatase.
[a] Number of assessable patients for the study characteristic.

patients in the group presented an ECOG PS of 2 and 3.

The patients had large tumor burden volume (tumor burden reflected by PSA, lactate dehydrogenases and alkaline phosphatases serum levels) (Table 1).

The Institut Gustave Roussy group included 23 patients. 48% (*N* = 11) of the patients in the group received AA in accordance with the COU-AA-301 trial, and 52% (*N* = 12) in accordance with the COU-AA-302 trial.

COU-AA-301 patients were pretreated with docetaxel; the majority experienced low pain (55% took no painkiller whereas 18.2% used strong opioids) and with a high volume tumor when included. COU-AA-302 patients were chemo-naive, with low pain (67% took no painkiller and 25% took level-1 analgesic) and with a low tumor burden when included.

The ECOG PS would never exceed 1 among the patients of the Institut Gustave Roussy group, including COU-AA-301 patients pretreated by docetaxel (Table 2).

Efficacy

After a median follow-up of 19.2 months (95% CI 15.7–28.8), 85% (*N* = 78) of patients from the Saint Louis patients group were dead, and the median overall survival reached 18 months (95% CI 14.7–25.4). Among the 14 survivors, 3 were still on AA. Among the 66 radiologically assessable patients the survival median without radiological progression was 7.3 months (CI 95% 5.7–10.3) (Fig. 1).

The duration of treatment and the effect of AA on overall survival and survival without progression seemed to be related to previous treatment by chemotherapy. Median length of treatment by AA was 7.5 months (95% CI 5.7–12) among the 58 patients pretreated with chemotherapy, versus 12.7 months (95% CI 8.2–35.9) among the 33 chemo-naive patients. Median survivals would reach 13.4 months (95% CI 10.2–19.1) and 36.4 months (95% CI 24.7–41.5) respectively. Radiological progression data were not available for 38 patients pretreated with chemotherapy and 27 chemo-naive patients, and spread from 5.7 months (95% CI 3.2–7.6) to 10.4 months (95% CI 6–12.4) (Table 3).

Toxicity

Among the patients of the Saint Louis group, severe toxicities grade 3 or 4 related to peripheral edemas, hypertension, heart failure, and elevated transaminases were recorded. Among the patients in the Gustave Roussy group, toxicities of grade 3 or 4 were due to hypertension and heart failure.

The proportions of toxicities all grades included—liver, heart, vascular (peripheral edemas)—were not statistically different between the two groups. The differences were about the proportions of hypokalemia and hypertension, all grades included—significantly higher among the patients in the Gustave Roussy group (Table 4).

The side effects among the patients in the Saint Louis group lead to 8 discontinuations of treatment, including 3 permanent discontinuations. The rate of permanent discontinuations and therapeutic pauses for toxicity reasons were not statistically different between the two groups. No toxic death was accounted for the whole patients in the trial (Table 5).

Data regarding survival without progression of toxicity imputable to AA were available for hypertension, hypokalemia and hepatic cytolysis among the patients in the Saint Louis group and the Gustave Roussy group.

The median survival time without cardiotoxicity was not reached for any of the two groups.

Among the patients in the Saint Louis group, median survival times or aggravation of hypertension or of hypokalemia could be superimposed at 7.5 months. Hepatic toxicity—assessed by the elevation of SGOT and SGPT levels—appeared earlier with median occurrence of 5.3 and 5.9 months respectively.

Hypertension, hypokalemia, and elevated liver transaminases levels appeared later in the Gustave Roussy group, with median occurrences of 10.3 months, 8.3 months and median not reached respectively. The differences between the two populations however were not statistically significant for the whole set of studied toxicities (Table 6).

Discussion

Our study reported survival and tolerance data on AA in real conditions of use inherent to a routine clinical practice.

