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A drug safety evaluation of abiraterone acetate in the treatment of prostate cancer

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Abstract

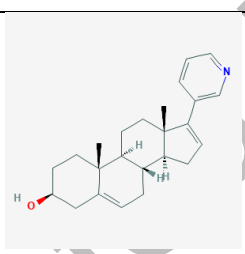
Introduction: To evaluate the safety profile characteristics of abiraterone acetate (AA) in the treatment of metastatic prostate cancer (mPCa).

Areas covered: In this literature review the authors evaluate safety data from phase III trials investigating the combination of abiraterone acetate plus prednisone (AAP) in patients with metastatic prostate cancer. In particular, the aim was to clarify its toxicity profile, long-term exposure impact, and the correlation with general health-related quality of life (HRQoL).

Expert opinion: Based on the studies reviewed, it appears that abiraterone acetate has favourable outcomes, is effective and well tolerated, mostly in asymptomatic or slightly symptomatic patients, and has recognised toxicity profile characteristics. Incidence of adverse events (AEs), such as mineralocorticoid- and corticosteroid-releated AEs, and hepatotoxicity is well known and widely described. Understanding the toxicity profile of AA could assist decision-making in clinical practice.

Key words: abiraterone acetate, metastatic prostate cancer, androgen receptor, toxicity, castration-resistant prostate cancer, hormone-naïve prostate cancer

Drug summary box

Drug name	Abiraterone acetate
Phase	Initial U.S. Approval: 2011
Indication	- metastatic castration-resistant prostate cancer (CRPC) - metastatic high-risk castration-sensitive prostate cancer (CSPC)
Pharmacology description Mechanism of action	Cytochrome P450 17A1 inhibitor. inhibition of CYP17 reduces androgen synthesis in the testes, the adrenal glands, and the prostate, resulting in reduced serum levels of testosterone and other androgens
Route of administration	1,000 mg orally once daily with prednisone 5 mg orally: - twice daily for metastatic castration-resistant prostate cancer (mCRPC) - once daily for newly diagnosed, high-risk, metastatic, castration-sensitive prostate cancer
Chemical structure	
Pivotal trials	COU-AA-301, COU-AA-302 STAMPEDE, LATITUDE

1. Introduction

Prostate cancer (PCa) is the second most common cancer in men and a leading cause of cancer-related deaths worldwide (1, 2). When the disease is diagnosed at the local or regional stages (3), external beam radiation therapy and surgery are the best options; however, after this initial treatment with curative intent, almost 34% of cancers will evolve into metastatic disease (4). Recent data suggest that about 5% of men are diagnosed with metastatic prostate cancer each year. Figures are increasing in the United States, with an incidence of PCa now 72% higher than in the last decade (5). Until 2014, advanced and metastatic prostate cancers were traditionally managed with androgen-deprivation therapy (ADT) (6). According to the literature, up to 80% of patients have a positive treatment response but progress to metastatic castration-resistant prostate cancer (mCRPC) is ultimately inevitable, with one third of patients developing resistance within one or two years (7). mCRPC is a clinically relevant phenotype with a high burden of mortality. Until 2010, it was usually managed with first-line, docetaxel-based chemotherapy (8). Recently, a large number of therapeutic options have emerged that show to increase survival and delay tumour progression when used before or after docetaxel (9). Key to these advances are a better understanding of androgen receptor (AR) pathways and the development of new target agents, most notably enzalutamide and abiraterone acetate (10, 11). Both of these drugs have received initial approval by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) for the treatment of mCRPC in both the pre- and post-docetaxel setting. Given their distinct mechanisms of action on AR signalling pathways, it is reasonable to expect that their toxicity profiles will also be different (12, 13); hence, several guideline treatments have been developed and PCa is now increasingly regarded as a chronic disease (14). Evidence from the literature suggests that these new hormonal agents improve survival in mPCa (15) and have a positive effect on patients' health-related quality of life (HRQoL); however, their toxicity profiles must be taken into account when selecting the most appropriate treatment (16).

The aim of this paper is to provide an overview of the safety profile of AA in the treatment of metastatic prostate cancer.

