ZYTIGA® (abiraterone acetate)
Administration of ZYTIGA Without Prednisone

SUMMARY

- Janssen cannot recommend any practices, procedures, handling or dosage and administration techniques that deviate from the approved product labeling.
- Abiraterone acetate is a 17α-hydroxylase/C17,20-lyase (CYP17) inhibitor. Mineralocorticoid effects resulting from CYP17 inhibition may be ameliorated by coadministration with a corticosteroid, which lowers adrenocorticotropic hormone (ACTH) and steroids upstream of the CYP17 blockade.[1]
- ZYTIGA has been evaluated in combination with prednisone in phase 3 studies for the treatment of metastatic castration-resistant prostate cancer (mCRPC) and metastatic high-risk castration-sensitive prostate cancer (CSPC). All patients in these studies received a gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy.[2-4]
- In a phase 2 study conducted in 58 patients with CRPC (>90% had metastatic disease) to determine the proportion of men requiring prednisone to manage mineralocorticoid toxicity during their ZYTIGA therapy, 7 (12.1%) patients initiated prednisone for adverse events (AEs), including hypertension (n=3, 5.2%) and hypokalemia (n=4, 7%). Fatigue was also reported and prednisone initiated (n=2, 3%). Forty (69%) patients experienced a decline in prostate-specific antigen (PSA) of ≥50% with the use of ZYTIGA alone.[5]
- In 2 other studies (phase 2 and phase 1/2) conducted in patients with mCRPC, ZYTIGA was initiated without prednisone, and side effects related to increased mineralocorticoid levels were managed by administering a mineralocorticoid-receptor antagonist (eplerenone) or low-dose glucocorticoids.[1, 6] In one of these studies, ZYTIGA was administered as a single agent and dexamethasone was added at time of disease progression.[1,7]

BACKGROUND

ZYTIGA has been evaluated in combination with prednisone in phase 3 studies for the treatment of mCRPC and metastatic high-risk CSPC. All patients in these studies received a GnRH analog or had prior bilateral orchiectomy.[2-4]

Rationale for Use With a Corticosteroid

Blocking CYP17 interrupts the negative feedback control of ACTH. Mineralocorticoid effects, such as hypertension, hypokalemia, and fluid retention, may result from high levels of ACTH and steroid precursors upstream of CYP17. These mineralocorticoid effects can be ameliorated by coadministration with a corticosteroid, which lowers ACTH and steroids upstream of the CYP17 blockade.[1]

CLINICAL DATA

Phase 2 Studies

McKay et al (2019)[5] evaluated the safety of ZYTIGA without prednisone in patients with CRPC (N=60).

Study Design/Methods

- Phase 2, single-arm, open-label, multicenter study (NCT02025010)
- Patients initially received ZYTIGA 1000 mg orally (PO) daily (QD) without prednisone.

- The study included patients with CRPC with controlled blood pressure (<140/90 mmHg while receiving ≤3 agents) and a normal potassium level without supplementation. Blood pressure elevation ≥140/90 mmHg (on 3 determinations) was treated with antihypertensives and/or a mineralocorticoid antagonist, and hypokalemia was treated with supplementation and/or mineralocorticoid antagonist.
- Patients with persistent or severe hypertension or hypokalemia were initiated on prednisone 5 mg twice daily.
- In patients not requiring prednisone for toxicity management, prednisone 5 mg twice daily was added at the time of PSA progression, as defined by Prostate Cancer Working Group 2 criteria, and subsequent PSA response was evaluated.
- Therapy continued until radiographic progression, significant toxicity, or withdrawal.
- **Primary endpoint:** proportion of men requiring prednisone to manage mineralocorticoid excess

Results

Patient Characteristics

- Of the 60 patients included, 58 received ≥1 dose of ZYTIGA.
- Median age was 68 years and 53 (91.4%) had metastatic disease. All patients had Eastern Cooperative Oncology Group (ECOG) performance status ≤1.
- Sixteen (27.6%) patients had received prior chemotherapy, 6 (10.3%) prior enzalutamide, and 4 (6.9%) prior ketoconazole.
- Twenty-six (44.8%) patients were receiving ≥1 antihypertensive agent.
- Median baseline PSA was 15.8 ng/mL.

