ZYTIGA® (abiraterone acetate)
Use of ZYTIGA in Patients with Diabetes

SUMMARY

- Patients with diabetes were not prospectively evaluated for efficacy and safety as a subset population in three pivotal phase 3 randomized studies (COU-AA-301, COU-AA-302 and LATITUDE) that evaluated ZYTIGA plus prednisone in metastatic prostate cancer; therefore, no conclusions about safety or efficacy can be drawn for these patients.[1-3]
    - A post-hoc evaluation of corticosteroid-associated adverse events of interest (CA-AEs) in patients with metastatic castration-resistant prostate cancer (mCRPC) enrolled in 2 of the pivotal studies (COU-AA-301 and COU-AA-302) showed diabetes mellitus of any grade occurred in 1.1% of patients, inadequate control of diabetes in 0.2%, and impaired glucose tolerance in 0.1%. The 3 most common grade ≥3 CA-AEs were hyperglycemia (2.0%), cataract (0.4%), and diabetes mellitus (0.4%). The investigator-reported discontinuation rate due to CA-AEs was 0.6% (8/1333) for the ZYTIGA plus prednisone group and 0.3% (3/934) for the placebo plus prednisone group. Diabetes mellitus led to study discontinuation in 1 patient within the placebo plus prednisone group.[4]
    - An initial assessment of patients with concomitant metformin use revealed improved overall survival (OS) in COU-AA-301 and COU-AA-302.[5]
    - A post-hoc analysis evaluated the effect of metformin and statin use on OS and prostate-specific antigen response rates (PSA-RR) in patients with mCRPC enrolled in the COU-AA-301 and COU-AA-302 studies. Metformin use was not associated with prolonged OS in the ZYTIGA plus prednisone (adjusted hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.5-1.006; *P*=0.054) and placebo plus prednisone groups (adjusted HR, 0.73; 95% CI, 0.46-1.15; *P*=0.17) of COU-AA-301 study in multivariate analysis. However, there was an association between metformin use and prolonged OS in both the ZYTIGA plus prednisone (adjusted HR, 0.69; 95% CI, 0.48-0.98; *P*=0.039) and placebo plus prednisone groups (adjusted HR, 0.66; 95% CI, 0.47-0.93; *P*=0.018) of COU-AA-302 study in multivariate analysis.[6]
- An analysis of the Prostate Cancer Registry (PCR), a prospective, real-world, observational study in patients with mCRPC, reported time to progression (TTP) and OS data for 1583 patients receiving initial therapy with either ZYTIGA plus prednisone, enzalutamide, or docetaxel. The efficacy outcomes are described below for 121 patients with diabetes receiving ZYTIGA plus prednisone. Safety data were not reported.[7]
- Hypoglycemia was reported in 2 published cases of patients with mCRPC and type 2 diabetes mellitus receiving ZYTIGA plus prednisone with glucose lowering agents and statins.[8] Additional case reports of patients with mCRPC and diabetes receiving ZYTIGA plus prednisone/prednisolone have been published.[9-13]
- Isolated cases of hypoglycemia have been reported when ZYTIGA plus prednisone/prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide. Blood glucose should be monitored in patients with diabetes.[14]

BACKGROUND

Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor that inhibits 17-α hydroxylase/C17,20-lyase (CYP17). Mineralocorticoid excess related adverse events (AEs), such as hypokalemia, fluid retention, and cardiovascular AEs which may result from high levels of adrenocorticotropic hormone (ACTH) and steroid precursors upstream of CYP17, provide rationale for the coadministration of ZYTIGA with a corticosteroid, such as prednisone.[15]

Two pivotal 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 mCRPC. In COU-AA-301, patients were randomized 2:1 and the primary endpoint was

OS.[1] In COU-AA-302, patients were randomized 1:1 and the coprimary endpoints were OS and radiographic progression-free survival (rPFS).[2] In LATITUDE, a pivotal, phase 3, randomized, placebo-controlled, multicenter clinical trial that enrolled patients who had metastatic high-risk castration-sensitive prostate cancer (CSPC), patients were randomized 1:1 to receive ZYTIGA 1,000 mg daily plus prednisone 5 mg once daily or placebos plus ADT. The coprimary endpoints in LATITUDE were rPFS and OS.[3] Patients with diabetes were not prospectively evaluated for efficacy and safety as a subset population in the 3 pivotal phase 3 randomized studies.

