ZYTIGA® (abiraterone acetate)
ZYTIGA - Cardiovascular Events

SUMMARY

- ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from cytochrome P450 (CYP)17 inhibition and is indicated for use in combination with prednisone/prednisolone.[1] Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure [BP], hypokalemia, or fluid retention, such as those with heart failure, recent myocardial infarction (MI), cardiovascular disease, or ventricular arrhythmia. Control hypertension and correct hypokalemia before treatment. Monitor BP, serum potassium and symptoms of fluid retention at least monthly. In postmarketing experience, QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalemia while taking ZYTIGA.[2]
- Two phase 3, randomized, double-blind, placebo-controlled, multinational studies assessed the safety and efficacy of ZYTIGA 1,000 mg daily plus prednisone 5 mg twice daily and androgen deprivation therapy (ADT) vs placebo plus prednisone and ADT in patients with metastatic castration-resistant prostate cancer (mCRPC).[3-6]
    - In COU-AA-301 (N=1195), the most common cardiac disorders at the interim analysis included grade 1/2 tachycardia (3% in the ZYTIGA plus prednisone group vs 2% in the placebo plus prednisone group, *P*=0.22) and grade ≤3 atrial fibrillation (2% in ZYTIGA plus prednisone group vs 1% in placebo plus prednisone group, *P*=0.29) with consistent results in the updated analysis.[3,4]
    - In COU-AA-302 (N=1088), grade 3/4 cardiac disorders were reported in 6% of patients receiving ZYTIGA plus prednisone compared to 3% in the placebo plus prednisone group at the second interim analysis (IA2) with consistent results in the final analysis after a median of 49.2 months follow-up.[5,6]
- In LATITUDE (N=1199), a phase 3, randomized, double-blind, placebo-controlled, multicenter study enrolled patients with newly diagnosed, metastatic high-risk castration-sensitive prostate cancer (CSPC) who received ZYTIGA 1,000 mg daily plus prednisone 5 mg once daily with ADT vs placebos with ADT. Grade 3 (3%) and grade 4 (1%) cardiac disorders were reported in the treatment group compared to 1% grade 3/4 cardiac disorders in the placebos with ADT group at interim analysis and also after a median 51.8 months at the final analysis. [1,7,8]
- The safety of ZYTIGA in patients with left ventricular ejection fraction (LVEF) <50% or New York Heart Association (NYHA) Class III or IV heart failure (in COU-AA-301) or NYHA Class II to intravenous (IV) heart failure (in COU-AA-302 and LATITUDE) has not been established because these patients were excluded from these randomized clinical trials.[1, 3,5]
- In a phase 1b, open-label, single-arm, multicenter study conducted to assess the effect of ZYTIGA and prednisone on QT interval, 33 patients with mCRPC received ZYTIGA 1,000 mg once daily in combination with prednisone 5 mg orally twice daily. No patient had a LVEF <50%. Assessments up to cycle 2, day 2 showed the upper bound of the 2-sided 90% confidence interval (CI) for the mean baseline-adjusted QT interval corrected using Fridericia's formula (QTcF) change was <10 milliseconds (ms). No patient discontinued therapy due to corrected QT interval (QTc) prolongation or adverse event (AE). No apparent relationship between change in QTcF and abiraterone plasma concentrations was observed.[9]
- QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalemia while taking ZYTIGA.[10-15]
- Cardiovascular events have been reported with ZYTIGA use based on real-world postmarketing data from the United States Food and Drug Administration Adverse Event Reporting System (FAERS).[16,17]

CLINICAL DATA

Phase 3 COU-AA-301 Study

de Bono et al (2011)[3] evaluated the efficacy and safety of ZYTIGA plus prednisone compared with placebo plus prednisone in patients with mCRPC whose disease had progressed after docetaxel-based chemotherapy (N=1195).

- Patients were randomized 2:1 and the primary endpoint was overall survival (OS). All patients received a concomitant gonadotropin releasing hormone (GnRH) analog or had a bilateral orchiectomy.
- Select exclusion criteria:
  - Uncontrolled hypertension (systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg); patients with a history of hypertension were permitted to participate if BP was controlled by antihypertensive therapy.
  - Clinically significant heart disease, including MI, arterial thrombotic events within previous 6 months, severe or unstable angina, NYHA Class III through IV heart disease, or baseline cardiac ejection fraction <50%.

