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

SUMMARY

- Johnson & Johnson cannot recommend any practices, procedures, or modifications that deviate from product labeling and are not approved by the regulatory agencies.
- In pivotal phase 3, randomized, double-blind, placebo-controlled, multicenter studies (COU-AA-301 and COU-AA-302), patients with metastatic castration-resistant prostate cancer (mCRPC) were randomized to receive the following: ZYTIGA 1,000 mg orally (PO) once daily (QD) plus prednisone 5 mg PO twice daily (BID) or placebo plus prednisone 5 mg PO BID. In a pivotal phase 3, randomized, double-blind, placebo-controlled, multicenter study (LATITUDE), patients with metastatic high-risk castration-sensitive prostate cancer (CSPC) were randomized to receive the following: ZYTIGA 1,000 mg PO QD with prednisone 5 mg PO QD or placebos PO QD. All patients in these studies received a gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy.[1-3]
- In a phase 2 open-label study, patients with mCRPC receiving ZYTIGA 1,000 mg PO QD were randomized to 1 of the following oral corticosteroid regimens: prednisone 5 mg BID, prednisone 5 mg QD, prednisone 2.5 mg BID, or dexamethasone 0.5 mg QD (N=164). The primary endpoint was the percentage of patients who did not experience mineralocorticoid excess (defined as grade ≥1 hypokalemia or grade ≥2 hypertension) through 24 weeks (6 cycles). Both the prednisone 5 mg QD and prednisone 2.5 mg BID groups did not meet the protocol criterion for the primary endpoint.[4]
- Another phase 2 study evaluated the use of ZYTIGA 750 mg PO QD plus prednisone 5 mg PO QD in patients ≥85 years old with advanced and/or mCRPC.[5]
- An additional phase 2 study evaluated the use of ZYTIGA 1,000 mg PO QD plus prednisone 5 mg PO QD in chemotherapy-naïve patients with diethylstilbestrol-refractory mCRPC.[6]

CLINICAL DATA

Clinical studies reporting the use of ZYTIGA with an alternative prednisone regimen for the treatment of patients with mCRPC are included in this section. No data describing the use of ZYTIGA with an alternative prednisone regimen in patients with metastatic high-risk CSPC were identified.

Phase 2 Studies

Attard et al (2019)[4] evaluated the mineralocorticoid effect and efficacy of alternative corticosteroid regimens in combination with ZYTIGA for the treatment of chemotherapy-naïve patients with mCRPC (N=164).

Study Design/Methods

- Phase 2, randomized, multicenter, open-label, 24-week study
- Patients receiving ZYTIGA 1,000 mg PO QD were randomized to 1 of 4 oral corticosteroid regimens:
    - prednisone 2.5 mg BID (n=40)
    - prednisone 5 mg QD (n=41)
    - prednisone 5 mg BID (n=41)
    - dexamethasone 0.5 mg QD (n=42)
- Patients with grade 3 or 4 hypokalemia and those who required diuretic treatment, a change in glucocorticoid dose, or palliative radiotherapy discontinued the main study treatment, but could enroll in the extension protocol and restart the main study treatment after improvement to grade ≤1 without disease progression.

- **Primary endpoint:** the percentage of patients who did not experience mineralocorticoid excess (defined as grade ≥1 hypokalemia or grade ≥2 hypertension) through 24 weeks (6 cycles). This endpoint was derived from treatment emergent adverse event (TEAE) data, defined using the Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the National Cancer Institute Common Terminology (NCI-CTCAE v4.0).
- **Secondary endpoints:** global safety profile by NCI CTCAE v4.0; changes in plasma adrenocorticotropic hormone (ACTH) and urinary metabolites; incidence of exogenous glucocorticoid adverse effects, ie changes in fasting serum insulin, homeostatic model assessment of insulin resistance (HOMA-IR; calculated as insulin × glucose ÷ 22.5), total lean body mass, total body fat, and bone mineral density; and clinical benefit, including antitumor activity from serum prostate-specific antigen (PSA) values, radiographic progression-free survival (rPFS), and influence on quality of life (QoL; based on the EuroQol 5-dimension questionnaire and Functional Assessment of Cancer Therapy-Prostate Cancer [FACT-P] questionnaire).

Results

Patient Characteristics

- Median age: 70 years (range, 50-90 years)
- All patients had testosterone levels <50 ng/dL achieved by surgical or medical castration.
- Most baseline characteristics were balanced across treatment groups except incidence of elevated blood pressure at baseline was 46.3% for prednisone 5 mg QD and ranged from 26.8-33.4% in the other groups. Also, the mean time from diagnosis to randomization was 101.4 months in the dexamethasone 0.5 mg QD group and ranged from 59.6 months to 69.2 months in the prednisone dosing groups.
- Patients taking any antihypertensive medication at baseline ranged from 39.0-56.1% across the treatment groups.

