ZYTIGA® (abiraterone acetate)
Retreatment with ZYTIGA in Metastatic Castration-Resistant Prostate Cancer

SUMMARY

- In a post hoc analysis of 55 patients with chemotherapy-naïve, metastatic castration-resistant prostate cancer (mCRPC) who were treated with ZYTIGA plus prednisone in a phase 3 study (COU-AA-302) and then received subsequent ZYTIGA plus prednisone therapy, the median time to prostate-specific antigen (PSA) progression (TTPP) after subsequent therapy was 3.9 months (range: 2.6 months-not estimable [NE]). The median treatment duration of subsequent therapy was 4 months (range, 2-9 months). Reasons for discontinuation of subsequent therapy included PSA progression (51%), clinical progression (31%), other (25%), radiographic progression (18%), therapy ongoing (11%), and adverse events (AEs; 5%).[1]
- In a retrospective analysis evaluating outcomes in 12 patients with mCRPC, 7 patients had a PSA decrease ≥50% following their first ZYTIGA plus prednisone treatment course, of which 6 (86%) had a PSA decrease ≥30% and 3 (46%) had a PSA decrease ≥50% with ZYTIGA plus prednisone retreatment. Median progression-free survival (PFS) was 2.3 months with a median treatment duration of 3.2 months. In those who did not have an initial PSA response to ZYTIGA plus prednisone, response to retreatment was also not observed.[2]

CLINICAL DATA

Post Hoc Analysis

Smith et al (2017)[1] conducted a post hoc analysis of clinical response in patients with chemotherapy-naive, asymptomatic, or mildly symptomatic mCRPC who were previously treated with ZYTIGA plus prednisone in the COU-AA-302 study,[3] and then received subsequent ZYTIGA plus prednisone therapy (n=55).

Study Design/Methods

- Post hoc analysis of the phase 3, randomized, placebo-controlled, multicenter COU-AA-302 study.
- The phase 3 COU-AA-302 study compared the clinical benefit of ZYTIGA plus prednisone vs placebo plus prednisone in patients with asymptomatic or mildly symptomatic mCRPC (N=1088). A total of 546 patients received ZYTIGA plus prednisone.[3]

Results

Patient Characteristics

- 55 patients received subsequent ZYTIGA plus prednisone after this initial treatment in COU-AA-302.
- Baseline characteristics are noted in Table: Baseline Patient Characteristics.

Baseline Patient Characteristics[1]

	Subsequent ZYTIGA Plus Prednisone (N=55)
Age, median (range), years	69 (49-90)
Time from initial diagnosis to first dose, median (range), years	4 (0-18)
PSA at initial diagnosis Median (range), ng/mL (n=46)	21 (3-4750)
Gleason score ≥8 at initial diagnosis, n (%)	26 (53)
Extent of disease, n (%) Bone, soft tissue, or node	55 (100)

Bone	46 (84)
Bone only	32 (58)
Soft tissue or node	23 (42)
Stratification by ECOG-PS, n (%)	
0	44 (80)
1	11 (20)
Prior prostate cancer therapy, n (%)	
Hormonal	55 (100)
Radiotherapy	32 (58)
Surgery	28 (51)
Other	14 (26)
Orchiectomy	6 (11)
Median baseline laboratory values	
PSA, ng/mL (range)	34 (1-1099)
Hemoglobin, g/dL (range)	13 (10-17)
LDH, IU/L (range)	184 (113-298)
ALP, IU/L (range)	84 (41-483)
Testosterone, ng/mL (range)	0.4 (0-1)
Abbreviations: ALP, alkaline phosphatase; ECOG-PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PSA, prostate-specific antigen.	

Efficacy

- Treatment and outcomes in the randomized study are summarized in Table: ZYTIGA Plus Prednisone Treatment and Outcomes in Randomized Study.

ZYTIGA Plus Prednisone Treatment and Outcomes in Randomized Study[1]

	Subsequent ZYTIGA Plus Prednisone (N=55)
Prior ZYTIGA plus prednisone exposure	
Treatment duration, median (range), months	11 (6-14)
Treatment cycles, median (range)	12 (2-37)
Reasons for treatment discontinuation	
Discontinued per protocol, n (%)	43 (78)
Unequivocal clinical progression only, n (%)	24 (44)
Radiographic progression only, n (%)	15 (27)
Radiographic and unequivocal clinical progression, n (%)	4 (7)
Adverse event, n (%)	4 (7)
Withdrawal of consent to treatment, n (%)	4 (7)
Other, n (%)	4 (7)
PSA response rate[a], n (%)	25 (46)
Best overall response[b]	
Complete response, n (%)	1 (2)
Partial response, n (%)	5 (9)
Stable disease, n (%)	25 (45)
Progressive disease, n (%)	4 (7)
Abbreviations: PSA, prostate-specific antigen. [a]Based on Prostate Cancer Working Group 2 criteria. [b]Based on Response Evaluation Criteria in Solid Tumors; not evaluable (n=20).	

- Response to subsequent ZYTIGA plus prednisone is summarized in Table: Clinical Response to Subsequent ZYTIGA Plus Prednisone Therapy.

Clinical Response to Subsequent ZYTIGA Plus Prednisone Therapy[1]

	Subsequent ZYTIGA Plus Prednisone (N=55)
Treatment duration, median (range), months	4 (2-9)
Median time to PSA progression on subsequent therapy[a], months (range)	3.9 (2.6, not estimable)
Outcomes during subsequent therapy, n (%)	27 (49)
≥50% PSA decline, n (%)	24 (44)
Clinical symptom improvement, n (%)	10 (18)
Radiographic improvement[b], n (%)	1 (2)
Reason for discontinuation during subsequent therapy[c]	
PSA progression, n (%)	28 (51)
Clinical progression, n (%)	17 (31)
Other, n (%)	14 (25)
Radiographic progression, n (%)	10 (18)
Therapy ongoing, n (%)	6 (11)
Adverse event, n (%)	3 (5)

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PSA, prostate-specific antigen.
[a]Based on Prostate Cancer Working Group 2 criteria.
[b]Refers to improvements as assessed by CT, MRI, or bone scans.
[c]Patients could be counted in >1 outcome or reason for discontinuation.