Cardiovascular-Related Safety

- Cardiac disorders and AEs associated with elevated mineralocorticoid levels (fluid retention/edema, hypokalemia, and hypertension) are summarized in Table: Cardiovascular-Related AEs of Special Interest.
  - The most common cardiac disorders included grade 1/2 tachycardia (3% in the ZYTIGA plus prednisone group vs 2% in the placebo plus prednisone group, *P*=0.22) and grade ≤3 atrial fibrillation (2% in ZYTIGA plus prednisone group vs 1% in placebo plus prednisone group, *P*=0.29).
  - Treatment discontinuation due to cardiac disorders occurred in 1.8% of patients in the ZYTIGA plus prednisone group vs 1.5% in the placebo plus prednisone group.[18]
  - Fatal cardiac events occurred in 1.1% of patients in the ZYTIGA plus prednisone group and 1.3% of patients in the placebo plus prednisone group.

Cardiovascular-Related AEs of Special Interest[3]

	ZYTIGA Group (n=791)			Placebo Group (n=394)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Fluid retention/edema	31[a]	2	<1	22	1	0
Hypokalemia	17[b]	3	<1	8	1	0
Cardiac disorders[c]	13	3	1	11	2	<1
Hypertension	10	1	0	8	<1	0

Abbreviation: AEs, adverse events.
[a]*P*=0.04 vs placebo + prednisone. [b]*P*<0.001 vs placebo + prednisone. [c]Cardiac disorders associated with ZYTIGA treatment, as defined by the standardized Medical Dictionary for Regulatory Activities (version 11.0) queries; included ischemic heart disease, myocardial infarction, supraventricular tachyarrhythmias, ventricular tachyarrhythmias, cardiac failure, and possible arrhythmia-related tests, signs, and symptoms.

- The updated analysis revealed consistent results, as summarized in Table: Cardiovascular-Related AEs of Special Interest - Updated Analysis.
  - The most common cardiac disorders included grade 1-2 tachycardia and grade ≤3 atrial fibrillation.
  - Nine patients (1%) in the ZYTIGA plus prednisone group and 5 patients (1%) in the placebo plus prednisone group experienced fatal cardiac AEs.

Cardiovascular-Related AEs of Special Interest - Updated Analysis[4]

	ZYTIGA Group (n=791)			Placebo Group (n=394)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Fluid retention/edema	33	2	<1	24	1	0
Hypokalemia	18	4	<1	9	<1	0
Cardiac disorders[a]	16	4	1	12	2	<1
Hypertension	11	1	0	8	<1	0

Abbreviation: AEs, adverse events.
[a]Cardiac disorders associated with ZYTIGA treatment, as defined by the standardized Medical Dictionary for Regulatory Activities (version 11.0) queries; included ischemic heart disease, myocardial infarction, supraventricular tachyarrhythmias, ventricular tachyarrhythmias, cardiac failure, and possible arrhythmia-related tests, signs, and symptoms.

Phase 3 COU-AA-302 Study

Ryan et al (2013)[5] evaluated the clinical benefit of ZYTIGA plus prednisone compared to placebo plus prednisone in asymptomatic or mildly symptomatic patients with chemotherapy-naïve mCRPC (N=1088).

- Patients were randomized 1:1 and the coprimary endpoints were OS and radiographic progression-free survival (rPFS). All patients received a concomitant GnRH analog or had a bilateral orchiectomy.
- Select exclusion criteria:
  - Uncontrolled hypertension (systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg); patients with a history of hypertension were permitted to participate if BP was controlled by antihypertensive therapy.
  - Clinically significant heart disease, including MI, arterial thrombotic events within previous 6 months, severe or unstable angina, NYHA Class II through IV heart disease, or baseline cardiac ejection fraction <50%.
  - Atrial fibrillation or other cardiac arrhythmia requiring medical treatment.