2. Body of review

2.1 Abiraterone acetate

Abiraterone acetate (AA) is an irreversible selective inhibitor of CYP17A1, a member of the CYP/CYP450 family that converts pregnanes into steroid hormones, including androgen precursors (17). AA blocks the synthesis of androgenic steroids in the testes, in the adrenal gland, and in prostate tumour tissues. This causes systemic suppression of androgen signalling, which underlies progression to mPCa and development of mCRPC. The recommended dose for abiraterone acetate is 1000 mg/dayly in combination with prednisone (the latter at a dose of 5 mg twice daily for mCRPC, and 5 mg once daily for newly diagnosed, high-risk, metastatic, castration-sensitive prostate cancer).

2.2 Mechanism of action

Pharmacokinetic data for AA are available from a few phase I studies (18, 19). Absorption is strongly influenced by food intake and therefore AA is routinely administered under fasting conditions. The molecule is converted to its active metabolite in the intraluminal environment of the intestine (20) and in the liver, reaching its maximum concentration (Cmax) of 1.2–5 μM in approximately 1-2 h. Clearance is biphasic, with a terminal half-life of 5–16 h (18, 19, 21). The main metabolite excreted is N-oxide abiraterone sulphate. There is significant inter-subject variability in Cmax and drug exposure, with apparent clearance being lower in CRPC patients than in healthy subjects (22). AA has minimal effects on hepatic drug metabolism (CYP3A4), glucocorticoid biosynthesis (CYP11B1), and mineralocorticoid synthesis (CYP11B2) but is known to block the CYP17A1 enzyme (17α-hydroxylase/17,20-lyase). CYP17A1 is found in prostatic, testicular, and adrenal tissues, and its expression is 17 times higher in mCRPCs than in primary prostate tumours. It is located in the endoplasmic reticulum and plays a significant role in androgen synthesis and cortisol production (19, 23-26). AA is the active metabolite formed upon hydrolysis and irreversibly inhibits CYP17 (27-30). Inhibition of hydroxylase activity in turn suppresses pregnenolone and progesterone hydroxylation, limiting the subsequent conversion of hydroxylated metabolites to dehydroepiandrosterone and androstenedione, respectively. This causes decreased testosterone and DHT levels and ultimately leads to testosterone blockade in all tissues. As a result, synthesis of hormones such as cortisol is reduced. Cortisol precursors are the ultimate converted products of 17α-hydroxypregnenolone and 17α hydroxyprogesterone (27). When all 17α hydroxylase activity is blocked, cortisol production is reduced and the negative feedback on adrenocorticotropic hormone (ACTH) secretion is affected. This leads to higher levels of ACTH production as found in the mineralocorticoid excess syndrome, which is

characterised by hypertension, fluid retention, and hypokalaemia and has been found to be responsive to the synergistic effect of prednisone, dexamethasone, or corticosterone at low doses (19, 24-26, 31-33).

2.3 Clinical applications

The effects of AA plus prednisone (AAP) in combination with ADT have been tested in large randomised clinical trials (RCTs). In the COU-AA-301 and COU-AA-302 registration trials, AA showed overall survival (OS) benefits both pre-and post-docetaxel (34, 35) and consequently became standard treatment for asymptomatic or mildly symptomatic docetaxel-naïve mCRCP patients with ECOG status 0-1. In the COU-AA-301 study, the most common AEs were fatigue, back pain (30%), nausea (30%), constipation (26%), and bone pain (25%). Incidence of fluid retention and oedema was 31%, while that of cardiac events (tachycardia and atrial fibrillation) was 13%. In the COU-AA-302 trial, AEs (arthralgia, peripheral oedema, hot flushes, diarrhoea, hypokalaemia, and hypertension) occurred more frequently for AAP than placebo. AEs of grade 1 or 2 were mostly reported. These included grade 1-3 fatigue (40%), fluid retention (29%), hypertension (22%), hypokalaemia (17%), and increased levels of alanine aminotransferase (12%) and aspartate aminotransferase (11%) (36). Incidence of AE-related deaths was 4% in the AA group and 3% in the placebo group. Notable benefits were prolonged OS and rPFS, delays in patient-reported pain progression and concurrent improvements in HRQoL parameters, including vitality, pain, general status, and urinary and sexual functioning. Median time to HRQoL deterioration was longer in patients in the AAP arm than in the placebo arm (12.7 months vs 8.3 months) (37). In this setting, AAP was an alternative to chemotherapy following progression to CRCP status. Building on the evidence in favour of AA, two recent RCTs investigated the efficacy and safety of AAP also in locally advanced and metastatic hormone-sensitive prostate cancer (mHSPC). One is the LATITUDE study (A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus ADT Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer [mHNPC] (38) and the other is the STAMPEDE study, G arm, (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) (39).