Efficacy and Safety

- A total of 40 (69%) patients achieved a PSA reduction of ≥50%. Twenty-eight (48.3%) patients experienced PSA progression at a median of 10.2 months (95% confidence interval [CI], 6.5-19.4 months). Of these, 21 (36.2%) initiated treatment with prednisone for PSA progression.
- Mineralocorticoid AEs of any grade occurred in 38 (66%) patients: hypertension in 28 (48.3%), hypokalemia in 15 (25.9%), and edema in 11 (19.0%) patients.
- The median number of days from the initiation of ZYTIGA to any-grade hypertension or hypokalemia was 56 days (range, 14-492 days) and 39 days (range, 17-534 days), respectively.
- Grade 3-4 mineralocorticoid toxicity occurred in 12 (21%) patients: hypertension in 9 (15.5%) patients, hypokalemia in 4 (6.9%) patients, and no grade ≥3 edema.
- Of the patients who developed hypertension during study, 42.9% (12 of 28 patients) had a prior history of hypertension and were receiving antihypertensives at baseline.
- A total of 33 (56.9%) patients required the use of antihypertensives and 11 (19.0%) patients required potassium supplementation.
- Mineralocorticoid antagonists were used in 28 (48.3%) patients (eplerenone [n=23], spironolactone [n=3], or both [n=2]).
- Seven (12.1%) patients initiated prednisone for mineralocorticoid AEs (hypokalemia in 4 [7%] and hypertension in 3 [5.2%] patients). Two patients initiated prednisone for fatigue (3.4%), 1 of whom experienced grade 3 fatigue.
- Patients with lower baseline levels of androstenedione (P=0.04), androsterone (P=0.01), dehydroepiandrosterone (P=0.03), and 17-hydroxyprogesterone (P=0.03) were more likely to develop mineralocorticoid toxicity. Additional details regarding the association of serum androgens and response have been published.[8]

Reid et al (2010)[6] evaluated the efficacy and safety of ZYTIGA in patients with CRPC who had previously received docetaxel (N=47).

Study Design/Methods

- Phase 2, single-arm, open-label, multicenter, 2-stage study.
- Patients received ZYTIGA 1000 mg PO QD in a fasted state for 28-day cycles.
- Anticipated effects due to increased mineralocorticoid levels (eg, hypokalemia, hypertension, fluid retention) were managed with either low-dose glucocorticoids or eplerenone (50-200 mg).
- **Primary endpoint:** proportion of patients achieving a ≥50% decline in PSA from baseline according to Prostate Specific Antigen Working Group (PSAWG) criteria, with confirmation 4 weeks or more later
- **Secondary endpoints:** PSA reductions of ≥30% and ≥90%, measurable disease response rate determined by Response Evaluation Criteria in Solid Tumors (RECIST) per investigators' assessment, time to PSA progression (TTPP), declines in circulating tumor cell (CTC) count, and safety and tolerability

Results

Patient Characteristics

- Median age: 67 years (range, 48-87 years)
- Median baseline PSA: 403 ng/mL (range, 9.9-10,325 ng/mL)
- Measurable disease at baseline via imaging scan: n=30
- Median alkaline phosphatase: 185 U/L (range, 34-110 U/L)
- Twenty-seven of 34 patients (also on a separate protocol) had baseline CTC counts ≥5 cells/7.5 mL blood.
    - Median CTC count: 36 cells (range, 5-1712 cells)
    - Fifty-two percent of patients had 5-50 cells and 48% had ≥50 cells.
- Baseline characteristics of patients are described in Table: Baseline Characteristics.

