ZYTIGA® (abiraterone acetate)
Use of ZYTIGA in Patients with Cardiovascular Disease

SUMMARY

- Patients with underlying cardiovascular disease were excluded from participating in the three phase 3, randomized, placebo-controlled registration studies of ZYTIGA plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) and metastatic high-risk castration-sensitive prostate cancer (CSPC).[1-3]
- Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, 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 or have underlying cardiovascular conditions while taking ZYTIGA.[4]
- 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 IV heart failure (in COU-AA-302 and LATITUDE) has not been established because these patients were excluded from these randomized clinical trials.[3,5,6]
- Two analyses of the Prostate Cancer Registry (PCR), a prospective, real-world, observational, multicenter study in patients with mCRPC, reported progression-free survival (PFS), time to progression (TTP), and/or overall survival (OS) data for patients that received second-line therapy with ZYTIGA plus prednisone after first-line docetaxel or initial therapy with either ZYTIGA plus prednisone, enzalutamide, or docetaxel. Results include a subset of patients with cardiovascular disease (Table: Efficacy Outcomes for Patients with mCRPC and Cardiovascular Disease that Received ZYTIGA plus Prednisone Post-Docetaxel and Table: Efficacy Outcomes for Patients with mCRPC and Cardiovascular Disease that Received ZYTIGA plus Prednisone).[7,8]
- In a prospective, real-world, observational, multicenter study that evaluated the efficacy and safety of patients with chemotherapy-naïve mCRPC receiving ZYTIGA plus prednisone (N=453), the presence of comorbidities, including cardiovascular disorders, was not associated with radiographic progression-free survival (rPFS) and OS based on univariate and multivariate analyses (Table: Univariate and Multivariate Results for Association of Comorbidities with rPFS and OS). Adverse events (AEs) that occurred in >3% of patients during treatment included: asthenia, edema, diarrhea, anemia, fatigue, fever, dyspnea, nausea, cough, constipation, pain, death unexpected, atrial fibrillation, hot flushes, pneumonitis, back pain, and urinary incontinence.[9]
- In another prospective analysis evaluating the cardiovascular safety profile of ZYTIGA plus prednisone in 87 patients with mCRPC and cardiovascular comorbidities or coronary artery disease (CAD) risk factors, 30% of patients experienced worsening of preexisting hypertension and 6% of patients developed hypertension. Two patients developed atrial fibrillation. Median LVEF were 64% and 63% at baseline and after treatment, respectively.[10]

BACKGROUND

Patients with underlying cardiovascular disease were excluded from participating in the phase 3, randomized, double-blind, placebo-controlled registration studies of ZYTIGA in patients with mCRPC and metastatic high-risk CSPC.

- In COU-AA-301, which was conducted in patients whose disease progressed after docetaxel-based chemotherapy, exclusion criteria included uncontrolled hypertension (≥160 mmHg systolic or ≥95 mmHg diastolic blood pressure) and clinically significant heart disease (myocardial infarction, arterial thrombotic events within previous

6 months, severe or unstable angina, NYHA Class III or IV heart failure, or baseline cardiac ejection fractions <50%).[1,6]

- In COU-AA-302, which was conducted in patients with mildly symptomatic or asymptomatic mCRPC who had not received prior chemotherapy, exclusion criteria included uncontrolled hypertension (≥160 mmHg systolic or ≥95 mmHg diastolic blood pressure), clinically significant heart disease (myocardial infarction, arterial thrombotic events within previous 6 months, severe or unstable angina, NYHA Class II or IV heart failure, or baseline cardiac ejection fraction <50%), and atrial fibrillation or other cardiac arrhythmia requiring medical therapy.[2,5]
- In LATITUDE, which was conducted in patients with metastatic high-risk CSPC, exclusion criteria included uncontrolled hypertension (≥160 mmHg systolic or ≥95 mmHg diastolic blood pressure), clinically significant heart disease (myocardial infarction, arterial thrombotic events within previous 6 months, severe or unstable angina, NYHA Class II-IV heart disease, or baseline cardiac ejection fraction <50%), and atrial fibrillation or other cardiac arrhythmia requiring medical therapy.[3,11]

CLINICAL DATA

Prospective Studies

Bjartell et al (2021)[7] evaluated the safety and efficacy outcomes of patients in the PCR with mCRPC receiving second-line therapy with ZYTIGA plus prednisone after first-line docetaxel (n=394), including a subset of patients with cardiovascular disease (n=234).