2.3.1 AA in mCRPC

In the COU-AA-301 and -302 studies, AEs related to AA were predominantly grade 1 or 2; consequently, the rate of drug discontinuation or dose reduction was low (9, 40). There were

no differences in all-grade toxicity with regard to nausea, constipation, bone pain, and arthralgia. Grade 3 (mostly fatigue, back pain, anaemia, and bone pain) and grade 4 adverse reactions occurred in less than 10% of patients (41).

In a recent study, Roviello et al demonstrated that CYP17 inhibitors significantly increase the risk of all-grade adverse events including hypokalaemia, hypertension, liver function test abnormalities, and cardiac events (RR ranging from 1.56 to 1.93). In particular, a major impact was observed in the incidence of all-grade liver function test abnormalities (RR=1.93). CYP17 inhibition also increased the risk of grade ≥ 3 cardiac disorders and hypokalaemia, and the incidence of all-grade and grade ≥ 3 cardiac disorders and all-grade hypertension. Hypokalaemia was found to be a direct consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Although the condition might be particularly dangerous, monitoring (at least once a month) allows for a timely correction (42).

Another recent meta-analysis on the risk ratio (RR) of cardiovascular events in mCRPC patients treated with hormonal agents pointed to an increased risk of all-grade cardiotoxicities (RR = 1.32) in the treatment group compared with placebo (43). Conversely, a study by Procopio et al showed no grade 3-4 adverse events in patients with pre-existing cardiac risk factors, including hypertension, cardiac ischaemia, arrhythmia, dyslipidaemia, and hyperglycaemia (44). In a real-life setting, Cindolo et al found relevant toxicity in 17 of 145 patients on AA therapy (12 with cardiovascular events and 5 with critical elevation of AST/ALT levels within 4 months) (45, 46). Fan et al assessed toxicity in chemotherapy-naïve mCRPC patients treated with AA, showing elevated alanine aminotransferase (ALT) (11.6%), hypokalaemia (9.3%), and hyperglycaemia (4.7%) (47).

Zhu et al conducted a meta-analysis on the safety profile of abiraterone acetate that included 9,520 patients. Summary incidence of all-grade AEs was 99.09% (95% CI: 98.70%-99.48%), RR of all-grade AEs was 1.01 (95% CI: 1.01-1.02, P<0.001), and incidence of high-grade AEs was 50.45% (95% CI: 48.40%-52.49%). Discontinuation of therapy due to AEs was 12.81% (95% CI: 11.38%-14.24%) and incidence of fatal AEs was 5.42% (95% CI: 1.79%-9.06%). Generally, AA was associated with a significantly increased risk of ALT, AST, arthralgia, cardiac events, diarrhoea, oedema, hypertension, and hypokalaemia. Likewise, with regard to high-grade AEs, the risk of ALT, AST, cardiac events, hypertension, and urinary tract infections was significantly high (48).

2.3.2 AA in mHSPC

Two RCTs, the LATITUDE and STAMPEDE trials, investigated the safety and efficacy of AA in mHSPC patients (38, 39). In the LATITUDE trial, the rates of serious adverse events were similar in the ADT alone and AA groups. Adverse events resulting in dose modification or interruption were 17% in the ADT alone arm and 32% in the AA arm. Treatment discontinuation rates were 10% in the ADT alone arm and 12% in the AA arm. In both the COU and LATITUDE trials, hypertension and hypokalaemia were more frequent in the AA group, even taking into account methodological differences in the calculation of hypertension. Considering that hypertension was calculated with a different method when compared to COU-trial, anyway tighter with hypokalaemia were more frequent in the AA group. AA had better pain control (37% risk reduction for worst pain progression) and pain interference progression (33% risk reduction). AA also showed benefits in OS and rPFS and improvements in fatigue progression (35% risk reduction) and fatigue interference progression (41% risk reduction). It also reduced the risk of HRQoL deterioration by 15%. In the STAMPEDE trial, the percentage of grade >3 adverse events was similar in both arms (11% in the ADT alone group and 15% in the AA group). Hypertension, respiratory disorders, and increased AST levels were also associated with AA.