In a non-selective population of mCRPC (Saint Louis group) previously treated with docetaxel for the majority, the overall survival and survival without radiological progression medians reached 18 and 7.3

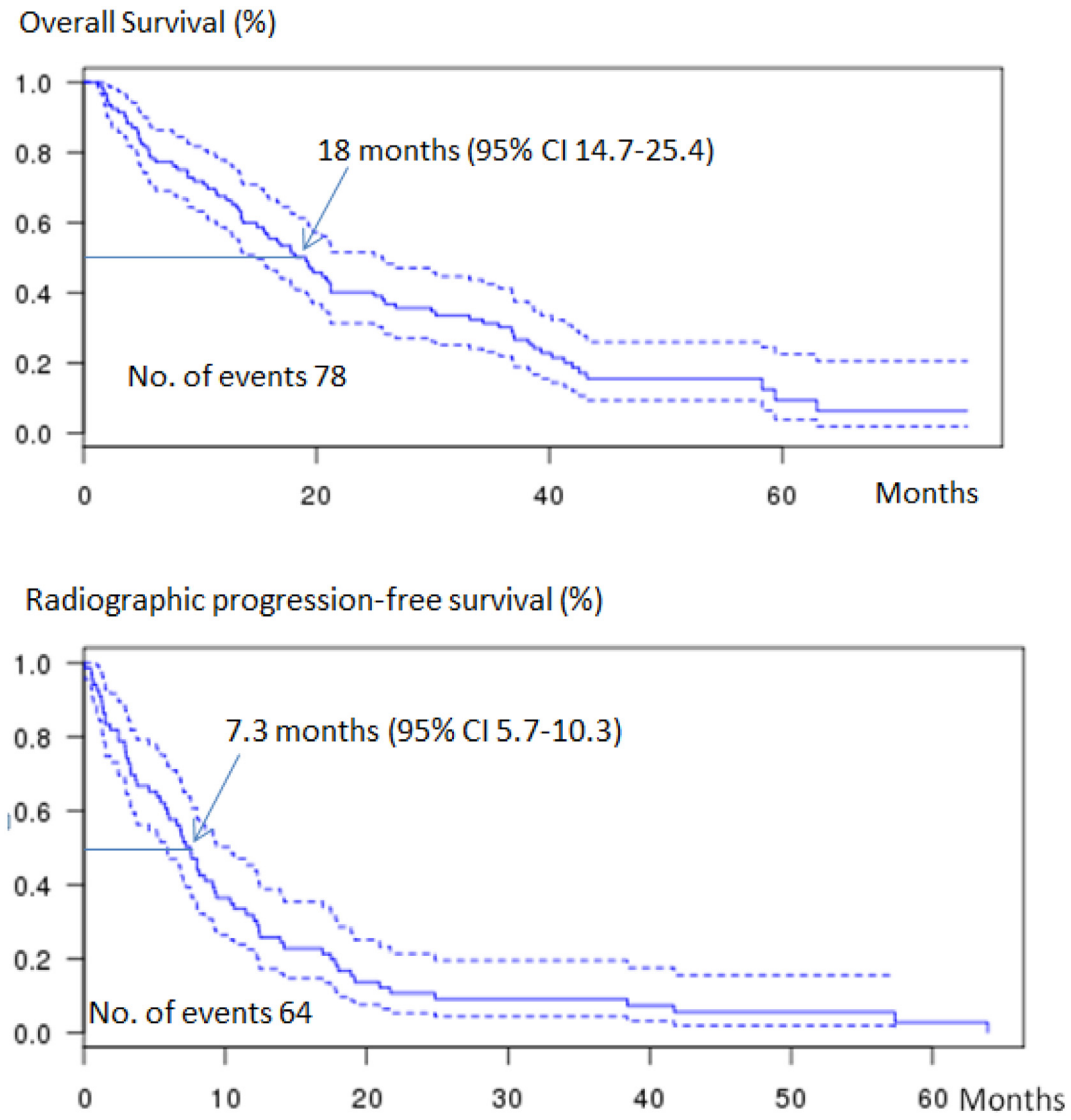

Fig. 1. Assessment of overall survival and survival without radiological progression on AA by the Kaplan–Meier method among the patients of the Saint Louis group; survival analyses were conducted according to treatment intent; the continued lines represent the median.

months by the end of median 19-month follow-up, respectively.

