ZYTIGA® (abiraterone acetate)
Use of ZYTIGA in Combination with an Alternative Corticosteroid

SUMMARY

- The safety and efficacy of ZYTIGA used in combination with alternative glucocorticoids, such as hydrocortisone, methylprednisolone, or dexamethasone, in patients with metastatic castration-resistant prostate cancer (mCRPC) have not been systematically evaluated in controlled, prospective, randomized, phase 3 clinical trials.
- In pivotal phase 3, international, randomized, double-blind, placebo-controlled, multicenter studies (COU-AA-301 and COU-AA-302), patients with 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, 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 QD or placebo 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 various prednisone regimens or dexamethasone 0.5 mg PO QD (N=164). After 24 weeks, prednisone 5 mg PO BID and dexamethasone 0.5 mg PO QD had a lower reported incidence of adverse events (AEs) associated with mineralocorticoid excess (grade ≥1 hypokalemia or grade ≥2 hypertension). At week 24, 63.4% of patients treated with prednisone 5 mg PO BID and 88.1% of patients treated with dexamethasone 0.5 mg PO QD had ≥50% reductions in prostate-specific antigen (PSA) levels. Two patients in the ZYTIGA plus dexamethasone group started medication for non-insulin dependent diabetes mellitus (NIDDM).[4]
- A phase 2, prospective study (SWITCH study) evaluated the efficacy of changing the glucocorticosteroid in patients with mCRPC who had progressed while receiving ZYTIGA 1,000 mg PO QD plus prednisone 5 mg PO BID (N=26). After switching to ZYTIGA plus dexamethasone 0.5 mg PO QD, the median biochemical progression free survival (PFS) was 5.3 months, and the median radiological PFS was 11.8 months. The most common AEs were muscle weakness (12%), hypertension (8%), and hyperglycemia (8%).[5]
- In a phase 1/2, multicenter, open-label, 2-stage study in patients with chemotherapy-naïve CRPC, ZYTIGA was administered as a single agent, and dexamethasone was added at the time of disease progression (N=54).[6]
- Results from a multicenter study that evaluated PSA response and PFS in patients who switched from prednisone 10 mg to dexamethasone 0.5 mg after asymptomatic biochemical progression have been reported.[7]

CLINICAL DATA

Prospective clinical studies reporting the use of ZYTIGA with an alternative corticosteroid regimen for the treatment of patients with mCRPC are included in this section. No data describing the use of ZYTIGA with an alternative corticosteroid regimen in patients with metastatic high-risk CSPC have been published.

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 corticosteroid regimens: prednisone 5 mg PO BID, prednisone 5 mg PO QD, prednisone 2.5 mg PO BID, or dexamethasone 0.5 mg PO QD.
- **Primary endpoint:** the percentage of patients who did not experience mineralocorticoid excess (grade ≥1 hypokalemia or grade ≥2 hypertension) through cycle 6.
- **Secondary endpoint:** the response rate defined as ≥50% decline in PSA and additional safety.

Results

Patient Characteristics

- Median age: 70 years (range, 50-90 years)
- Elevated blood pressure at baseline was observed in 26.8% to 46.3% of patients in the 4 treatment groups and 39.05 to 56.1% of patients were receiving antihypertensive medications.

Efficacy

- The median duration of treatment was 12.9 months for all groups combined.
- A ≥50% decrease in PSA at 24 weeks was observed in the following percentage of 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 radiographic PFS ranged from 12.8 months (prednisone 5 mg QD) to 26.6 months (dexamethasone 0.5 mg QD).

Safety

- Prednisone 5 mg PO BID and dexamethasone 0.5 mg PO QD were most effective in preventing AEs associated with mineralocorticoid excess.
- The efficacy and safety results are summarized in Table: Phase 2 Study of ZYTIGA and Low-Dose Glucocorticosteroids.

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

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

Abbreviations: ACTH, adrenocorticotropic hormone; BID, twice daily; CI, confidence interval; QD, once daily.
[a]Patients who completed 24 weeks (6 cycles) of therapy or who discontinued early and experienced hypertension (grade ≥2) or hypokalemia.
[b]Investigator reported no hypokalemia or hypertension (grade ≥2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0) over 24 weeks.

- Significant increases in fasting insulin and homeostatic model assessment of insulin resistance (HOMA-IR) were observed in the dexamethasone group only. At 24 weeks, the fasting serum insulin level was 47.5 pmol/L (95% confidence interval [CI], 18.8-76.2 pmol/L; *P*=0.002) and the HOMA-IR was 1.99 (95% CI, 0.59-3.38; *P*=0.01).