CLINICAL DATA

Prospective Study

Chowdhury et al (2020)[7] evaluated the outcomes of patients with mCRPC and diabetes 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, 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 for the patients who had not received previous mCRPC treatment at baseline and patients treated with first-line ZYTIGA plus prednisone are reported below in Table: Patient Characteristics.
- Among patients with diabetes receiving ZYTIGA plus prednisone (n=121), the median age was 77.0 years (range, 54-93) and 47.7% of patients had a Gleason score 8-10 at initial diagnosis.

Patient Characteristics[7]

	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)
Abbreviations: 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 11.5 months (95% CI, 9.1-16.1) in all patients receiving ZYTIGA plus prednisone and patients with diabetes receiving ZYTIGA plus prednisone, respectively.
- Outcomes for patients with diabetes 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 Diabetes that Received ZYTIGA plus Prednisone.

- Safety data were not reported.

Efficacy Outcomes for Patients with mCRPC and Diabetes that Received ZYTIGA plus Prednisone[7]

	All Patients Receiving ZYTIGA plus Prednisone (n=754)	Patients with Diabetes Receiving ZYTIGA plus Prednisone (n=121)
Median TTP, months (95% CI)	9.6 (8.4-10.8)	12.0 (9.8-16.4)
Median OS, months (95% CI)	27.1 (25.3-28.9)	30.8 (21.7-NE)
Abbreviations: CI, confidence interval; NE, not estimable; OS, overall survival; TTP, time to progression.		

Additional Analyses of COU-AA-301 and COU-AA-302

Wilson et al (2022)[6] conducted a post-hoc secondary analysis that evaluated the effect of metformin and statins on OS and PSA-RR in the ZYTIGA plus prednisone and placebo plus prednisone groups of the COU-AA-301 (N=1195) and COU-AA-302 (N=1088) studies.

- Results for metformin are provided below. Please refer to the publication for the complete analysis.
- In the COU-AA-301 study:
  - A total of 104 patients were reported to be taking metformin, 73 (9.2%) patients in the ZYTIGA plus prednisone group and 31 (7.8%) patients in the placebo plus prednisone group.
  - In the ZYTIGA plus prednisone group, there was no definitive association between median OS and patients taking vs not taking metformin in the univariate (19.4 months vs 15.6 months; HR, 0.76; 95% CI, 0.55-1.05; *P*=0.098) or multivariate (adjusted HR, 0.71; 95% CI, 0.5-1.006; *P*=0.054) analyses. The proportion of patients with PSA-RR was greater among patients taking vs not taking metformin (41.1% vs 28.6%; *P*=0.026).
  - In the placebo plus prednisone group, OS was not prolonged among patients taking vs not taking metformin in the univariate (14.0 months vs 11.1 months; HR, 0.85; 95% CI, 0.54-1.32; *P*=0.47) or multivariate (adjusted HR, 0.73; 95% CI, 0.46-1.15; *P*=0.17) analyses. There was no difference in PSA-RR among patients taking vs not taking metformin (3.2% vs 5.8%; *P*=0.55).
- In the COU-AA-302 study:
  - A total of 134 patients were reported to be taking metformin, 66 (12.1%) patients in the ZYTIGA plus prednisone group and 68 (12.5%) patients in the placebo plus prednisone group.
  - In the ZYTIGA plus prednisone group, there was no association between median OS and patients taking vs not taking metformin in the univariate analysis (not reached [NR] vs NR; HR, 0.81; 95% CI, 0.48-1.36; *P*=0.42); however, there was an association between prolonged OS and metformin use in the multivariate analysis (adjusted HR, 0.69, 95% CI, 0.48-0.98; *P*=0.039). The proportion of patients with PSA-RR was greater among patients taking vs not taking metformin (72.7% vs 60.0%; *P*=0.046).
  - In the placebo plus prednisone group, there was no association between a significant difference in OS and patients taking vs not taking metformin in the univariate analysis (NR vs 26.6 months; HR, 0.68; 95% CI, 0.42-1.11; *P*=0.12); however, there was an association between prolonged OS and metformin use in the multivariate analysis (adjusted HR, 0.66; 95% CI, 0.47-0.93; *P*=0.018). Additionally, there was no significant difference in PSA-RR among patients taking vs not taking metformin (27.9% vs 23.3%; *P*=0.41).
- After pooling HR across both studies and treatment groups, OS was prolonged among those treated with metformin (pooled HR, 0.77; 95% CI, 0.62-0.95).
- Between all groups, the rates of all AEs and grade 3 or 4 AEs were similar.