Cardiovascular-Related Safety

- Mineralocorticoid-related AEs and cardiac disorders at the time of the IA2 are summarized in Table: Cardiovascular-Related AEs of Special Interest (IA2). Additionally, data from the third interim analysis (IA3) are summarized in Table: Cardiovascular-Related Safety Analyses per Time on Therapy (IA3).
- Treatment discontinuation due to cardiac disorders occurred in 0.9% of patients in the ZYTIGA plus prednisone group vs 0.7% in the placebo plus prednisone group.[19]
- Deaths due to cardiac disorders occurred in 0.6% of patients in the ZYTIGA plus prednisone group vs 0.4% in the placebo plus prednisone group.[19]

Cardiovascular-Related AEs of Special Interest (IA2)[5]

	ZYTIGA Group (n=542), %		Placebo Group (n=540), %	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Fluid retention/edema	28	<1	24	2
Hypokalemia	17	2	13	2
Hypertension	22	4	13	3
Cardiac disorders[a]	19	6	16	3
Atrial fibrillation	4	1	5	<1

Abbreviations: AEs, adverse events; IA2, second interim analysis.
[a]Cardiac disorders included ischemic heart disease, myocardial infarction, supraventricular tachyarrhythmia, ventricular tachyarrhythmia, cardiac failure, and possible arrhythmia-related investigations, signs, and symptoms.

Cardiovascular-Related Safety Analyses per Time on Therapy (IA3)[20]

Exposure	ZYTIGA Group			Placebo Group		
	n	Grade 1-2, %	Grade 3-4, %	n	Grade 1-2, %	Grade 3-4, %
Cardiac disorders						
<3 months	542	5	<1	540	4	1
12-15 months	302	3	1	184	7	<1
≥24 months	154	6	<1	76	9	0
Hypertension						
<3 months	542	7	1	540	6	2
12-15 months	302	4	<1	184	2	2
≥24 months	154	1	<1	76	1	0

Abbreviation: IA3, third interim analysis.

- The incidence of cardiac-related AEs of special interest reported at the time of the final analysis, after a median follow up of 49.2 months, is summarized in Table: Cardiovascular-Related AEs of Special Interest (Final Analysis).

Cardiovascular-Related AEs of Special Interest (Final Analysis)[6]

	ZYTIGA Group (n=542), %				Placebo Group[a] (n=540), %			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Fluid retention/edema	30	1	0	0	23	1	<1	0
Hypokalemia	16	2	<1	0	11	2	0	0
Hypertension	15	5	0	0	11	3	0	0
Cardiac disorders	4	6	1	<1	14	3	<1	<1
Atrial fibrillation	7	1	<1	<1	4	<1	0	0

Abbreviation: AEs, adverse events.
[a]Prior to crossover.

Phase 3 LATITUDE Study

Fizazi et al (2017)[7] evaluated the efficacy and safety of ZYTIGA in combination with prednisone and ADT vs placebos and ADT for the treatment of newly diagnosed, metastatic high-risk CSPC (N=1199).

- Patients were randomized 1:1 and the coprimary endpoints were OS and rPFS. All patients received a concomitant GnRH analog or had a bilateral orchiectomy.
- Select exclusion criteria:[1]
  - Uncontrolled hypertension (systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg); patients with a history of hypertension were permitted to participate if BP was controlled by antihypertensive therapy.
  - Clinically significant heart disease, including MI, arterial thrombotic events within previous 6 months, severe or unstable angina, NYHA Class II through IV heart disease, or baseline cardiac ejection fraction <50%.
  - Atrial fibrillation or other cardiac arrhythmia requiring pharmacotherapy.

Cardiovascular-Related Safety

- Grade 3 mineralocorticoid-related effects (hypertension and hypokalemia) were more common events of special interest in the ZYTIGA plus prednisone with ADT group, as shown in Table: Cardiovascular-Related AEs of Special Interest.
- Ten patients (2%) in the ZYTIGA plus prednisone with ADT group and 6 patients (1%) in the placebos with ADT group had died of cardiac disorders.

Cardiovascular-Related AEs of Special Interest[7,a]

AE, n (%)	ZYTIGA Group (n=597)			Placebo Group (n=602)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hypokalemia	122 (20)	57 (10)	5 (1)	22 (4)	7 (1)	1 (<1)
Hypertension	219 (37)	121 (20)	0	133 (22)	59 (10)	1 (<1)
Cardiac disorders	74 (12)	15 (3)	5 (1)	47 (8)	6 (1)	0
Atrial fibrillation	8 (1)	2 (<1)	0	2 (<1)	1 (<1)	0

Abbreviation: AE, adverse event.
[a]Among other events of special interest, grade 3 peripheral edema was reported in 0.3% of patients in the ZYTIGA group and in 0.5% of patients in the placebo group; grade 3 or 4 fluid retention or congestive heart failure was not reported in either group.