Retrospective Analysis

Leibowitz-Amit et al (2014)[2] conducted a retrospective analysis to evaluate outcomes in patients with mCRPC who were retreated with ZYTIGA following prior treatment (N=12).

Study Design/Methods

- Clinical, laboratory, and radiological data were evaluated from electronic patient records.
- PSA response was defined (according to the Prostate Cancer Working Group 2 [PCWG2] criteria) as a PSA decline of >50% from baseline, maintained for ≥3 weeks.
- Biochemical PFS was defined as the time between initiation of ZYTIGA retreatment and PSA progression (as defined by PCWG2).
- Monthly PSA measurements were performed during the first 3 months of ZYTIGA therapy and every 1–3 months thereafter, according to physicians' discretion.
- Radiological assessment was not performed at predetermined intervals and thus, radiological PFS could not be reliably determined.

Results

Patient Characteristics

- Baseline characteristics are noted in Table: Baseline Patient Characteristics at Start of ZYTIGA Retreatment.
- Eleven out of 12 (92%) patients had discontinued their first course of ZYTIGA treatment due to biochemical progression, accompanied by clinical progression in 7 men (58%) and radiological progression in 6 patients (50%). One patient discontinued treatment due to financial reasons, despite a decreasing PSA.
- Eleven patients (92%) had received prior docetaxel treatment, either before the first exposure of ZYTIGA or following it.
- Four patients (33%) were treated with enzalutamide prior to rechallenge with ZYTIGA.
- Four patients who had received ZYTIGA prior to chemotherapy in the COU-AA-302 study were prescribed ZYTIGA prior to study unblinding. Three of these patients did not have a confirmed PSA response during the study.

- Three patients had requested retreatment with ZYTIGA (1 requesting retreatment prior to initiation of chemotherapy) and 4 were retreated based on a previous prolonged response to the drug.
- One patient was retreated with ZYTIGA due to the initial treatment course being discontinued for financial reasons.

Baseline Patient Characteristics at Start of ZYTIGA Retreatment[2]

	Subsequent ZYTIGA Plus Prednisone (N=12)
Age, median (range), years	71.2 (51.2–85.7)
Metastatic extension, n (%) Bone only Bone plus lymph nodes Visceral disease	 6 (50) 4 (33) 2 (17)
ECOG-PS, n (%) 0 1 ≥2	 2 (17) 3 (25) 7 (58)
Median PSA, ng/mL (range)	270 (6.4–2836)
Median hemoglobin, g/L (range)	107 (83–137)
Median albumin, g/L (range)	36 (34–43)
Median time from first ZYTIGA cessation to retreatment, months (range)	6.6 (1.6–22.4)
Median number of treatment lines from first ZYTIGA cessation to retreatment (range)	1 (0–3)
Median number of treatment lines from mCRPC diagnosis to ZYTIGA plus prednisone retreatment (range)	4 (3–6)
Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group performance status; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.	

Efficacy

- Outcomes following retreatment with ZYTIGA plus prednisone are summarized in Table: Response Characteristics to ZYTIGA Plus Prednisone Retreatment.
- Of the seven patients who had a PSA decrease ≥50% after the first ZYTIGA plus prednisone treatment course, 6 (86%) had a PSA decrease ≥30% and three (46%) had a PSA decrease ≥50%, with a median PFS of 2.3 months.
- There were no PSA decreases ≥30% among the 5 men who did not have an initial response to ZYTIGA plus prednisone, and the median PFS in this group of men was 1.1 months.

Response Characteristics to ZYTIGA Plus Prednisone Retreatment[2]

	PSA Decrease ≥50% with First ZYTIGA Plus Prednisone Treatment (n=7)	**PSA Decrease <50% with First ZYTIGA Plus Prednisone Treatment (n=5)**
PFS on first ZYTIGA treatment course, months (range)	9.7 (5.5–14.9)	2.2 (0.9–3.7)
Duration of first ZYTIGA treatment, months (range)	11 (5.5–22.3)	4.4 (1.9–5.7)
PSA decrease ≥ 30% with ZYTIGA retreatment, n (%)	5 (86)	0
PSA decrease ≥50% with ZYTIGA retreatment, n (%)	3 (46)	0
PFS on ZYTIGA retreatment, months (range)	2.3 (1.1–5)	1.1 (0.5–6.2)

Duration of ZYTIGA retreatment, months (range)	3.2 (1.6–5)	2.5 (1.3–6.2)
Abbreviations: PFS, progression-free survival; PSA, prostate-specific antigen.		

Safety

- Toxicities observed with ZYTIGA plus prednisone retreatment was predictable and no serious AEs were reported.

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 22 August 2023.

REFERENCES

1. Smith MR, Saad F, Rathkopf DE, et al. Clinical outcomes from androgen signaling-directed therapy after treatment with abiraterone acetate and prednisone in patients with metastatic castration-resistant prostate cancer: post-hoc analysis of COU-AA-302. *Eur Urol*. 2017;72(1):10-13.
2. Leibowitz-Amit R, Alimohamed N, Vera-Badillo FE, et al. Retreatment of men with metastatic castrate-resistant prostate cancer with abiraterone. *Prostate*. 2014;74(14):1462-1464.
3. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368:138-148.