- Two patients started medications for NIDDM; both were in the dexamethasone group.

Romero-Laorden et al (2018)[5] evaluated the efficacy of switching the glucocorticosteroid from prednisone to dexamethasone in patients with mCRPC who had progressed while being treated with ZYTIGA 1,000 mg PO QD plus prednisone 5 mg PO BID (SWITCH study; N=26).

Study Design/Methods

- Phase 2, prospective, multicenter, open-label, single-arm study in Spain
- Patients had clinically stable mCRPC with PSA progression (as defined by Prostate Cancer Working Group 2 [PCWG2] criteria) and/or limited radiographic progression after ≥12 weeks of ZYTIGA plus prednisone.
- All patients were switched to ZYTIGA 1,000 mg PO QD plus dexamethasone 0.5 mg PO QD.
- **Primary endpoint:** proportion of patients with PSA decline ≥30% (PSA30) after week 6 and confirmed at least 2 weeks later.
- **Secondary endpoint:** proportion of patients with PSA decline ≥50% at week 12, median time to biochemical and radiological progression, overall survival (OS).

Results

Patient Characteristics

- Median age: 73.0 years (range, 60-85 years)
- Median baseline PSA: 36.1 ng/mL (range, 4.46-965.2 ng/mL)
- Chemotherapy-naïve: 53.8%
- All patients had experienced biochemical (PSA) progression and 12 (46.2%) had experienced radiological progression (new lesions or increased size) while receiving ZYTIGA plus prednisone.
    - Median duration of ZYTIGA plus prednisone was 6.2 months (range, 3.0-31.3 months).

Efficacy

- Median duration of ZYTIGA plus dexamethasone was 8.6 months (range, 1.8-28.5, months).
- After ≥6 weeks, 46.2% of patients had PSA declines ≥30% and 34.6% had PSA declines ≥50% at week 12.
- The median biochemical PFS with ZYTIGA plus prednisone was 5.4 months. After the switch to ZYTIGA plus dexamethasone, the median biochemical PFS was 5.3 months (95% CI, 3.1-7.5 months) and the median radiological PFS was 11.8 months (95% CI, 6.6-17.1 months).
- The median OS since initiation of dexamethasone with ZYTIGA was 20.9 months (95% CI, 10.0-31.7 months).

Safety

- The most common grade 1-2 AEs reported in patients receiving ZYTIGA plus dexamethasone were muscle weakness (12%), hypertension (8%), and hyperglycemia (8%). There were no grade 3 or 4 AEs.
- AEs are summarized in Table: Treatment-Related AEs for Patients Treated with ZYTIGA plus Prednisone or Dexamethasone.

Treatment-Related AEs in Patients Treated with ZYTIGA plus Prednisone or Dexamethasone[5]

N	ZYTIGA + Prednisone		ZYTIGA + Dexamethasone	
	Grade 1	Grade 2	Grade 1	Grade 2
Hypertension	1	2	1	1
Hyokalemia	2	0	0	0
Edema	1	0	0	0
Hyperglycemia	1	0	1	1
Hypertransaminasemia	1	0	0	0
Hypotension	0	0	1	0
Muscle weakness	0	0	3	0
Total events	6	2	6	2

Abbreviation: AE, adverse event.

Phase 1/2 Study

Attard et al (2009)[6] 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), 1,000 mg (n=42), or 2,000 mg (n=4) PO QD.
  - Dexamethasone 0.5 mg PO QD was added to ZYTIGA in all patients at progression.
- **Primary endpoint:** the rate of a ≥50% decline in PSA after 12 weeks, confirmed by a second PSA 4 weeks later in patients treated with 1,000 mg PO QD.
- **Secondary endpoints:** the rate of a ≥30% decline in PSA, rate of response in measurable lesions by radiologic assessment, changes in circulating tumor cell (CTC) counts, and median time to PSA progression (TTPP), defined by the PSA Working Group 1 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%)
  - Thirty-two of 42 patients had evidence of bony metastases.
- Seventeen of 42 patients had baseline CTC counts ≥5 cells/7.5 mL blood.
- Lactate dehydrogenase raised: n=13 or normal: n=29
- Patient characteristics are described in Table: Baseline Characteristics.

Baseline Characteristics[6,a]

Characteristic	n
ECOG performance status	
0	20
1	22
Gleason score	
6	8
7	10
8	16
9	4

10	1
Unknown	3
Sites of metastases	
Increasing PSA only	4
Lymph nodes only	4
Visceral only	1
Lymph nodes and visceral	1
Bone only	14
Bone and lymph nodes	12
Bone, lymph nodes, and visceral	6
Prior hormone therapies	
LHRH analogues	42
Antiandrogens	41
Dexamethasone	14
Diethylstilboestrol	20
Ketoconazole	2

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen.
[a]Baseline characteristics of patients receiving a 1,000 mg-dose of ZYTIGA.

