ZYTIGA® (abiraterone acetate)
ZYTIGA - Hepatotoxicity

SUMMARY

- Marked increases in liver enzymes, leading to drug discontinuation or dosage modification, have occurred in controlled clinical studies. In the combined data of 5 randomized clinical trials, grade 3-4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increases (≥5X upper limit of normal [ULN]) were reported in 6% of 2230 patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to ALT and AST increases or abnormal hepatic function occurred in 1.1% of 2230 patients taking ZYTIGA. In these clinical trials, no deaths clearly related to ZYTIGA were reported due to hepatotoxicity events.[1-5]
- In the LATITUDE randomized study, serum transaminases (ALT and AST) and bilirubin levels were measured at baseline, every 2 weeks for the first 3 months of treatment with ZYTIGA plus prednisone, and monthly thereafter. Serum total bilirubin, AST, and ALT were measured immediately if clinical symptoms or signs suggestive of hepatotoxicity developed. If at any time AST or ALT rose above 5X the ULN, or the bilirubin rises above 3X ULN, ZYTIGA treatment was interrupted and liver function monitored closely. Re-treatment with ZYTIGA occurred at a reduced dose level only after return of liver function tests (LFTs) to the patient's baseline or to AST and ALT ≤2.5X ULN and total bilirubin ≤1.5X ULN. For patients who resumed treatment, serum transaminases and bilirubin were monitored at a minimum of every 2 weeks for 3 months and monthly thereafter. If an LFT abnormality recurred after the second dose reduction with 500 mg once daily, ZYTIGA was discontinued. If patients developed severe hepatotoxicity (ALT ≥20 X ULN) anytime during ZYTIGA treatment, therapy was discontinued, and the patient was not retreated with study drug. ZYTIGA was permanently discontinued for patients who developed a concurrent elevation of ALT >3X ULN and total bilirubin >2X ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.[6]
- In postmarketing experience, there have been ZYTIGA-associated severe hepatic toxicity, including fulminant hepatitis, acute liver failure and deaths.[7, 8]

CLINICAL DATA

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 metastatic castration-resistant prostate cancer (mCRPC). In COU-AA-301, patients were randomized 2:1, and the primary endpoint was overall survival (OS). In COU-AA-302, patients were randomized 1:1, and the coprimary endpoints were OS and radiographic progression-free survival (rPFS).[1, 2]

A third phase 3, randomized, placebo-controlled, multicenter clinical trial enrolled patients who had metastatic high-risk castration-sensitive prostate cancer (CSPC). ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg once daily and ADT in the active treatment arm. Placebos plus ADT were given to control patients. In LATITUDE, patients were randomized 1:1, and co-primary endpoints were OS and rPFS.[5, 9]

COU-AA-301 Study: Phase 3 Study in mCRPC With Prior Docetaxel

de Bono et al (2011, 2012)[1,10] evaluated the efficacy and safety of ZYTIGA plus prednisone compared to placebo plus prednisone in patients with mCRPC whose disease had progressed after docetaxel-based chemotherapy (N=1195).

- **Select exclusion criteria:**[11] serum bilirubin ≥1.5X ULN; abnormal aminotransferase levels (defined as levels of AST or ALT that were ≥2.5X ULN; however, patients with known liver metastasis who had levels of AST or ALT that were ≤5X ULN were eligible to participate); active or symptomatic viral hepatitis or chronic liver disease.

Hepatic-Related Safety

- LFT abnormalities were deemed of special interest and were more common in the ZYTIGA group than in the placebo group, as shown in Table: Hepatic-Related AEs.[1]

Hepatic-Related AEs[1]

%	ZYTIGA Group (n=791)			Placebo Group (n=394)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
LFT abnormalities	10	3	<1	8	3	<1
Abbreviations: AEs, adverse events; LFT, liver function test.						

- The updated analysis revealed consistent results, as summarized in Table: Hepatic-Related AEs - Final Analysis.[10]

Hepatic-Related AEs - Final Analysis[10]

%	ZYTIGA Group (n=791)			Placebo Group (n=394)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
LFT abnormalities	11	4	<1	9	3	<1
Abbreviations: AEs, adverse events; LFT, liver function test.						

COU-AA-302 Study: Phase 3 Study in Chemotherapy-Naïve mCRPC

Ryan et al (2013, 2014, 2015)[2, 12-14] 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).

- **Select inclusion criteria:**[15] serum bilirubin <1.5X ULN; AST or ALT <2.5X ULN.
- **Select exclusion criteria:**[15] known brain, liver, or visceral organ metastasis.

Hepatic-Related Safety

- The following hepatic-related safety results were reported at the second interim analysis:[2]
  - Median duration of follow up: 22.2 months
  - Grade 3 or 4 adverse events (AEs) were reported in 48% of patients in the ZYTIGA group and in 42% of patients in the placebo group.
  - Grade 3 and 4 hepatotoxicity events were reported in 8% of patients in the ZYTIGA group compared to 3% of patients in the placebo group.
- Hepatic-related safety results, identified as special interest and reported at the final analysis after a median follow up of 49.2 months, are summarized in Table: Hepatic-Related AEs (Final Analysis).[14]

Hepatic-Related AEs (Final Analysis)[14]

%	ZYTIGA Group (n=542)				Placebo Group[a] (n=540)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
ALT increased	9	5	<1	0	4	<1	<1	0
AST increased	12	3	0	0	4	<1	0	0

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]Prior to crossover.

LATITUDE Study: Phase 3 Study in Metastatic High-Risk CSPC

Fizazi et al (2017, 2019)[5,6,9] evaluated the efficacy and safety of ZYTIGA in combination with prednisone and ADT vs placebos and ADT for the treatment of metastatic high-risk CSPC (N=1199). After the first interim analysis, treatment was unblinded and patients in the placebo group could crossover to open-label treatment with ZYTIGA, prednisone, and ADT (n=72).

- **Select inclusion criteria:**[6] total bilirubin ≤1.5X ULN; AST or ALT ≤2.5X ULN.
- **Select exclusion criteria:**[6] active or symptomatic viral hepatitis or chronic liver disease.

Hepatic-Related Safety

- At the final analysis for OS, the median duration of follow-up was 51.8 months (interquartile range, 47.2-57.0).[9]
- Hepatic AEs of special interest are shown in Table: Hepatic-Related AEs (Final Analysis).
- Drug-related, increased liver function tests (AST, ALT, gamma-glutamyl transferase) lead to treatment discontinuation in 13 patients in the ZYTIGA group and 3 patients in the placebo group.[16]

Hepatic-Related AEs (Final Analysis)[9]

AE, n (%)	ZYTIGA Group (n=597)			Placebos Group (n=602)			Crossover Group (n=72)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hepatotoxicity	146 (24)	49 (8)	4 (1)	109 (18)	21 (3)	0	7 (10)	3 (4)	0
ALT increased	101 (17)	32 (5)	2 (<1)	77 (13)	8 (1)	0	5 (7)	2 (3)	0
AST increased	92 (15)	26 (4)	1 (<1)	68 (11)	9 (1)	0	5 (7)	1 (1)	0

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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 17 July 2023. Summarized in this response are relevant data from 3 phase 3 registrational studies. Information regarding the use of ZYTIGA in patients with baseline hepatic impairment is not included in this response.

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