Transaminase increase was the earliest detected side effect (median time to event: 5.3 months). Later toxicities included hypokalemia and high blood pressure (median time to event: 7.5 months). The comparison of time to events did not show any significant difference between patients from the Saint Louis and the Gustave Roussy groups.

The proportions of hypokalemia and hypertension among patients in the Gustave Roussy group were significantly higher to that observed among the patients of the Saint Louis group. This observation could be imputable to higher clinical and biological monitoring, and/or systematic reporting by the clinician of any abnormality in a context of clinical trial. Of note, long-term follow-up of pivotal clinical trials reported no excess in steroid-related side effects with time [18].

Our toxicity data were similar to those from the literature: mostly grade 1 or 2 toxicity associated to a low proportion of therapeutic discontinuation. In the final analysis of the COU-AA-301 trial, 33% of peripheral edemas 18% of hypokalemia, 16% of heart failure, and 11% of liver toxicity and hypertension were reported among patients previously treated with chemotherapy [19].

For the chemo-naive selective population, it was reported 23% of

Table 3
Survival data and median time of exposure to AA, according to whether a prior cytotoxic treatment was undertaken or not among the patients of the Saint Louis group; data from pivotal studies COU-AA-301 and COU-AA-302 are also reported for comparison.

Saint Louis group	Median months (95% CI) Saint Louis chemo-naive patients, *N* = 33	COU-AA-302 patients *N* = 546	Saint Louis pretreated patients *N* = 58	COU-AA-301 patients *N* = 797
Time of exposure to AA	12.7 (8.2–35.9)	13.8 (8.3–27.4)	7.5 (5.7–12)	7.4 (0.2–25.6)
Overall survival	36.4 (24.7–41.5)	34.7 (32.7–36.8)	13.4 (10.2–19.1)	15.8 (14.8–17.0)
Radiographic PFS[a]	10.4 (6–12.4)	16.5 (NA)	5.7 (3.2–7.6)	5.6 (5.6–6.5)

Abbreviation: NA, not available.

[a] 27 chemo-naive patients and 38 patients pretreated were assessable for survival without radiological progression (PFS).

Table 4
Comparison of mineralocorticoids and hepatic toxicity profiles on AA on routine (Saint Louis) and selective (Gustave Roussy) trial populations.

Adverse event	No. of patients (%) Saint Louis, N = 93	Gustave Roussy, N = 23	*P*-value[b]
Hypokalemia			
N[a]	87	23	
Grade 1–4	19 (22)	11 (48)	0.01
Grade 3 or 4	0	0	
Peripheral edemas			
N[a]	62	23	
Grade 1–4	12 (19)	4 (17)	1
Grade 3 or 4	3 (5)	0	
Heart failure			
N[a]	63	23	
Grade 1–4	8 (13)	1 (4)	0.43
Grade 3 or 4	3 (5)	1 (4)	
AST increased			
N[a]	86	23	
Grade 1–4	4 (5)	4 (17)	0.09
Grade 3 or 4	2 (2)	0	
ALT increased			
N[a]	87	23	
Grade 1–4	6 (7)	3 (13)	0.38
Grade 3 or 4	0	0	
Hypertension			
N[a]	60	23	
Grade 1–4	21 (35)	21 (91)	<0.05
Grade 3 or 4	4 (7)	3 (13)	

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a] Number of assessable patients for the side effect of the study.
[b] Proportions of adverse events per population are compared using the Chi[2] test and the Fisher exact test for small samples.

Table 5
Proportions and modalities of AA treatment discontinuation among the patients in the Saint Louis and the Gustave Roussy groups.

Discontinuation for toxicity reasons	No. of patients Saint Louis, *N* = 93	Gustave Roussy, *N* = 23	*P*-value[b]
N[a]	90	23	
Permanent discontinuation	3 (3.3)	1 (4.3)	1
Therapeutic pause	5 (5.6)	2 (8.7)	0.6

[a] Number of assessable patients for the modality of study discontinuation.
[b] Proportions are compared using the Fisher exact test for small samples.