- A higher number of grade 3 or 4 cardiac disorder and hypokalemia AEs were reported in patients taking statins with ZYTIGA plus prednisone vs patients not taking statins with ZYTIGA plus prednisone in COU-AA-301 (cardiac disorder, 8.5% vs 3.8%; hypokalemia, 6.8% vs 4.3%) and COU-AA-302 (cardiac disorder, 8.7% vs 3.2%; hypokalemia, 3.9% vs 1.6%).

Fizazi et al (2016)[4] evaluated the safety of long-term use of prednisone, with or without ZYTIGA in patients with mCRPC from 2 randomized, phase 3, registration studies, COU-AA-301 and COU-AA-302 (N=2267). Patients received prednisone for a median of 8.3 months (range, 0.1-34.9 months). Incidence of any-grade CA-AEs after any prednisone exposure was 25%, 26%, and 23% for all patients, the ZYTIGA plus prednisone group, and the placebo plus prednisone group, respectively; incidence of grade ≥3 CA-AEs was 5%, 5%, and 4%, respectively. The most common, any-grade CA-AEs were hyperglycemia (7.4%, 7.8%, and 6.9% for all patients, ZYTIGA plus prednisone, and placebo plus prednisone, respectively) and weight increase (4.3%, 3.9%, and 4.8%, respectively). Diabetes mellitus of any grade occurred in 1.1% of patients, inadequate control of diabetes in 0.2%, and impaired glucose tolerance in 0.1%. The 3 most common grade ≥3 CA-AEs were hyperglycemia (2.0%), cataract (0.4%) and diabetes mellitus (0.4%). The investigator-reported discontinuation rate due to CA-AEs was 0.6% (8/1333) for the ZYTIGA plus prednisone group and 0.3% (3/934) for the placebo plus prednisone group. Diabetes mellitus led to study discontinuation in 1 patient within the placebo plus prednisone group. One patient experienced a CA-AE resulting in death (in the COU-AA-301 study). The sponsor assessment of the cause of death was upper gastrointestinal hemorrhage.

Hamilton et al (2014)[5] conducted an exploratory analysis evaluating the effect of concomitant medication use, including metformin, on OS in the treatment and placebo arms of COU-AA-301 and COU-AA-302. Initial assessments of concomitant metformin use revealed improved OS (COU-AA-301, P=0.0263; COU-AA-302, P=0.084). Multivariate analysis was not performed due to low numbers of patients and imbalance between groups. No safety data were reported.

Case Reports

Case reports were identified in the literature, each of which reported safety data following ZYTIGA plus prednisone/prednisolone use in a patient with diabetes.[8,10-13]

Vo et al (2022)[9] described a case report of an 83-year-old man with a history of diabetes, hypertension, coronary artery disease, and prostate cancer with bone metastases who was admitted with a complicated urinary tract infection and a concurrent asymptomatic incidental coronavirus disease 2019 (COVID-19) infection. The patient had been receiving prostate cancer treatment for ≥10 years, consisting of ZYTIGA 1000 mg daily and prednisone 5 mg daily with an injection every 3 months. A urine culture report reported *Pseudomonas mendocina* with fluoroquinolone resistance. His urinary symptoms were completely resolved with a 7-day course of ceftriaxone and cefepime.

Tucci et al (2019)[8] described 2 cases of severe hypoglycemia in patients with mCRPC and type 2 diabetes mellitus who received ZYTIGA plus prednisone, glucose lowering agents, and statins. The first case report described a 69-year-old patient. After 2 weeks of treatment with ZYTIGA plus prednisone and gliclazide 200 mg/day, the patient reported symptomatic hypoglycemia episodes (minimum blood glucose level of 40 mg/dL in the morning fasting state). Gliclazide was reduced to 160 mg/day and was then replaced with glimepiride 2 mg/day due to persistent hypoglycemic episodes. Following the switch to glimepiride, no additional hypoglycemic episodes were reported, and the patient continued ZYTIGA plus prednisone. The second case report described a 79-year-old patient. After 5 days of treatment with ZYTIGA plus prednisone and repaglinide 4 mg/day, the patient experienced severe hypoglycemia (<30 mg/dL) that required hospitalization. ZYTIGA plus prednisone were stopped for 7 days and were then restarted along with repaglinide 2 mg/day. The patient then experienced severe hypoglycemic episodes, and repaglinide was stopped and substituted with insulin.