- The incidence of cardiac-related AEs of special interest reported at the time of the final analysis, after a median follow up of 51.8 months, is summarized in Table: Cardiovascular-Related AEs of Special Interest (Final Analysis).

Cardiovascular-Related AEs of Special Interest (Final Analysis)[1,8]

AE of Special Interest, %	ZYTIGA Group (n=597)		Placebo Group (n=602)		Crossover Group (n=72)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Cardiac disorders[a]	3	1	1	0	0	0
Fluid retention/edema	1	0	1	0	0	0
Hypertension	22	<1	10	<1	4	0
Hypokalemia	11	1	1	<1	3	0

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
[a]Cardiac disorder was defined based on adverse event preferred terms from MedDRA Version 18.0 dictionary.

- Treatment discontinuation due to cardiac disorders at final analysis occurred in 2.2% of patients in the ZYTIGA plus prednisone with ADT group vs 0.3% in the placebos with ADT group.[21]
- Deaths due to cardiac disorders were reported in 2.2% of patients in the ZYTIGA plus prednisone with ADT group vs 1.0% in the placebos with ADT group at final analysis.[21]

QT Prolongation and/or Torsades de Pointes

Phase 1/2 Studies

In a phase 1b, open-label, single-arm, multicenter study conducted to assess the effect of ZYTIGA and prednisone on QT interval, 33 patients with mCRPC received ZYTIGA 1,000 mg once daily in combination with prednisone 5 mg orally twice daily. No patient had a LVEF <50%. Assessments up to cycle 2, day 2 showed the upper bound of the 2-sided 90% CI for the mean baseline-adjusted QTcF change was <10 ms. No patient discontinued therapy due to QTc prolongation or AEs. No apparent relationship between change in QTcF and abiraterone plasma concentrations was observed.[9]

Additionally, in a retrospective analysis of electrocardiogram (ECG) data from 3 phase 1/2, single-arm, open-label studies (N=124), no patients had QTc prolongation after administration of ZYTIGA plus prednisone.[22]

Case Reports

Rodieux et al (2015)[10] described a 74 year old patient with hypertension, diabetes, anxiety disorder, and mCRPC who had life-threatening Torsade de Pointes associated with a prolonged QTc interval. The patient presented with cardiac arrest. Lab results included severe hypokalemia (2.5 milliequivalent [mEq]/L) and mild hypocalcemia (4.1 mEq/L). The patient was taking ZYTIGA, in addition to other medications, and was found to have poor adherence to prednisone. ZYTIGA was discontinued during the admission. The patient's serum potassium returned to normal by day 2 and the QTc interval gradually decreased by day 6. The patient was discharged 2 weeks later.

Khan et al (2016)[11] described a 77 year old patient with ischemic heart disease, previous coronary artery bypass grafting, atrial fibrillation, and mCRPC who had recurrent Torsades de Pointes due to hypokalemia (2.7 mmol/L) with a prolonged QTc interval. The patient was taking ZYTIGA plus prednisone, in addition to other medications. ZYTIGA was discontinued during admission, and the patient was discharged after remaining stable. The patient's electrolytes remained normal at clinic follow-up 1 month later.

Morales et al (2021)[12] described a 70 year old patient with hyperlipidemia, hypertension, and mCRPC who presented with recurrent syncope without prodrome. ECG revealed frequent ventricular ectopy, non-sustained episodes of Torsade de Pointes, severe hypomagnesemia (0.8 mg/dL), and hypokalemia (2.4 mEq/L). Additional testing revealed mild coronary artery disease and moderately depressed LVEF. After electrolyte disturbances were corrected, the QT interval normalized. The patient was taking ZYTIGA, in addition to other medications. ZYTIGA was discontinued during the admission, and the patient returned to baseline and was discharged. Of note, the patient was not receiving prednisone at the time of admission.