These findings have led to the development of new guidelines for the management of mPCa (49, 50) recommending AA as a primary treatment. However, the search for new AR-modulating compounds is ongoing and no exisisting recommendation can be regarded as final or definitive.

2.4 Safety evaluation

Safety of AA has been tested in RCTs in different settings, such as pre-chemotherapy CRPC, post-chemotherapy CRPC, and metastatic, hormone-sensitive or high-risk locally advanced disease. The combination treatment of ADT with AA and prednisone showed consistent safety results in each clinical trial (Table 1) (34). Interestingly, results were similar in the STAMPEDE and LATITUDE trials (34, 35) and also mirrored those of the COU-AA-301 and COU-AA-302 studies. In particular, the frequency of hypertension, oedema, and hypokalaemia in the STAMPEDE trial was comparable to or lower than in the other studies mentioned. In the LATITUDE trial, on the other hand, mineralocorticoid-mediated adverse events were slightly more frequent. The authors suggest that these differences could be due to the somewhat longer duration of AA treatment (35).

Adverse events had similar rates in 3 out of 4 of the clinical trials examined and affected more than 90% of patients (up to 99% of patients in the COU-AA-302 and STAMPEDE trials) (34, 35, 39). High-grade (i.e. 3-5) adverse events were reported in approximately 50% of patients in the COU-AA-302 and STAMPEDE studies, and even higher rates were reported in the LATITUTE trial (Table 2). Conversely, the COU-AA-301 study consistently reported lower rates of overall and high-grade adverse events. Post-hoc analyses of the COU-AA-301 and COU-AA-302 studies provide evidence in support of the long-term safety of AAP. The overall incidence of corticosteroid-related AEs in the AAP and placebo groups was 25.5% and 23.3%, respectively, with weight increase and hyperglycaemia being the most commonly reported. Incidence of >3 grade AEs was 5.1% in the AAP arm and 3.7% in the placebo arm (51).

In a recent randomised study, Attard et al evaluated the safety of AA with 4 glucocorticoid regimens and reported that combination with dexamethasone appears to be particularly active but may be associated with adverse metabolic consequences (52). However, it is of note that the corticosteroid-associated adverse events may be reduced with a different corticosteroid dosage and schedule. Fizazi et al explored the incidence of long-term corticosteroid-related adverse events in patients from the COU-AA-301 and COU-AA-302 studies (51). The main adverse events were hyperglicaemia and weight increase, which led the authors to conclude that low-dose corticosteroid treatment is safe and tolerable also in the long term (51). Using an alternative corticosteroid or switching from one corticosteroid to another may also be a way to prolong AA efficacy. Fenioux et al tested the effects of switching from prednisone to dexamethasone at symptomatic PSA progression in mCRPC patients, achievinglonger progression-free survival and PSA decline without significant changes efficacy and tolerance (53).

The role of diet should also be considered. In a recent phase-two trial, 72 patients were allocated to either a low-fat or a standard diet. Patients in the low-fat arm showed a higher, albeit not statistically significant, number of events than those in the standard arm (32.4 vs. 17.6%) (54).

2.5 Safety in special populations: **elderly patients**

Use of AAP in the elderly warrants a thorough investigation of its potential side effects. A study by Smith et al showed that AAP has similar clinical benefits and tolerability in older and younger men and therefore qualifies as a valid choice for patients who may not tolerate other

therapies with greater toxicity (55). Mineralocorticoid-related events were similar between the two groups and so were discontinuation rates. On the other hand, incidence of cardiac disorders and fluid retention was higher in older patients. Another ongoing clinical trial is investigating the incidence and severity of cognitive impairment in elderly men during treatment, focusing on quality of life, autonomy, and treatment compliance (56).