Baseline Characteristics[6]

Characteristic	n
ECOG performance status	
0	16
1	27
2	4
Gleason score	
<6	4
6-7	20
8-9	17
10	1
Unknown	5
Predominant metastases	
Bone only	4
Visceral only	0

Characteristic	n
Soft tissue only	1
Bone and soft tissue	33
Bone and visceral	1
Soft tissue and visceral	1
Bone, soft tissue, and visceral	7
Prior hormone therapies	
LHRH analogs	47
Antiandrogens	46
Steroids	27
Estrogens	17
Ketoconazole	8
Prior chemotherapy	
Docetaxel	47
Vinorelbine	3
ECarboF	1
Mitoxantrone	8
Cyclophosphamide	2
Carboplatin	2
Estramustine	2
Paclitaxel	2
Abbreviations: ECarboF, epirubicin plus carboplatin plus fluorouracil; ECOG, Eastern Cooperative Oncology Group; LHRH, luteinizing hormone-releasing hormone.	

Efficacy

PSA Changes and Disease Responses

- A PSA decline of ≥50% from treatment initiation was observed in 24 patients (51%) at least once on study.
- PSA decline of ≥30%: n=32 (68%), and PSA decline of ≥90%: n=7 (15%)
- Of the 30 patients with measurable disease at baseline, a partial response (PR) was observed in 8 patients (27%).

TTPP

- The median TTPP was 169 days (95% CI, 113-281 days).
    - Five patients continued ZYTIGA at data cutoff for 913+, 886+, 795+, 726+, and 698+ days, respectively.

Declines in CTC Count

- Decline in CTC count to <5: n=11 (41%) of 27 evaluable patients
    - Decline of ≥50%: n=17 (63%)
    - Decline of ≥30%: n=18 (67%)

Symptomatic Improvements

- The changes in ECOG performance score from baseline are summarized in Table: ECOG Performance Score Change From Baseline (n=46).

ECOG Performance Score Change From Baseline (n=46)[6]

Baseline ECOG Performance Score	n	Postbaseline ECOG Performance Score, n		
		0	1	2
0[a]	16	15	-	-
1	27	10	17	-
2	4	-	1	3
Total	47	25	18	3

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]Post-treatment performance status not reported in 1 patient.

Safety

- All patients were evaluable for safety.
- Hypokalemia, hypertension, and fluid retention were managed with low-dose glucocorticoids or eplerenone.
- Three deaths occurred on study due to pneumonia, progressive disease, and asystolic cardiac arrest. Two were not considered treatment-related and the third was attributed to a myocardial infarct or pulmonary embolism, though a postmortem was not conducted. The third patient also had a history of diabetes, cardiac disease, and bony metastases.
- The most frequent treatment-related adverse reactions are summarized in Table: Most Frequent Treatment-Related Adverse Reactions (≥10% of Patients, N=47).

Most Frequent Treatment-Related Adverse Reactions (≥10% of Patients, N=47)[6]

Adverse Reaction, n (%)	Grade 1	Grade 2	Grade 3	Grade 4
Anorexia	4 (9)	4 (9)	1 (2)	-
Constipation	1 (2)	4 (9)	-	-
Fatigue	2 (4)	10 (21)	3 (6)	-
Headache	3 (6)	2 (4)	-	-
Hyperglycemia	1 (2)	5 (11)	-	-
Hypertension	3 (6)	5 (11)	-	-
Hypokalemia	25 (53)	-	1 (2)	-
Nausea	3 (6)	2 (4)	2 (4)	-
Peripheral edema	2 (4)	5 (11)	-	-
Transaminases[a]	-	-	-	1 (2)

[a]Not reported in ≥10% of patients.

Phase 1/2 Study

Attard et al (2009)[1] evaluated the efficacy and safety of ZYTIGA in patients with chemotherapy-naïve CRPC (N=54).