Efficacy and Safety

- The median duration of treatment was 12.9 months for all groups combined (n=163 evaluable for safety as 1 patient in the prednisone 2.5 mg BID group did not receive treatment); 19 discontinued before week 24 without an adverse event (AE) of either grade ≥1 hypokalemia or grade ≥2 hypertension (n=144 evaluable for the primary endpoint).
- The primary endpoint and additional safety results are summarized in Table: Phase 2 Study of ZYTIGA and Low-Dose Glucocorticoids.
- A ≥50% decrease in PSA at 24 weeks was observed in the following percentage of randomized patients: 88.1% in the dexamethasone 0.5 mg QD group, 78.0% in the prednisone 5 mg QD group, 63.4% in the prednisone 5 mg BID group, and 60% in the prednisone 2.5 mg BID group.
- Median rPFS was 26.6 months (95% confidence interval [CI]: 20.9-not evaluable [NE] months) with dexamethasone 0.5 mg QD; 18.5 months (95% CI: 10.0-26.7 months) with prednisone 5 mg BID; 15.3 months (95% CI: 8.4-29.5 months) with prednisone 5 mg QD; and 12.8 months (95% CI: 7.4-20.9 months) with prednisone 2.5 mg BID.
- Plasma ACTH and urinary mineralocorticoid metabolites after 8 weeks were higher with prednisone 2.5 mg BID and 5 mg QD than with 5 mg BID or dexamethasone 0.5 mg QD. The level of urinary glucocorticoid metabolites appeared higher in patients who did not meet the study primary endpoint, regardless of the glucocorticoid regimen.
- Total lean body mass decreased in the prednisone groups and total body fat increased in the prednisone 5 mg BID and dexamethasone groups.
- In the dexamethasone group, there was an increase in serum insulin and HOMA-IR, while total bone mineral density decreased.

- Patient-reported QoL in this population, which was asymptomatic or minimally symptomatic at baseline, remained stable in all groups during the study.
- Grade 4 hypertension and Grade 4 hypokalemia were not reported. No patient discontinued study treatment for persistent hypertension.

Phase 2 Study of ZYTIGA and Low-Dose Glucocorticoids[4]

	Prednisone 2.5 mg BID n=35[a]	Prednisone 5 mg QD n=38[a]	Prednisone 5 mg BID n=34[a]	Dexamethasone 0.5 mg QD n=37[a]
Met primary endpoint[b], n (%) 95% CI	21 (60) (44-74)	14 (37) (23-53)	24 (71) (54-83)	26 (70) (54-83)
Investigator reported adverse events				
Grade ≥2 hypertension and Grade ≥1 hypokalemia, n (%)	3 (9)	1 (3)	2 (6)	2 (5)
Grade ≥2 hypertension alone, n (%)	10 (29)	18 (47)	7 (21)	6 (16)
Grade ≥1 hypokalemia alone, n (%)	1 (3)	5 (13)	1 (3)	3 (8)
Median change from baseline to cycle 3 in plasma ACTH, pmol/L *P*-value vs baseline	+3.97 <0.001	+8.95 <0.001	-1.07 0.16	-1.82 0.02

Abbreviations: ACTH, adrenocorticotropic hormone; BID, twice daily; CI, confidence interval; QD, once daily.
[a]Patients completed 24 weeks of treatment (6 cycles) or discontinued treatment early and experienced either hypertension (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] grade ≥2) or hypokalemia.
[b]Investigator reported neither hypertension (NCI-CTCAE grade ≥2) nor hypokalemia during the first 24 weeks (6 cycles).

Another phase 2 study (**Petrioli et al 2015**) evaluated the use of ZYTIGA 750 mg PO QD plus prednisone 5 mg PO QD in patients ≥85 years old with advanced and/or mCRPC (N=26). Results including PSA response, time to PSA progression, overall survival, and pain response have been reported.[5]

An additional phase 2 study (**Bastos et al 2021**) evaluated the use of ZYTIGA 1,000 mg PO QD plus prednisone 5 mg PO QD in chemotherapy-naïve patients with diethylstilbestrol-refractory mCRPC (N=46). Results included time to PSA progression, overall survival, PSA response, maximum PSA change from baseline, and safety.[6]

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 12 March 2025.

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