ZYTIGA® (abiraterone acetate)
ZYTIGA - Dosage and Administration of ZYTIGA - Prednisone Regimen

SUMMARY

- Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17-α hydroxylase/C17,20-lyase (CYP17). Blocking CYP17 also interrupts the negative feedback control of adrenocorticotropic hormone (ACTH).
- The resulting high levels of ACTH and steroid precursors upstream of CYP17 may lead to increased mineralocorticoid effects such as hypertension, hypokalemia, and fluid retention.[1, 2] Coadministration of a corticosteroid suppresses ACTH, resulting in a reduction of steroids upstream of the CYP17 blockade that may ameliorate these mineralocorticoid effects.[2]
- In pivotal phase 3, international, randomized, double-blind, placebo-controlled, multicenter studies conducted to evaluate the efficacy and safety of ZYTIGA and prednisone in patients with mCRPC who had received chemotherapy containing docetaxel (COU-AA-301)[1] and in asymptomatic or mildly symptomatic patients with chemotherapy-naïve mCRPC (COU-AA-302),[3] patients were randomized to receive the following: ZYTIGA 1,000 mg PO once daily plus prednisone 5 mg PO twice daily or placebo plus prednisone 5 mg PO twice daily. A gonadotropin-releasing hormone (GnRH) analog or prior orchiectomy was required in both arms.
- In the pivotal phase 3, international, randomized, double-blind, placebo-controlled, multicenter study conducted to evaluate the efficacy and safety of ZYTIGA and prednisone in patients with newly diagnosed, metastatic high-risk CSPC (LATITUDE)[4], patients were randomized to receive ZYTIGA 1,000 mg PO daily in combination with prednisone 5 mg PO once daily or placebos. A GnRH analog or prior orchiectomy was required in both arms.[1, 2, 4]

BACKGROUND

Prednisone Regimens in Pivotal Trials

The prednisone dose used in LATITUDE was lower than that used in COU-AA-301 and COU-AA-302. A higher prednisone dose in COU-AA-301 and COU-AA-302 was selected because it is commonly used as the standard of care in combination with approved chemotherapy agents or as monotherapy for palliation of symptoms in advanced prostate cancer. Prednisone is not considered a standard of care in newly diagnosed metastatic high-risk CSPC and is therefore not included in the control arm. The use of prednisone 5 mg once daily is to help mitigate the symptoms of mineralocorticoid excess caused by CYP17 inhibition. The LATITUDE protocol did allow the prednisone dose to be increased to 10 mg/day if required to manage mineralocorticoid toxicities.[5-7]

CLINICAL DATA

COU-AA-301 Study

de Bono et al (2011)[8, 9] 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).

Study Design/Methods

- Phase 3, randomized, double-blind, placebo-controlled, multinational study
- Patients were randomized 2:1 to receive the following:
  - ZYTIGA 1,000 mg PO once daily and prednisone 5 mg PO twice daily (n=797) or
  - Placebo and prednisone 5 mg PO twice daily (n=398)
  - A GnRH analog, or prior orchiectomy was required in both arms

- Study treatment was continued until disease progression (defined as a 25% increase in prostate-specific antigen [PSA] over the patient's baseline/nadir together with protocol-defined radiographic progression and symptomatic or clinical progression), initiation of new treatment, unacceptable toxicity, or withdrawal.
- **Primary endpoint:** overall survival (OS)
- **Secondary endpoints**: PSA response rate (proportion of patients with a decrease in PSA ≥50% from baseline, which was confirmed ≥4 weeks later by an additional PSA evaluation); time to PSA progression (TTPP); and radiographic progression-free survival (rPFS)

Results

Safety

- All patients who received any study medication were included in the safety analysis (n=1185). Adverse events (AEs) leading to treatment discontinuation were similar between the ZYTIGA group and the placebo group (19% and 23%, respectively; *P*=0.09).
- AEs associated with elevated mineralocorticoid levels resulting from CYP17 inhibition (fluid retention and edema, hypokalemia, and hypertension), as well as cardiac disorders and liver function test abnormalities, were deemed of special interest and were more common in the ZYTIGA group than in the placebo group (55% vs 43%, *P*<0.001).
- The updated analysis revealed consistent results with the first interim analysis for AEs of special interest as summarized in Table: Adverse Events - Updated Analysis.[9]

Adverse Events - Updated Analysis[9]

	ZYTIGA Plus Prednisone (n=791)			Placebo Plus Prednisone (n=394)		
%	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
AEs of Special Interest						
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
LFT abnormalities	11	4	<1	9	3	<1
Hypertension	11	1	0	8	<1	0

Abbreviations: AE, adverse event; LFT, liver function test.
[a]Cardiac disorders 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.

COU-AA-302 Study

Ryan et al (2013, 2014, 2015)[3, 10-12] evaluated the efficacy and safety of ZYTIGA plus prednisone compared to placebo plus prednisone in asymptomatic or mildly symptomatic patients with chemotherapy-naïve mCRPC (N=1088).