Another possible way to detect risks is to analyse safety data from spontaneous reporting systems. EudraVigilance is a system designed for collecting reports of suspected side effects. These reports are used to evaluate the benefits and risks of medicines during development and to monitor safety following authorisation in the European Economic Area (EEA). EudraVigilance has been in use since December 2001 (57). A retrospective analysis of population-based data from the EudraVigilance database showed that abiraterone acetate is well tolerated, with age having only a marginal effect on adverse events. Elderly patients, however, seem to be at higher risk of cardiac and metabolic disorders (Table 3).

As use of abiraterone acetate becomes more widespread, a higher number of adverse events are being reported in clinical trials, the only exception being a recently documented reduction in cardiac events (57). Similar considerations may also apply to other drugs used to treat prostate cancer, such as enzalutamide.

2.6 Comparison with safety of other drugs

In a recent network meta-analysis, Kassem et al. compared AA to the new standard of care in mHSPC treatment, docetaxel. The authors reported a relative risk of treatment-related mortality in the docetaxel + ADT and AA + ADT groups of 1.93 and 1.35, respectively, with no differences in mortality between the two arms. Differences were however found in grade 3-4 haematological adverse events (higher in the docetaxel group) and corticosteroid-related complications (higher in the AA group) (58). When comparing quality of life results in the same setting, Feyerabend et al. showed a slight benefit for AA over docetaxel (59). A recent long-term analysis of the STAMPEDE arm comparing AA and docetaxel showed similar rates of grade 3-5 adverse events (40 vs. 48%) (60).

In chemotherapy-naïve mCRPC, current guidelines recommend other treatments (61). Among these, and similar to AA, enzalutamide has a comparably favourable toxicity profile. It acts on the androgen axis and inhibits dihydrotestosterone binding to androgen receptors, androgen receptor translocation to the nucleus, and androgen receptor binding to DNA in the adrenal glands, the testes, andwithin the tumour microenvironment. The most frequently reported AEs

are hot flushes and fatigue for enzalutamide, and hypokalaemia, fluid retention, and transaminase increase for AA. In a study by Hussein et al, AEs of special interest related to enzalutamide administration were hypertension (12%), major adverse cardiovascular events (5%), and mental impairment disorders (5%). The most common AEs leading to death were cardiac events (1%, nine patients) (62).

Recently, Moreira et al found that patients receiveing enzalutamide have a higher risk of all-grade fatigue but not all-grade or high-grade cardiovascular events, while AA is associated with all-grade and high-grade cardiovascular toxicity (63). In their meta-analysis, the authors concluded that AA is safe even in patients with cardiac morbidity, although cardiotoxicity may well represent a life-threatening side effect. They also warned against underestimating enzalutamide-related fatigue, given that the latter is known to have a significant impact on patients' QoL, with repercussions on both their psychological status and self-care abilities.

Another meta-analysis by Zhu J et al compared the toxicity profiles of abiraterone acetate and enzalutamide and assessed the risk of associated adverse events (48). Results demonstrated that AA increases the risk of all-grade and high-grade AEs. Most adverse events were secondary to elevated mineralocorticoid levels resulting from CYP17 blockade, with hypertension, hypokalaemia, cardiac events, and increased risk of liver test abnormalities being the most frequently reported. Conversely, enzalutamide was not associated with any significant increase of all-grade and high-grade adverse events, and its AE profile seemed mostly to include back pain, fatigue, hot flushes, and increased risk or hypertension. A few episodes of seizures were also reported, which were supposedly caused by acid-gated chloride channel inhibition.

One advantage of abiraterone acetate and enzalutamide over other therapies is their oral administration; however, their toxicity profile characteristics should be taken into consideration when selecting the most appropriate treatment.

2.7 Conclusion

In summary, treatment with AAP and ADT showed improved efficacy outcomes in terms of OS and rPFS, an acceptable safety profile, and consistent efficacy with a positive risk-benefit balance.

3. Expert opinion

In recent years, several mechanisms have been proposed to explain the progression to castration-resistant prostate cancer status. These include AR upregulation, induction of AR splice variants, AR point mutations, upregulation of glucocorticoid receptors, activation of alternative oncogenic signalling pathways, neuroendocrine transformations, and immune evasion through PD-L1 upregulation (64, 65). It seems thus reasonable to suggest that AR could be a viable therapeutic target in prostate cancer treatment (65). A better understanding of the way androgen receptor pathways work in prostate cancer has led to the development of new agents targeting the AR axis. These agents have shown to improve survival in mCRPC and more recently mHSPC patients. Treatement choices should be based on a balance of efficacy and safety and on detailed knowledge of the toxicity profile of each molecule under consideration.