Kimata et al (2019)[10] reported 2 cases of elderly patients with castration-resistant prostate cancer (CRPC) and diabetes receiving peritoneal dialysis. Both received ZYTIGA (750 mg orally once daily) and prednisolone (5 mg orally once daily). Although the prostate-specific antigen (PSA) level increased in both cases, there was no manifestation of disease progression (clinical and radiographic) for 22 months in case 1 and 8 months in case 2. The only >grade 3 AE reported for either patient was hypokalemia.

Schattner et al (2019)[11] described the case of a 74-year-old man with newly diagnosed metastatic prostate cancer and diabetes who experienced aortic dissection treated with interposition graft replacement and rehabilitation. He was receiving multiple medications including an antihypertensive, statin, metformin, and LHRH analog, and had received chest radiation. He had begun ZYTIGA plus prednisone 2 weeks prior to the event.

Rodieux et al (2015)[12] described 1 case report of 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.

Neyra et al (2015)[13] described a case report of a 76-year-old man with a history of type 2 diabetes, chronic kidney disease (CKD), hypertension, hypothyroidism, antiphospholipid antibody syndrome, prior strokes, and metastatic prostate cancer who presented with rhabdomyolysis-induced acute kidney injury 3 weeks after receiving denosumab and ZYTIGA, in addition to multiple other chronic medications. The patient responded well to intravenous (IV) fluids with discontinuation of denosumab, ZYTIGA, and rosuvastatin, resulting in normalization of creatine kinase and recovery of kidney function.

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 20 August 2024.

Additional studies of ZYTIGA have been published including patients with diabetes at baseline, or diabetes as identified as a comorbidity in a percentage of the study patients, but outcomes were not separately evaluated and reported for patients with diabetes. Retrospective studies, drug interaction evaluations, and real-world analyses were not included. Use of ZYTIGA in patients with cardiovascular disease, a common comorbidity in older patients with diabetes, is summarized as a separate topic and also addressed in product labeling.

REFERENCES

1. 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.

2. 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.

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

4. Fizazi K, Chi KN, de Bono JS, et al. Low incidence of corticosteroid-associated adverse events on long-term exposure to low-dose prednisone given with abiraterone acetate to patients with metastatic castration-resistant prostate cancer. *Eur Urol*. 2016;70(3):438-444.

5. Hamilton RJ, Li J, Naini V, et al. Effect of concomitant medication use on outcomes of treatment and placebo arms of the COU-AA-301 and COU-AA-302 studies of abiraterone acetate (AA) in metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol*. 2014;32(15, suppl):e16045-e16045.

6. Wilson B, Armstrong AJ, de Bono J, et al. Effects of metformin and statins on outcomes in men with castration-resistant metastatic prostate cancer: secondary analysis of COU-AA-301 and COU-AA-302. *Eur J Cancer*. 2022;170:296-304.

7. Chowdhury S, Bjartell A, Lumen N, et al. Real-world outcomes in first-line treatment of metastatic castration-resistant prostate cancer: the prostate cancer registry. *Targ Oncol*. 2020;15(3):301-315.

8. Tucci M, Roca E, Ferrari L, et al. Abiraterone and prednisone therapy may cause severe hypoglycemia when administered to prostate cancer patients with type 2 diabetes receiving glucose-lowering agents. *Endocrine*. 2019;64(3):724-726.

9. Vo T, Maisuradze N, Maglakelidze D, et al. Pseudomonas mendocina urinary tract infection: a case report and literature review. *Cureus*. 2022;14(3):e23583.

10. Kimata R, Tomita Y, Kondo Y. Safety of abiraterone acetate administration in elderly patients receiving peritoneal dialysis with castration-resistant prostate cancer: two case reports. *J Nippon Med Sch*. 2019;86(2):135-138.

11. Schattner A, Dubin I, Drahy AIY. Abiraterone and aortic dissection. *Am J Ther*. 2019;26(5):e624-e625.

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

13. Neyra JA, Rocha NA, Bhargava R, et al. Rhabdomyolysis-induced acute kidney injury in a cancer patient exposed to denosumab and abiraterone: a case report. *Bmc Nephrol*. 2015;16:118.

14. Data on File. Abiraterone Acetate. CCDS. Janssen Research & Development, LLC. EDMS-ERI-22171594; 2021.

15. Attard G, Reid AH, Yap TA. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J Clin Oncol*. 2008;26(28):4563-4571.