Table 6
Median occurring time of side effects on AA among the patients of the Saint Louis and Gustave Roussy groups.

Median occurring time of side effects	Months (95% CI) Saint Louis	Gustave Roussy	*P*-value[a]
Hypertension	7.5 (3.7–15)	10.3 (6.5–19.7)	0.16
Hypokalemia	7.5 (5.7–NA)	8.3 (3.7–NA)	0.53
AST increased	5.9 (3.1–NA)	NA (3.8–NA)	0.12
ALT increased	5.3 (3–8)	5.1 (3–NA)	0.5

Abbreviations: ALT, alanine aminotransferase; NR, not reached; AST, aspartate aminotransferase.
[a] Chi-square test.

liver toxicity and 19% of heart failure on AA. Transaminase increase was observed within the first 3 months of treatment, whereas heart failure appeared later [14]. Finally, updating of survival and tolerance data analyses after 27 additional months showed no further toxicity [11].

The practical recommendations on the clinical and biological surveillance in patients receiving treatment with abiraterone should be updated in the light of the latest tolerance data analyses. Transaminase increase should be closely monitored in the initial 5 months period, while kalemia and blood pressure should be monitored for a prolonged period up to 7 months.

In our study, the overall and progression-free survival medians in the population formerly treated with docetaxel were similar to that of the pivotal trial COU-AA-301, and reached 13.4 and 7.5 months, respectively. The scope of the benefit as reported in COU-AA-301 appeared to endure in a routine clinical practice, despite the stringent selection of patients for inclusion [10,19].

In the chemo-naive subgroup in our research, the overall survival (median: 36.4 months) was similar to that reported in the final analysis of COU-AA-302 [11]. A 6-month differential in survival without radiographical progression was however observed between our trial (median: 10.4 months) and the interim analysis of COU-AA-302 (median: 16.5 months) [14]. Progression-free survival did not seem to be a valid substitution criterion of overall survival in this subgroup of chemo-naive patients. In this regard, it was reported that a bone scintigraphy modification after 12 weeks of treatment by AA was non-specific, and would associate for 50% of mCRPC with an improvement after re-evaluation 12 weeks later [20]. In addition, early PSA response during therapy with abiraterone in mCRPC remained prognostic for overall survival and may help identify patients with early resistance to abiraterone [21].

AA recently demonstrated efficacy among patients with *de novo* metastatic castration-sensitive metastatic prostate cancer [12,13]. New interrogations regarding the efficacy and the tolerance of AA in this indication can be raised. In the LATITUDE trial, the incidence of grade-3 hypertension in the AA group was superior to the observed incidence in the placebo group, respectively 20 and 10% and the difference was greater comparatively to previous trials involving patients refractory to castration. The same observation was drawn regarding the incidence of grade 3 hypokalemia among the patients in the AA group (10%) and placebo group (1%) [12].

This may be due to the fact that patients also clearly lived longer when they received AA in LATITUDE (and therefore they were at a higher risk to develop side effects) or to the 5 mg daily dose of prednisone used in this trial and in the STAMPEDE trial.

Our results are nonetheless biased because of the retrospective collection: the estimates of median times were restricted to patients for whom the adverse events were regularly collected over the follow-up time. We also did not analyze treatments used beyond progression on AA, one key question nowadays that active treatments are being used earlier and sequentially [22]. Others have reported mostly maintained activity for taxanes such as docetaxel or cabazitaxel [23,24], and mild activity for enzalutamide [25,26]. Data on quality of life were also not collected. Furthermore, the previously demonstrated survival benefit for abiraterone in COU-AA-301 and COU-AA-302 patients is accompanied by improvements in patient-reported quality of life and a significant delay in deterioration when compared with prednisone [27,28].

To conclude, the benefit in survival among patients treated with AA for a mCRPC is similar between the pivotal trials and the routine clinical practice trial. There is no additional toxicity in a non-selective population. Transaminase increase occurs early and should be closely monitored in the initial 5 months period. Later cardiovascular and electrolytic adverse events should be monitored for a prolonged period up to 7 months.

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