In this review we provide an overview of the safety profile of AA in the treatment of prostate cancer based on data from RCTs. We also refer to the most recent meta-analyses to better understand the actual incidence of AEs in clinical practice. All main guidelines specify which new hormonal agents are available in chemotherapy-naïve settings. More than 50% of mPCa patients never receive secondary treatment, mostly because of differences in management strategies across specialties, or knowledge of indications and contraindications, as well as existing comorbidities and patient ineligibility, presumably due to concerns about toxicity (66). The mPCa disease continuum, ranging as it does from patients with low-volume disease and low PSA levels to those with more rapidly progressive disease and high burden, is another variable worth considering. Usually, patients with symptomatic disease have the worst prognosis. Evidence from the STAMPEDE and LATITUDE trials suggests that early treatment in patients with high-risk and hormone-naïve mPC may enhance the therapeutic effects observed in mCRPC patients.

In this scenario, treatment decision-making should be enformed by a thorough understanding of a given drug profile. The most frequent adverse events of abiraterone acetate are known, particularly those related to mineralocorticoid excess, notably hypokalaemia, fluid retention, hypertension, and cardiac disorders, all largely preventable by the coadministration of low-dose glucocorticoids. Several strategies have been attempted to minimise the risk of serious cardiac AEs, including the addition of oral potassium or selective mineralocorticoid antagonists (67). In this respect, the identification of early predictive markers of AEs could help exclude patients at increased risk of cardiac toxicity during AA treatment.

Abiraterone acetate has been the first no-chemo option in patients with metastatic hormone naïve PCa or mCRPC. Specifically, it has shown to have significant effects on overall survival with an acceptable profile, as observed after 4.5 years of treatment in the latest update of the LATITUDE trial (68).

The introduction of abiraterone and enzalutamide has completely changed the clinical management of patients with metastatic, castration-resistant PCA, since these agents increase overall survival without reducing the possible efficacy of subsequent chemotherapy. This opens a new era in CRPC management and will hopefully help identify new treatment paradigms. The availability of new therapies, in turn, makes it imperative to identify the optimum drug sequencing in the management of metastatic prostate cancer. Treatment choices ultimately depend on factors such as physician's preference and patient's health status. If a decision to start AAP is made, close monitoring for corticosteroid events is mandatory (69). Among possible complications, hyperglycaemia and diabetes must be given careful consideration. In particular, patients with non-insulin-dependent diabetes mellitus may become insulin-dependent when treated with AAP, and episodes of hyperglycaemia warrant dose adjustments if corticosteroid use is to be interrupted (70). Moreover, when prednisone is reduced or stopped, patients should be monitored for signs of adrenocortical insufficiency. On the other hand, data reported in the literature for a total treatment period of 4.5 years indicate similar serious adverse event rates and discontinuation rates for AAP and placebo.

Data on the ideal sequencing of anti-androgen therapies, both alone and in combination with other treatments, are also needed. Khalaf et al sought to address this issue in a clinical trial; however, they were ultimately unable to make any recommendations and simply pointed out that continuing with enzalutamide after an initial treatment with abiraterone could be an option, given that 34% of patients in their sample responded to such treatment (71).

The possibility to use AA as an adjuvant or neoadjuvant treatment in locally advanced disease is still a matter of debate and ongoing studies will hopefully clarify this aspect in the near future.

Further studies are ongoing to evaluate the possible role of AA in association with chemotherapy, enzalutamide or apalutamide, an AR antagonist which has been recently released to manage patients with non-metastatic CRPC. In a few years, the availability of a generic drug may further increase use in clinical practice. Until now, treatment with AAP plus ADT has demonstrated to be effective and well tolerated, with a positive risk-benefit balance.

It is anticipated that for the next 5 years AAP will remain one of the pillars of metastatic hormone-sensitive and castration-resistant PCA.

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** of interest*

*** of considerable interest*

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Tables

Table 1 – Adverse events of abiraterone acetate in phase III clinical trials. Events reported for all grades as frequencies (%) in the treatment arm.