Study Design/Methods

- Phase 1/2, multicenter, open-label, 2-stage study
- Patients received ZYTIGA 250 mg (n=4), 500 mg (n=4), 750 mg (n=4), 1000 mg (n=42), or 2000 mg (n=4) PO QD.
  - All patients received dexamethasone 0.5 mg QD with ZYTIGA at progression.
- **Primary endpoint:** the rate of a ≥50% decline in PSA levels after 12 weeks, confirmed by a second PSA assessment 4 weeks later in patients treated with 1000 mg QD
- **Secondary endpoints:** the rate of a ≥30% decline in PSA, rate of response in measurable lesions by radiologic assessment, changes in CTC counts, and median TTPP defined by the PSAWG I criteria

Results

Patient Characteristics

- Median age: 70 years (range, 50-84 years)
- Median baseline PSA: 110 ng/mL (range, 9.7-964 ng/mL)
- Measurable disease at baseline via computed tomography scan: n=24 (57%)
- Seventeen of 42 patients had baseline CTC counts ≥5 cells/7.5 mL blood.
- Lactate dehydrogenase raised: n=13; or normal: n=29

Efficacy

PSA Changes and Disease Responses

- In patients receiving 1000 mg QD dosing, a PSA decline of ≥50% from treatment initiation was observed in 28 (67%) of 42 evaluable patients at least once on study.
  - PSA decline of ≥90%: n=8 (19%)
  - PSA decline of ≥30%: n=30 (71%)
  - Pretreatment levels of dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), androstenedione (continuous variable), and estradiol were associated with increased probability of a ≥50% PSA decline and median TTPP with ZYTIGA.
- Of 24 patients with baseline measurable disease, PR was observed in 9 patients (37.5%).
  - Overall, 16 patients (66%) had no evidence of progression at 6 months.

TTPP

- Median TTPP for patients receiving ZYTIGA (1000 mg QD) alone: 225 days (95% CI, 162-287 days)
- Median TTPP for patients receiving 1000 mg QD dosing and had a ≥90% and ≥50% decline in PSA was 393 days (95% CI, 252-533 days) and 253 days (95% CI, 122-383 days), respectively.
- The median TTPP for all patients (N=54) who received any amount of study medication was 588 days (95% CI, 40-767 days), with a median TTPP on ZYTIGA alone of 229 days (95% CI, 157-301 days).

- Median TTPP for patients with a ≥50% and ≥90% decline in PSA was 339 days (95% CI, 136-542 days) and 477 days (95% CI, 350-604 days), respectively.
- The median TTPP from addition of dexamethasone until stopping both ZYTIGA and dexamethasone (n=39) was 151 days (95% CI, 117-185 days).

Declines in CTC Count

- Decline in CTC count from baseline to <5/7.5 mL blood: n=11 (59%) of 17 evaluable patients; decline of ≥30%: n=12 (70%)

Mass Spectrometry Analyses

- **Attard et al (2012)**[7] also reported results of a mass spectrometry-based analysis of the steroidogenic effects of CYP17A1 inhibition in samples taken from the 42 patients with chemotherapy-naïve CRPC who were treated with ZYTIGA 1000 mg.

Safety

- Forty-two patients were available for safety evaluation.
- Secondary mineralocorticoid excess characterized by hypokalemia (n=37, 88%), hypertension (n=17, 40%), and fluid overload (n=13, 31%) was reported.
  - Management included eplerenone 50-200 mg QD, except in 3 patients who required glucocorticoid replacement for symptomatic fluid overload associated with migraine headaches (n=2).
- One patient with a history of asthma required high-dose corticosteroids for worsening asthma and was maintained on dexamethasone 0.5 mg QD.
- Hot flushes were reported (n=4) and managed with venlafaxine (n=2).
- Grade 3 transaminase elevation (n=2) was reported after 10 weeks and 27 weeks of therapy, respectively, and resolved with treatment interruption. One patient was rechallenged and the transaminase elevation recurred. Grade 2 asymptomatic transaminase elevation occurred in 1 patient after 16 weeks of therapy. The patient was managed with treatment interruption and restarted ZYTIGA 750 mg QD.
- Grade 1 headaches (n=4) and grade 1 joint aches were also reported.
- No other adverse reactions grade ≥2 or occurring in >2 patients were reported.

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 27 September 2023. Relevant prospective studies are included in this response.

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