Study Design/Methods

- Prospective, international, multicenter, real-world, observational study of 3003 patients with mCRPC (NCT02236637)
- Patients who received ZYTIGA plus prednisone post-docetaxel either received ZYTIGA plus prednisone after receiving docetaxel as first-line mCRPC treatment prior to PCR participation or received first-line docetaxel at the start of the PCR and went on to receive ZYTIGA plus prednisone as second-line therapy during the study period.
- **Outcome measures**: PFS and OS

Results

Patient Characteristics

- Select baseline characteristics are reported below in Table: Patient Characteristics.

Patient Characteristics[7]

	All Patients who Received ZYTIGA plus Prednisone post-Docetaxel for mCRPC at Baseline (n=394)	Patients who Received ZYTIGA plus Prednisone post-Docetaxel for mCRPC with CV Comorbidities at Baseline (n=234)
Median age, years (range)	70.0 (46-89)	72.0 (48-89)
Gleason score 8-10[a], n (%)	217 (59.1)	126 (57.3)
ECOG performance status, n (%)	n=367	n=220
2	26 (7.0)	19 (8.6)
3	4 (1.1)	3 (1.4)
Bone metastases, n (%)	n=271	n=169
≥5	113 (41.7)	75 (44.4)
CV comorbidity requiring treatment, n (%)	234 (59.4)	231 (98.7)
Hypertension	194 (49.2)	187 (79.9)
Angina pectoris	20 (5.1)	19 (8.1)
Myocardial infarction	25 (6.3)	25 (10.7)

Arrhythmia	29 (7.4)	26 (11.1)
Thromboembolic disease	10 (2.5)	8 (3.4)
Cerebrovascular accident	8 (2.0)	8 (3.4)
Transient ischemic attack	8 (2.0)	8 (3.4)
Other CV	61 (15.5)	61 (26.1)

Abbreviations: CV, cardiovascular; ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; SD, standard deviation.
[a]At initial diagnosis.

Efficacy and Safety

- In patients receiving ZYTIGA plus prednisone post-docetaxel, the median treatment duration was 9.0 months (95% CI, 6.9-10.6) and 8.7 months (95% CI, 7.10-10.3) in patients with and without baseline cardiovascular disease, respectively.
- Outcomes for patients with cardiovascular disease receiving ZYTIGA plus prednisone post-docetaxel compared to all patients receiving ZYTIGA plus prednisone post-docetaxel are reported below in Table: Efficacy Outcomes for Patients with mCRPC and Cardiovascular Disease that Received ZYTIGA plus Prednisone Post-Docetaxel.
- Treatment-emergent adverse events (TEAEs), TEAEs that led to treatment discontinuation, and treatment-emergent severe AEs were reported in 56.3%, 11.7%, and 29.7% of all patients receiving ZYTIGA plus prednisone post-docetaxel and in 56.4%, 11.4%, and 29.9% of patients with cardiovascular disease that received ZYTIGA plus prednisone post-docetaxel, respectively.

Efficacy Outcomes for Patients with mCRPC and Cardiovascular Disease that Received ZYTIGA plus Prednisone Post-Docetaxel[7]

	All Patients who Received ZYTIGA plus Prednisone post-Docetaxel for mCRPC at Baseline (n=394)	**Patients who Received ZYTIGA plus Prednisone post-Docetaxel for mCRPC with CV Comorbidities at Baseline (n=234)**
Median PFS, months (95% CI)	5.8 (5.2-6.6)	6.0 (5.0-8.0)
Median OS, months (95% CI)	23.4 (20.1-30.6)	23.1 (19.4-30.0)

Abbreviations: CI, confidence interval; CV, cardiovascular; mCRPC, metastatic castration-resistant prostate cancer; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Chowdhury et al (2020)[8] evaluated the outcomes of patients with mCRPC and cardiovascular disease within a subset of patients receiving initial therapy with either ZYTIGA plus prednisone, enzalutamide, or docetaxel utilizing the PCR (n=1583).

Study Design/Methods

- Prospective, international, multicenter, real-world, observational study of 3003 patients with mCRPC and a history of progression despite testosterone <50 ng/dL, androgen deprivation therapy (ADT), and/or history of orchiectomy in routine clinical practice (NCT02236637)
- This analysis of the PCR evaluated patients treated with ZYTIGA plus prednisone or prednisolone, enzalutamide, docetaxel, other chemotherapy, or radium-223 as initial therapy for mCRPC.
- **Outcome measures**: TTP and OS

Results

Patient Characteristics

- Patients treated with other chemotherapy or radium-223 were excluded because the number of patients were too low.
- Select baseline characteristics are reported below in Table: Patient Characteristics.