Table 2 – Grade 3 to 5 adverse events of abiraterone acetate in phase III clinical trials. Events reported for all grades as frequencies (%) in the treatment arm.

Table 3: Age influence on adverse events in patients treated with AAP and ENZ (Eudra Vigilance 20 October 2018).

Table 1 – Adverse events of abiraterone acetate in phase III clinical trials. Events reported for all grades as frequencies (%) in the treatment arm.

	Post-chemothearpy CRPC	**Pre-chemotherapy CRPC**	**Hormone-sensitive prostate cancere**	
Adverse event type	**COU-AA-301**	**COU-AA-302**	**STAMPEDE**	**LATITUDE**
Anaemia	198 (25)			54 (9)
Thrombocytopoenia	30 (4)			
Neutropoenia	8 (1)			
Febrile neutropoenia	3 (<1)			
Diarrhoea	156 (20%)	127 (23)		
Fatigue	372 (47)	215 (40)	21 (2)	77 (13)
Asthenia	122 (15)			
Back pain	262 (33)	180 (33)		10 (18)
Nausea	258 (33)	130 (24)		
Vomiting	11 (24)			
Haematuria	73 (9)			
Abdominal pain	102 (13)			
Limb pain	156 (20)	93 (17)		
Dyspnoea	116 (15)			
Constipation	223 (28)	128 (24)		
Pyrexia	80 (10)			
Arthralgia	239 (30)	159 (29)		
Urinary tract infection	105 (13)			
Pain (Muskoskeletal pain)	38 (5)	88 (16)	68 (7)**	
Bone pain	216 (27)	113 (21)		74 (12)
Fluid retention (oedema)	261 (33)	159 (29)	5 (1)	
Hypokalaemia	143 (18)	93 (17)	12 (1)	122 (20)
Cardiac disorders	126 (16)	110 (20)	24 (2)	74 (12)
Liver test abnormalities	89 (11)	125 (33)	70 (7)	185 (31)
Hypertension	88 (11)	118 (22)	44 (5)	219 (37)
Hot flushes		123 (23)	129 (14)*	
Cough		98 (18)		

*Included as endocrine disorders with impotence; ** Muskoskeletal disorders

Table 2 – Grade 3 to 5 adverse events of abiraterone acetate in phase III clinical trials. Events reported for all grades as frequencies (%) in the treatment arm.

	Post-chemothearpy CRPC	Pre-chemotherapy CRPC	Hormone-sensitive prostate cancere	
Adverse event type	COU-AA-301	COU-AA-302	STAMPEDE	LATITUDE
Total	610 (77)	538 (99)	943 (99)	558 (93)
Grade 3-5	182 (24)	267 (49)	443 (47)	374 (63)

Table 3: Age influence on adverse events in patients treated with AAP and ENZ (Eudra Vigilance 20 October 2018). PRR1: [65-85] vs <65; PRR2: >85vs<65. *statistically significant p<0,05, PRR: pooled relative risk.

	ABIRATERONE					ENZALUTAMIDE				
Age	**< 65**	**[65-85]**	**>85**	**PRR1**	**PRR 2**	**< 65**	**[65-85]**	**>85**	**PRR1**	**PRR 2**
Total Adverse Events	**1090**	**6299**	**1613**			**4170**	**24134**	**7417**		
Blood and lymphatic system disorders	29	180	36	1,07 (0,72-1,58)	0,83 (0,51-1,35)	64	255	61	0,69 (0,52-0,90)*	0,54 (0,37-0,76)*
Cardiac disorder (Atrial Fibrillation)	39	335	94	1,48 (1,07-2,05)*	1,62 (1,12-2,32)*	47	463	201	1,70 (1,26-2,29)*	2,40 (1,75-3,29)*
Ear and labyrinth disorders	3	16	4	0,92 (0,26-3,16)	0,90 (0,20-3,97)	12	128	35	1,84 (1,02-3,32)	1,64 (0,85-3,15)
Endocrine disorders	3	46	10	2,65 (0,83-8,52)	2,23 (0,61-8,07)	5	16	11	0,55 (0,20-1,51)	1,23 (0,43-3,55)
Eye disorders	14	47	9	1,59 (0,88-2,87)	0,43 (0,18-0,98)*	27	268	61	1,71 (1,15-2,54)*	1,27 (0,80-1,99)
Gastrointestinal disorders (Abdominal pain, nausea, Constipation, Diarrea)	74	357	99	0,83 (0,66-1,06)	0,89 (0,66-1,19)	224	1880	306	1,45 (1,26-1,66)*	0,76 (0,65-0,90)*
General disorders and administration site conditions (astenia, fatigue pain…)	187	1125	345	1,04 (0,90-1,19)	1,23 (1,05-1,45)*	1080	5861	2118	0,94 (0,89-0,99)*	1,10 (1,03-1,17)*
Hepatobiliary disorders	52	260	37	0,87 (0,64-1,15)	0,48 (0,31-0,72)*	25	118	24	0,82 (0,53-1,25)	0,54 (0,31-0,94)*
Immune system disorders	0	7	5			12	52	15	0,74 (0,40 -1,40)	0,70 (0,32-1,50)