Study Design/Methods

- Phase 3, randomized, double-blind, placebo-controlled, multinational study
- Patients were randomized to receive:
    - ZYTIGA 1,000 mg PO once daily and prednisone 5 mg PO twice daily (n=546) or
    - Placebo and prednisone 5 mg PO twice daily (n=542)
    - GnRH analog, or prior orchiectomy was required in both arms[5]
- Treatment continued until radiographic or clinical (cytotoxic chemotherapy, radiation or surgical treatment for cancer, pain requiring chronic opioids, or Eastern Cooperative Oncology Group performance status [ECOG-PS] decline to 3 or more) disease

progression, unacceptable toxicity, or withdrawal. Patients were allowed to continue blinded study medication after radiographic progressive disease in absence of unequivocal clinical progressive disease.[5]
- **Coprimary endpoints:** OS and rPFS
- **Secondary endpoints:** time to opiate use (for cancer pain); time to initiation of chemotherapy; time to ECOG-PS deterioration; TTPP based on Prostate Cancer Working Group 2 (PCWG2) criteria

Results

Safety

- AEs at the time of the final OS analysis were similar to those previously reported, after nearly 27 months of additional follow-up. An additional long-term analysis of patients receiving ≥4 years of treatment (n=41) reported that the frequency of all grade and grade 3/4 AEs was similar to those receiving <4 years of treatment (n=505).[13]
- Grade 3/4 AEs were reported in 54% and 44% of patients, and AEs leading to treatment discontinuation were reported in 13% and 10% of patients in the ZYTIGA plus prednisone group and placebo plus prednisone group, respectively.
- The most common AEs at the final OS analysis resulting in death in the ZYTIGA group plus prednisone group were disease progression and general physical health deterioration as a sign of clinical progression in 3 (1%) and 3 (1%) patients, respectively, and no treatment-related deaths occurred. The most common AEs at the long-term subsequent analysis (≥4 years of therapy vs <4 years) were fatigue, diarrhea, arthralgia, back pain, and edema peripheral, and the majority were grade 1/2. No patient in the ≥4-year cohort had AEs leading to treatment discontinuation or had died at the time of analysis.[13] AEs of special interest in the final analysis are described in the Table: Adverse Events of Special Interest (Final Analysis).

Adverse Events of Special Interest (Final Analysis)[3]

	ZYTIGA Plus Prednisone (n=542)				Placebo Plus Prednisone[a] (n=540)			
AEs of Special Interest, %	**Grades 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grades 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
ALT ↑	9	5	<1	0	4	<1	<1	0
AST ↑	12	3	0	0	4	<1	0	0

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase.
[a]Prior to cross-over.

LATITUDE Study

Fizazi et al (2017, 2019)[4, 14] evaluated the efficacy and safety of ZYTIGA plus prednisone with ADT vs placebos plus ADT for the treatment of newly diagnosed, metastatic high-risk CSPC (N=1199).

Study Design/Methods

- Phase 3, randomized, double-blind, placebo-controlled, multicenter study
- Patients were randomized 1:1 to receive either ZYTIGA 1,000 mg plus prednisone 5 mg PO daily with ADT (GnRH agonist or orchiectomy) or placebos with ADT
- **Co-primary endpoints:** OS and rPFS

- **Secondary endpoints:**
    - Time to next skeletal-related event (symptomatic skeletal event): either clinical/pathologic fracture, spinal cord compression, or surgery or palliative radiation to bone
    - TTPP by PCWG2 criteria
    - Time to next therapy for prostate cancer
    - Time to initiation of chemotherapy
    - Time to pain progression

Results

Safety

- Grade 3/4 AEs were reported in 63% of patients in the ZYTIGA plus prednisone with ADT group and 48% of patients in the placebos with ADT group.
- The number of patients with serious AEs (28% vs 24%) and AEs leading to death (5% vs 4%) was similar between the ZYTIGA plus prednisone with ADT vs placebos with ADT groups, respectively.
- The frequency of AEs leading to treatment discontinuation was 12% vs 10% and dose modification/interruption was 32% vs 17% in the ZYTIGA plus prednisone with ADT vs the placebos with ADT groups, respectively.
- Grade 3 or 4 mineralocorticoid-related effects (hypertension and hypokalemia) and transaminase increase were more common events of special interest in the ZYTIGA plus prednisone with ADT group (see Table: Summary of Special Interest Adverse Events at Final Analysis).

Summary of Special Interest Adverse Events at Final Analysis[14]

	ZYTIGA Plus Prednisone (n=597)		**Placebos Plus Prednisone (n=602)**		**Crossover to ZYTIGA Plus Prednisone (n=72)**	
AEs of Special Interest, %	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
ALT increase	5	<1	1	0	3	0
AST increase	4	<1	1	0	1	0
Cardiac disorder	3	1	1	0	0	0
Cataract	1	0	<1	0	0	0
Fluid retention/edema	1	0	1	0	0	0
Hypertension	22	<1	10	<1	4	0
Hepatotoxicity	8	1	3	0	4	0
Hypokalemia	11	1	1	<1	3	0
Osteoporosis[a]	2	0	2	<1	0	0

[a]Including osteoporosis-related fractures
Abbreviations: ADT, androgen deprivation therapy; AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase.

Long-term Corticosteroid Use Study

Fizazi et al (2016)[15] conducted an analysis to determine whether long-term use of low-dose prednisone with or without ZYTIGA leads to corticosteroid-associated adverse events (CA-AEs) in patients with mCRPC based on results of the COU-AA-301 and COU-AA-302 studies (N=2267). Patients received 5 mg PO twice a day of prednisone, with a median exposure of 8.3 months (range, 0.1-34.9 months). Of these, 1333 patients received ZYTIGA plus prednisone.

The incidence of grade ≥3 CA-AEs for any prednisone exposure was 4.5%, 5.1%, and 3.7% for all patients, ZYTIGA plus prednisone, and prednisone alone, respectively. When assessed by duration of exposure to prednisone, in 3-month intervals for a median of 8.3 months

(range, 0.1-34.9 months), any-grade CA-AEs ranged between 0% and 12%, but no discernable trend was observed. Grade ≥3 CA-AEs ranged between 1% and 2% when assessed by duration of exposure to prednisone.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File databases (and/or other resources, including internal/external databases) was conducted on 27 September 2023.

Data summarized within this scientific response have been limited to the phase 3 pivotal studies (COU-AA-301, COU-AA-302, and LATITUDE).

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