Efficacy

PSA Changes and Disease Responses

- In patients receiving 1,000 mg QD dosing, a PSA decline ≥50% from treatment initiation was observed in 28 of 42 (67%) evaluable patients at least once on study.
  - PSA decline ≥90%: n=8 (19%)
  - PSA decline ≥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 the 24 patients with measurable disease at baseline, a partial response 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 (1,000 mg PO QD) alone was 225 days (95% CI, 162-287 days).
- Median TTPP for patients receiving 1,000 mg PO QD with 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, 409-767 days), with a median TTPP on ZYTIGA alone of 229 days (95% CI, 157-301 days).
  - Median TTPP for patients who had 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%) in 17 evaluable patients
  - Decline ≥30%: n=12 (70%)

AKR1C3 Analysis

Ni et al (2020)[8] evaluated the effect of AKR1C3 (an enzyme contributing to the resistance of abiraterone acetate) on the switch from prednisone to dexamethasone in patients with mCRPC receiving ZYTIGA (N=43).

Study Design/Methods

- Patients with mCRPC treated with ZYTIGA between 2016 and 2018 were included in the single-center study.
- After biochemical progression with ZYTIGA plus prednisone, patients received ZYTIGA plus dexamethasone.
- AKR1C3 expression was detected by immunohistochemical staining from rebiopsy of primary prostate lesions at the time of mCRPC.
- Kaplan-Meier curves were used to analyze the association between AKR1C3 and treatment outcomes.

Efficacy

- Nineteen of 43 (44.19%) patients were AKR1C3 positive.
- Eighteen of 43 patients (41.86%) had 30% PSA decline.
- The 30% PSA decline rate was comparable between patients with and without AKR1C3 expression (31.6% vs 50.0%; *P*=0.224).
- In the whole cohort, median PSA PFS and OS were 4.93 months and 31.57 months, respectively.
- AKR1C3 expression was associated with statistically shorter median PSA PFS (4.5 months vs 7.73 months; *P*=0.01) and numerically lower median OS (25.43 months vs 39.37 months; *P*=0.274).
- No safety data were reported.

Mass Spectrometry Analyses

Attard et al (2012)[9] also reported results of mass spectrometry-based analyses of the steroidogenic effects of cytochrome P450 17A1 (CYP17A1) inhibition in samples taken from the 42 patients with chemotherapy-naïve CRPC, who were treated with ZYTIGA 1,000 mg PO QD.

Safety

- A total of 42 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 observed after 10 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 therapy was restarted at 750 mg QD of ZYTIGA.
- Grade 1 headaches (n=4) and grade 1 joint aches were also reported.
- No other AEs ≥grade 2 or occurring in >2 patients were reported.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) was conducted on 22 August 2024. Retrospective and observational studies, along with case studies, were not included in this summary.

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. Attard G, Merseburger AS, Arlt W, et al. Assessment of the safety of glucocorticoid regimens in combination with abiraterone acetate for metastatic castration-resistant prostate cancer. *Jama Oncol*. 2019;5(8):1159-1167.

5. Romero-Laorden N, Lozano R, Jayaram A, et al. Phase II pilot study of the prednisone to dexamethasone switch in metastatic castration-resistant prostate cancer (mCRPC) patients with limited progression on abiraterone plus prednisone (SWITCH study). *Br J Cancer*. 2018;119(9):1052-1059.

6. Attard G, Reid AH, A'Hern R, et al. Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. *J Clin Oncol*. 2009;27(23):3742-3748.

7. Belenchón IR, Calahorro CM, García IO, et al. Switching from prednisone to dexamethasone in metastatic castration resistant prostate cancer treated with abiraterone acetate in a multicenter study. *Eur Urol Open Sci 2020*. 2020;19(Suppl. 2):e897-898.

8. Ni Y, Zhao J, Chen J, et al. The effect of AKR1C3 on the switch from prednisone to dexamethasone in metastatic castration-resistant prostate cancer patients receiving abiraterone. *J Clin Oncol*. 2020;38(6, suppl):133-133.

9. Attard G, Reid AH, Auchus RJ, et al. Clinical and biochemical consequences of CYP17A1 inhibition with abiraterone given with and without exogenous glucocorticoids in castrate men with advanced prostate cancer. *J Clin Endocrinol Metabolism*. 2012;97(2):507-516.