Infections and infestations	44	337	113	1,32 (0,97-1,80)	1,72 (1,22-2,41)*	105	915	322	1,50 (1,23-1,84)*	1,72 (1,38 - 2,14)*
Injury, poisoning and procedural complications	47	374	118	1,37 (1,02-1,85)	1,68 (1,20-2,33)*	264	1570	683	1,02 (0,91-1,16)	1,45 (1,26-1,67)*
Investigations	125	667	149	0,92 (0,77-1,10)	0,80 (0,63-0,99)*	300	1712	446	0,98 (0,87-1,11)	0,83 (0,72-0,96)*
Metabolism and nutrition disorders (descreased apetite, fluid retention)	48	381	104	1,37 (1,02-1,84)*	1,45 (1,03-2,02)*	117	1006	345	1,48 (1,23-1,79)*	1,65 (1,35-2,03)
Musculoskeletal and connective tissue disorders (back pain, arthralgia, bone pain)	52	218	41	0,72 (0,53-0,97)*	0,53 (0,35-0,79)*	250	1228	297	0,84 (0,74-0,96)*	0,66 (0,56-0,78)*
Neoplasms benign, malignant and unspecified (incl cysts and polyp	130	563	110	0,74 (0,62-0,89)	0,57 (0,44-0,72)*	616	2588	713	0,72 (0,67-0,78)*	0,65 (0,58-0,72)*
Nervous system disorders (headache)	59	302	81	0,89 (0,67-1,16)	0,92 (0,66-1,27)	318	2023	627	1,09 (0,98-1,23)	1,10 (0,97-1,26)
Psychiatric disorders	24	85	39	0,61 (0,39-0,95)	1,09 (0,66 - 1,80)	145	761	219	0,90 (0,76-1,07)	0,85 (0,69-1,04)
Renal and urinary disorders	31	226	47	1,26 (0,87-1,82)	1,01 (0,65 - 1,58)	75	476	145	1,09 (0,86-1,39)	1,08 (0,82-1,43)
Reproductive system and breast disorders	5	19	5	0,65 (0,24-1,76)	0,67 (0,19-2,30)	21	81	18	0,66 (0,41-1,07)	0,48 (0,25-0,90)*
Respiratory, thoracic and mediastinal	35	250	75	1,23 (0,87-1,75)	1,43 (0,97-2,12)	91	764	285	1,45 (1,17-1,79)*	1,76 (1,39-2,22)*

disorders										
Skin and subcutaneous tissue disorders	24	125	22	0,90 (0,59-1,40)	0,61 (0,34-1,08)	98	556	125	0,98 (0,79-1,21)	0,71 (0,55-0,93)*
Social circumstances (Disability, walking aid)	2	8	4	0,69 (0,14-3,26)	1,34 (0,25-7,28)	17	66	34	0,67 (0,39 -1,14)	1,12 (0,63-2,01)
Surgical and medical procedures	28	164	34	1,01 (0,68-1,50)	0,81 (0,49-1,33)	123	613	153	0,86 (0,71-1,04)	0,70 (0,55-0,88)*
Vascular disorders(hypertension, flushing)	34	205	50	1,04 (0,73-1,49)	0,98 (0,64-1,50)	134	734	173	0,94 (0,79-1,13)	0,72 (0,58-0,90)*