Riad et al (2021)[13] described a 78-year-old man with hypertension and mCRPC who presented with progressive generalized weakness and shortness of breath. Laboratory results revealed a potassium level of 2.2 mmol/L, magnesium level of 2.4 mg/dL, and normal kidney and hepatic functions. The initial ECG showed atrial fibrillation with a rapid ventricular rate, frequent premature ventricular contractions, and a prolonged QTc (634 ms). Overnight, the patient developed multiple episodes of Torsade de Pointes, became pulseless, and underwent advanced cardiac life support, including defibrillation. The patient was taking ZYTIGA in addition to other medications. The patient was started on IV lidocaine and dopamine infusion to augment the heart rate and assist in shortening the QTc. A slight improvement in potassium level (2.8 mmol/L) was observed despite a total of 220 mEq of IV potassium chloride. The patient received spironolactone and amiloride for urinary potassium reabsorption, in addition to hydrocortisone, to reduce the effect of ZYTIGA on increasing mineralocorticoid synthesis. After this, his potassium level normalized. Upon discharge, the patient was advised to discontinue ZYTIGA indefinitely and follow-up with his oncologist for further evaluation and management of cancer. At 3 months follow-up after discharge, the patient was symptomatically well and had normal electrolyte levels after discontinuation of ZYTIGA.

McBride et al (2021)[14] analyzed post-marketing reports of QT prolongation and/or Torsades de Pointes associated with ZYTIGA. Searches of the FAERS and literature were conducted for all cases of QT prolongation or Torsades de Pointes with ZYTIGA use from April 28, 2011 to May 1, 2019. The details of the 9 cases identified are presented in Table: Postmarketing Cases of QT Prolongation/TdP Reported with ZYTIGA. Hypokalemia was observed with Common Terminology Criteria for Adverse Events (CTCAE) grade 3-4 QTc prolongation in 6 cases. Two of the cases with hypokalemia were not taking concomitant corticosteroids.

Postmarketing Cases of QT Prolongation/TdP Reported with ZYTIGA[14]

Case	Age (Years)	Time to Onset (Days)	Peak QTc[a] (ms)	TdP	Lowest Potassium (mEq/L)	Corticosteroid	QT Prolonging Medications	Clinical Outcome	Other
1[10]	74	180	620	Y	2.5	N	None	Hospitalization, Resolved	HTN, DM, "mild hypocalcemia", Mg normal day 1
2[11]	77	180	650	Y	2.7	Y	goserelin	Hospitalization, Resolving	Prior CABG, AF, Mg, Ca normal
3	79	41	NR	Y	2.6	NR	Leuprolide	Hospitalization, Died 6 days later[b]	CAD, HTN
4	84	233	NR	Y	"hypopotassemia"	NR	None	Hospitalization, Resolved	Concomitant captopril suggests HTN or HF
5	66	NR	NR	Y	"hypokalemia"	Y	NR	Hospitalization, NR	HTN, DM, hyperlipidemia, "hypomagnesemia, hyponatremia" at time of admission
6	79	NR	629	N	2.7	Y	Triptorelin	Hospitalization, NR	Concurrent HF, pneumonia, Mg low day 1
7	71	86	"prolonged QT"	N	NR	Y	Leuprolide	Hospitalization, Resolved	HF, HTN, arrythmia
8	82	4	"prolonged QT"	N	NR	N	None	NR	HTN
9	66	505	"CTCAE Grade 3"	N	4.0	Y	Possible leuprolide[c]	Hospitalization, Resolved	"former smoker"

Abbreviations: AF, atrial fibrillation; Ca, calcium; CABG, coronary artery bypass graft; CAD, coronary artery disease; CTCAE, Common Terminology Criteria for Adverse Events; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; mEq, milliequivalent; Mg, magnesium; ms, milliseconds; N, no; NR, not reported; QTc, corrected QT interval; TdP, Torsades de Pointes; Y, yes.

[a]Method used for calculating QTc was not specified by reporters. CTCAE grades of QTc interval prolonged start with Grade 1, QTc 450-480 ms.

[b]Reported cause of death was cardiac arrest. The patient experience fatal cardiac arrest 6 days after an episode of TdP with severe hypokalemia.

[c]Case narrative reported a history of leuprolide therapy but did not clearly document concomitant leuprolide with ZYTIGA.