- Among patients with cardiovascular disease receiving ZYTIGA plus prednisone (n=504), the median age was 77 years (range, 50-94) and 49.8% of patients had a Gleason score 8-10 at initial diagnosis.

Patient Characteristics[8]

	Patients who had not Received Previous mCRPC Treatment at Baseline (n=1874)	Patients Treated with First-Line ZYTIGA plus Prednisone (n=754)
Mean age, years (SD)	73.1 (8.58)	75.3 (8.20)
Gleason score 8-10[a], n (%)	949 (55.4)	344 (51.0)
ECOG performance status ≥2, n (%)	189 (10.9)	57 (8.0)
Bone metastases ≥5, n (%)	548 (39.3)	203 (36.9)
CV comorbidity requiring treatment, n (%)	1221 (65.2)	504 (66.8)
Hypertension	1002 (53.5)	411 (54.5)
Angina pectoris	115 (6.1)	34 (4.5)
Myocardial infarction	133 (7.1)	48 (6.4)
Arrhythmia	154 (8.2)	62 (8.2)
Thromboembolic disease	55 (2.9)	21 (2.8)
Cerebrovascular accident	48 (2.6)	19 (2.5)
Transient ischemic attack	34 (1.8)	14 (1.9)
Other CV	300 (16.0)	139 (18.4)

Abbreviations: CV, cardiovascular; ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; SD, standard deviation.
[a]At initial diagnosis.

Efficacy and Safety

- The median treatment duration was 11.2 months (95% CI, 9.8–12.2) and 11.1 months (95% CI, 9.5–12.7) in all patients receiving ZYTIGA plus prednisone and patients with cardiovascular disease receiving ZYTIGA plus prednisone, respectively.
- Outcomes for patients with cardiovascular disease receiving ZYTIGA plus prednisone compared to the total population included in the registry receiving ZYTIGA plus prednisone are reported below in Table: Efficacy Outcomes for Patients with mCRPC and Cardiovascular Disease that Received ZYTIGA plus Prednisone.
- A total of 72.0% of patients with cardiovascular disease receiving ZYTIGA plus prednisone discontinued treatment due to disease progression.
- Death was reported in 6.9% of patients with cardiovascular disease receiving ZYTIGA plus prednisone.

Efficacy Outcomes for Patients with mCRPC and Cardiovascular Disease that Received ZYTIGA plus Prednisone[8]

	All Patients Receiving ZYTIGA plus Prednisone (n=754)	Patients with Cardiovascular Disease Receiving ZYTIGA plus Prednisone (n=504)
Median TTP, months (95% CI)	9.6 (8.4-10.8)	9.7 (8.2-11.2)
Median OS, months (95% CI)	27.1 (25.3-28.9)	27.4 (23.0-30.3)

Abbreviations: CI, confidence interval; NE, not estimable; OS, overall survival; TTP, time to progression.

Procopio et al (2020)[9] reported the second interim analysis results of a study that prospectively evaluated the efficacy and safety of patients with chemotherapy-naïve mCRPC receiving ZYTIGA plus prednisone (N=453).

Study Design/Methods

- Prospective, real-world, observational, multicenter study in Italy

- **Key inclusion criteria**: metastatic adenocarcinoma of the prostate; asymptomatic or mildly symptomatic according to clinical judgement; naïve to chemotherapy; surgically or medically castrated; who failed ADT and in whom chemotherapy was not clinically indicated; starting treatment with ZYTIGA within 30 days after the baseline visit according to clinical practice
- **Key exclusion criteria**: prior chemotherapy; participating in a clinical trial
- **Key outcome measures**: rPFS, OS, and safety

Results

Patient Characteristics

- Select baseline characteristics are reported below in Table: Patient Characteristics.
- A total of 56% of patients had stable and well-compensated cardiovascular disorders, of which 46% of patients had hypertension.

Patient Characteristics[9]

	Patients Receiving ZYTIGA plus Prednisone (N=453)
Median age, years (range)	77 (51-93)
≥75 years, n (%)	265 (58.5)
ECOG PS 0, n (%)	251 (56.7)
Number of comorbidities, n (%)	
0	142 (31.3)
1	138 (30.5)
≥2	173 (38.2)
Cardiovascular disorder, n (%)	260 (57.4)
Hypertension, %	48.6
History of myocardial infarction, %	5.5
Arrhythmia, %	4.4
Cardiomyopathy, %	3.5
Angina pectoris, %	0.7
Atherosclerosis, %	0.4
Other, %	8.8
Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status.	