Lee et al (2022)[15] described a 61-year-old patient with a history of mCRPC who presented with a sudden episode of syncope while standing. ECG revealed sinus bradycardia with the presence of U-waves and a prolonged QT interval. The patient had multiple episodes of nonsustained ventricular tachycardia upon arrival at the emergency room, which rapidly progressed to Torsades de Pointes. Laboratory tests revelated severe hypokalemia (2.4 mEq/L). The patient was taking ZYTIGA, in addition to other medications. Initially, potassium was repleted with 60 mEq of oral potassium, followed by 40 mEq of IV potassium over 4 hours. Potassium levels were maintained above 4 mEq/L with additional 140 mEq IV potassium (final 4.6 mEq/L). ZYTIGA and prednisone were restarted upon discharge as hypokalemia was a preventable cause of ventricular arrhythmia. The patient continued daily potassium supplementation of 40 mEq and had no recurrence of ventricular arrhythmias or syncope, with the maintenance of normal potassium levels.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) was conducted on 12 February 2024. Summarized in this response are relevant data from the 3 phase 3 pivotal studies (COU-AA-301, COU-AA-302, and LATITUDE), a phase 1b assessment of QT interval, and case reports of QT prolongation and/or Torsades de Pointes.

REFERENCES

1. Fizazi K, Tran NP, Fein L, et al. Supplementary appendix for: Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2019;20(5):686-700.

2. Data on File. Abiraterone Acetate. Investigator's Brochure. Janssen Research and Development, LLC. EDMS-ERI-14497303; 2023.

3. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.

4. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13(10):983-992.

5. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138-148.

6. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015;16(2):152-160.

7. Fizazi K, Tran NP, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352-360.

8. Fizazi K, Tran NP, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2019;20(5):686-700.

9. Tolcher AW, Chi KN, Shore ND, et al. Effect of abiraterone acetate plus prednisone on the QT interval in patients with metastatic castration-resistant prostate cancer. *Cancer Chemother Pharmacol*. 2012;70(2):305-313.

10. Rodieux F, Nieto N, Sunthorn H, et al. Abiraterone acetate-induced life-threatening Torsade de Pointes. *Ann Pharmacother*. 2015;49(1):152-153.

11. Khan A, Kneale B. Life threatening Torsades de Pointes due to abiraterone-induced hypokalemia in a patient with metastatic prostate cancer. *New Zealand Medical J*. 2016;129(1445):124-127.

12. Morales X, Garnica D, Isaza D, et al. Syncope due to non-sustained episodes of Torsade de Pointes associated to androgen-deprivation therapy use: a case presentation. *BMC Cardiovasc Disor*. 2021;21(1):136.

13. Riad M, Allison JS, Nayyal S, et al. Abiraterone induced refractory hypokalemia and Torsades de Pointes in a patient with metastatic castration-resistant prostate carcinoma: a case report. *Eur Heart J Case Rep*. 2021;5(12):ytab462.

14. McBride L, Woronow D, Nayernama A, et al. Abiraterone acetate-associated QT prolongation and Torsades de Pointes: postmarketing cases reported to FDA. *J Oncol Pharm Pract*. 2021;27(5):1315-1316.

15. Lee DH, Money DB, Deshpande A, et al. A case of abiraterone-related hypokalemia leading to Torsades de Pointes and cardiac arrest. *Cureus*. 2022;14(3):e23678.

16. Zhang KW, Reimers MA, Calaway AC, et al. Cardiovascular events in men with prostate cancer receiving hormone therapy: an analysis of the FDA Adverse Event Reporting System (FAERS). *J Urol*. 2021;206(3):613-622.

17. Liu Y, Zhang H, Jiang Y, et al. Cardiovascular adverse events associated with new-generation androgen receptor pathway inhibitors (ARPI) for prostate cancer: a disproportionality analysis based on the FDA Adverse Event Reporting System (FAERS). *Clin Genitourin Cancer*. 2023;21(5):594-601.e2.

18. Data on File. Clinical Study Report Protocol COU-AA-301. Johnson & Johnson Pharmaceutical Research & Development, LLC. EDMS-ERI-16890604; 2010.

19. Data on File. Clinical Study Report Protocol COU-AA-302. Janssen Research & Development, LLC. EDMS-ERI-26967604; 2012.

20. Rathkopf DE, Smith MR, de Bono JS, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). *Eur Urol*. 2014;66(5):815-825.

21. Data on File. Clinical Study Report Protocol 212082PCR3011. Janssen Research & Development, LLC. EDMS-ERI-174764142; 2019.

22. Ryan C, Danila D, Tolcher A, et al. QT/QTc studies of abiraterone acetate in patients with metastatic castration-resistant prostate cancer (mCRPC): analysis of 3 phase 1/2 studies. Poster presented at: European Multidisciplinary Cancer Congress; September 23-27, 2011; Stockholm, Sweden.