Efficacy and Safety

- The median follow-up time was 18.1 months.
- The median treatment duration was 14 months (interquartile range [IQR], 7.2-20.5).
- The median rPFS was not reached. The 1- and 2- year probability of rPFS were 73.9% and 56.2%, respectively.
- The median OS was not reached. The 1- and 2-year survival rates were 87.3% and 70.4%, respectively.
- The presence of comorbidities, including cardiovascular disorders, was not associated with rPFS and OS based on univariate and multivariate analyses (Table: Univariate and Multivariate Results for Association of Comorbidities with rPFS and OS).
- A total of 285 patients discontinued treatment with ZYTIGA plus prednisone due to: disease progression (n=184), death (n=27), personal choice (n=17), adverse reaction (n=14), and AEs (not drug-related) (n=11).
- AEs that occurred in >3% of patients during treatment include (total): asthenia (15.2%), edema (6.9%), diarrhea (6.5%), anemia (6.1%), fatigue (6.1%), fever (6.1%), dyspnea (5.2%), nausea (5.2%), cough (4.8%), constipation (4.3%), pain (4.3%), death unexpected (3.5%), atrial fibrillation (3.0%), hot flushes (3.0%), pneumonitis (3.0%), back pain (3.0%), and urinary incontinence (3.0%).

Univariate and Multivariate Results for Association of Comorbidities with rPFS and OS[9]

	rPFS		OS	
	Univariate HR (95% CI) *P*-value	**Adjusted HR (95% CI)[a] *P*-value**	**Univariate HR (95% CI) *P*-value**	**Adjusted HR (95% CI)[a] *P*-value**
Number of comorbidities				
None	1[b]	1[b]	1[b]	1[b]
≥1	1.014 (0.715-1.438) 0.937	0.983 (0.684-1.412) 0.924	1.187 (0.768-1.834) 0.439	1.088 (0.685-1.727) 0.722
Type of comorbidity				
Cardiovascular disorder	-	1.03 (0.71-1.49) 0.883	-	1.10 (0.68-1.77) 0.705

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.
[a]Model adjusted for age, PSA at baseline, presence of comorbidities, visceral metastases, bone metastases, and using ECOG PS as stratification factor.
[b]Reference category.

Prati et al (2018)[10] prospectively evaluated the cardiovascular safety profile of ZYTIGA in patients with mCRPC and cardiovascular comorbidities and/or CAD risk factors (N=87).

Study Design/Methods

- Patients received 1,000 mg of ZYTIGA orally once daily (QD) and prednisone 5 mg twice daily (BID) until disease progression, symptomatic deterioration or unacceptable toxicity. The dose of ZYTIGA was reduced or discontinued for grade 3-4 adverse reactions.
- Cardiotoxicity was defined as a median of ≥10% LVEF reduction compared to baseline, or absolute LVEF value <50%.
- A baseline cardiologic evaluation was performed by assessing the presence of CAD risk factors and cardiovascular comorbidities.
- CAD risk factors included: hypertension, according to the guidelines issued by the European Society of Cardiology/European Society of Hypertension at the time of the study (mild: 140–159/90–94 mmHg; moderate: 160–179/100–109 mmHg; severe: >180/>110 mmHg); Type 2 diabetes, according to the criteria applied by the Italian Society of Diabetology, was defined as two consequent determination of fasting glucose level above 126 mg/dL or glycemia >200 mg/dL after 2 hours of a meal with 75 g glucose or hemoglobin A1c level >48 mmol/mol; dyslipidemia was defined as triglyceride level >150 mg/dL and high density lipoprotein cholesterol <40 mg/dL; smoking habit (current/former smoker vs never smoker); and overweight and obesity [body mass index (BMI) >25 kg/m^2].
- Cardiovascular comorbidities were defined by the presence of ≥1 of the following: chronic ischemia, chronic heart failure, atrial fibrillation and/or other rhythm alterations.

Results

Patient Characteristics

- Median age was 66 years (range, 50-81 years).
- All patients received prior ADT. Fifty-eight patients (67%) had received previous chemotherapy and 42 (48%) had bone metastases. No patient had visceral metastases.
- At baseline, 96% of patients had ≥1 CAD risk factor: hypertension, n=70 (80%); diabetes, n=13 (15%); obesity, n=37 (42%); tobacco smoke, n=34 (39%); and dyslipidemia, n=31 (35.5%).

- Preexisting cardiovascular comorbidities included diastolic dysfunction (22%), rhythm alterations (16%), and valvulopathies (15%), and chronic heart failure (9%). An implantable defibrillator and pacemaker were noted in one patient each.
- The most frequently prescribed antihypertensive therapies at baseline were angiotensin-converting enzyme inhibitors (41%), followed by diuretics (25%), beta-blockers (18%), angiotensin converting enzymes (14%), and calcium antagonists (10%).

Efficacy and Safety

- Median treatment duration of ZYTIGA was 9 months (range, 1-44 months).
- Median OS was 16.1 months (95% CI, 11.8–20.3 months) and median PFS was 8.0 months (95% CI, 5.3–10.8 months).
- A total of 26 (30%) patients experienced worsening of preexisting heart disease while on ZYTIGA, while 4 patients (5%) developed hypertension and 26 (30%) had worsening hypertension.
- Median LVEF was 64% and 63% at baseline and following treatment with ZYTIGA, respectively. Reduction in LVEF and diastolic function changes were not statistically significant (P<0.005). No patient had an LVEF decline ≥10%.
- Two patients (2%) developed atrial fibrillation, which led to temporary interruption of therapy; ZYTIGA was resumed once atrial fibrillation had reverted. No cases of ischemic heart disease were reported.

Additional Studies

Wilk et al (2022)[12] conducted a prospective, observational study to evaluate the role of serum cardiac biomarkers and geriatric assessment in response to therapy among patients with mCRPC receiving ZYTIGA plus prednisone either before or after chemotherapy with docetaxel (N=49). Patient comorbidities included: hypertension (n=35), atrial fibrillation (n=13), CAD (n=6), and heart failure (n=5). Patients with uncontrolled cardiovascular disease were not eligible. The median LVEF was 59%, the median D-dimer concentration was 0.735 µg/mL, the median high sensitivity troponin T (hs-TnT) concentration was 0.11 ng/mL, and median N terminal pro-brain natriuretic peptide (NT-proBNP) was 303.8 pg/mL. In the univariate analysis, factors associated with inferior TTF included: history of CAD (HR, 3.02; 95% CI, 1.19-7.66; P=0.015); LVEF <50% (HR, 2.53; 95% CI, 1.03-6.17; P=0.041); age-adjusted D-dimer greater than the upper reference limit (URL; HR, 3.53; 95% CI, 1.81-6.85; P<0.001); hs-TnT greater than the URL (HR, 2.17; 95% CI, 1.13-4.16; P=0.016); NT-proBNP ≥300 pg/mL (HR, 2.3; 95% CI, 1.22-4.34; P=0.01). In multivariate analysis, age-adjusted D-dimer greater than the URL remained statistically significant in prediction of inferior TTF (P=0.003).

Campora et al (2016)[13] conducted a study investigating the association between the cardiac biomarkers NT-proBNP and TnT and serious cardiac AEs during treatment with ZYTIGA plus prednisone or dexamethasone in 17 patients with mCRPC, included 8 patients with prior cardiac disease. A total of 5 patients (29%) experienced grade 3-4 serious cardiac AEs, including arrhythmia, acute coronary syndrome (ACS), and heart failure. All 5 patients had a prior history of cardiovascular disease, including ACS (n=3), atrial fibrillation (n=1), and first-degree atrioventricular block (n=1). Each patient discontinued ZYTIGA treatment after the serious cardiac AE.

Case Reports

A case report described a 74-year-old patient with hypertension, diabetes, anxiety disorder, and mCRPC who had life-threatening Torsades de Pointes associated with a prolonged QT interval and severe hypokalemia (2.5 mEq/L). The patient was taking ZYTIGA, in addition to other medications, and was found to have poor adherence to prednisone.[14]

Another case report 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. The patient was taking ZYTIGA, in addition to other medications.[15]

An additional case report[16] described a 70-year-old patient with hyperlipidemia, hypertension, and mCRPC who presented with recurrent syncope without prodrome. Electrocardiogram (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 CAD 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 admission, and the patient returned to baseline and was discharged. Of note, the patient was not receiving prednisone at the time of admission.

One additional case report[17] 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.

An analysis of postmarketing reports of QT prolongation and/or Torsades de Pointes associated with ZYTIGA was conducted.[18] Searches of the FDA Adverse Event Reporting System (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[18]

Case	Age (years)	Time to onset (days)	Peak QTc[a] (ms)	TdP	Lowest Potassium (mEq/L)	Corticosteroid	QT Prolonging Medications	Clinical Outcome	Other
1[14]	74	180	620	Y	2.5	N	None	Hospitalization, Resolved	HTN, DM, "mild hypocalcemia", Mg normal day 1
2[15]	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 experienced 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.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 17 December 2024. Summarized in this response are relevant data from prospective studies and case reports of Torsades de Pointes. Drug interaction and retrospective studies were not included.

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