ZYTIGA® (abiraterone acetate)
Use of ZYTIGA in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

SUMMARY

- **COU-AA-301** (NCT00638690) was a phase 3, randomized, double-blind, placebo-controlled, multinational study of ZYTIGA plus prednisone vs placebo plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) and disease progression after docetaxel-based chemotherapy (N=1195). The primary endpoint was overall survival (OS).[1]
    - At the preplanned interim analysis after 552 deaths, ZYTIGA plus prednisone demonstrated a statistically significant improvement in OS vs placebo plus prednisone (median OS: 14.8 months vs 10.9 months, respectively; hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.54-0.77; *P*<0.001).[1] An updated survival analysis, conducted after 775 deaths (97% of the planned events for final analysis) were observed, demonstrated consistent results with those reported from the interim analysis (median OS: 15.8 months vs 11.2 months, respectively; HR, 0.74; 95% CI, 0.64-0.86; *P*<0.0001).[2]
    - The most commonly reported adverse events (AEs) included fatigue, back pain, nausea, constipation, bone pain, and arthralgia, which occurred at similar frequency in both groups. Urinary tract infections were more frequent in the ZYTIGA plus prednisone group. AEs associated with elevated mineralocorticoid levels due to cytochrome P450 17 (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 plus prednisone group.[1] The updated analysis revealed consistent results with the first interim analysis for safety.[2]
- **COU-AA-302** (NCT00887198) was a phase 3, randomized, double-blind, placebo-controlled, multinational study of ZYTIGA plus prednisone vs placebo plus prednisone in asymptomatic or mildly symptomatic patients with chemotherapy-naïve mCRPC (N=1088). The co-primary endpoints were radiographic progression-free survival (rPFS) and OS.[3,4]
    - With a median follow-up of 49.2 months at final analysis after 741 deaths were observed, ZYTIGA plus prednisone significantly prolonged OS vs placebo plus prednisone (median OS, 34.7 months vs 30.3 months, respectively; HR, 0.81; 95% CI, 0.70-0.93; *P*=0.0033). Of note, 44% of patients included in the placebo plus prednisone treatment arm received subsequent ZYTIGA.[3]
    - ZYTIGA plus prednisone prolonged median rPFS based on blinded central radiographic review, as compared to placebo plus prednisone (median not reached vs median of 8.3 months, respectively; HR, 0.43; 95% CI, 0.35-0.52; *P*<0.001).[4] ZYTIGA plus prednisone also demonstrated a statistically significant improvement for all secondary endpoints vs placebo plus prednisone, including a delay in time to opiate use for cancer pain and initiation of chemotherapy.[3,4]
    - Incidence of (all grades) special interest AEs, including fluid retention or edema, hypokalemia, hypertension, cardiac disorders, and elevated hepatic enzymes, were more common with ZYTIGA plus prednisone.[4] AEs at the time of the final analysis were similar to those reported after nearly 27 months of additional follow-up.[3] An additional long-term safety analysis of patients receiving ≥4 years of treatment (n=41) reported similar all grade and grade 3/4 AEs to those receiving <4 years of treatment.[5]

CLINICAL DATA

COU-AA-301 Study

de Bono et al (2011)[1,2] 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 orally (PO) once daily and prednisone 5 mg PO twice daily (n=797) or placebo and prednisone 5 mg PO twice daily (n=398)
  - Androgen deprivation therapy (ADT), a GnRH analog, or prior orchiectomy was required in both arms.[6]
- Study treatment continued until disease progression documented as based on prostate-specific antigen (PSA) concentration, radiographic imaging, and clinical findings.
- Select inclusion criteria: prior treatment with docetaxel; ongoing medical or surgical castration (serum testosterone ≤50 ng/dL); and disease progression defined as 2 consecutive increases in the PSA concentration over a reference value or radiographic evidence of disease progression in soft tissue or bone with or without disease progression on the basis of the PSA value.
- Select exclusion criteria: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels ≥2.5 times upper limit of normal (ULN; however, patients with liver metastasis and AST or ALT ≤5 times ULN were eligible); serious coexisting nonmalignant disease; active or symptomatic viral hepatitis or chronic liver disease; uncontrolled hypertension; history of pituitary or adrenal dysfunction; clinically significant heart disease; or prior ketoconazole.
- **Primary endpoint:** 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 rPFS
- **Exploratory endpoints:** objective response rate (ORR) based on imaging studies; time to skeletal-related event (SRE); and rate of pain palliation

Results

Patient Characteristics

- The following patient demographics and baseline disease characteristics were balanced between the treatment arms: median age: 69 years (range, 39-95 years); 1 prior cytotoxic chemotherapy (70%) regimen and 2 prior regimens (30%); Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-1 (89%) and a Brief Pain Inventory-Short Form (BPI-SF) median score of 3 (patients reported worst pain over the previous 24 hours); and bone metastasis (90%).

Efficacy

- A planned interim analysis was conducted after 552 deaths were observed, with a median follow-up of 12.8 months. ZYTIGA plus prednisone demonstrated a statistically significant improvement in OS vs placebo plus prednisone (median OS: 14.8 months vs 10.9 months, respectively; HR, 0.65; 95% CI, 0.54-0.77; $P<0.001$).

- An updated survival analysis, conducted after 775 deaths (97% of the planned events for final analysis) were observed, demonstrated consistent results with the interim analysis (median OS: 15.8 months vs 11.2 months; HR, 0.74; 95% CI, 0.64-0.86; *P*<0.0001). Survival benefit was observed across multiple patient subgroups.[2]
- Median number of treatment cycles was 8 (range, 1-28 cycles) and 4 (range, 1-27 cycles) cycles for the ZYTIGA plus prednisone and placebo plus prednisone groups, respectively.[2]
- A post-hoc analysis was conducted to evaluate the effect of ZYTIGA plus prednisone by previous docetaxel use. Patients had longer median OS than those in the placebo plus prednisone group, irrespective of reason for discontinuation of docetaxel or the time between discontinuation of docetaxel and initiation of study drug. There was no significant difference in median OS between treatment groups for patients who received docetaxel for ≤3 months and was significantly longer in the ZYTIGA plus prednisone group for patients who received docetaxel for >3 months.[2]
- Additional endpoints are described in the Table: Secondary and Exploratory Endpoints.

Secondary and Exploratory Endpoints[1,2]

	ZYTIGA Plus Prednisone (n=797)	Placebo Plus Prednisone (n=398)	HR (95% CI)	*P* Value
Secondary Endpoints				
PSA response rate IA (confirmed)[1] Updated analysis[a,2]	 29.1% 29.5%	 5.5% 5.5%	 - 	 <0.001 <0.0001
Median TTPP IA[1] Updated analysis[b,2]	 10.2 months 8.5 months	 6.6 months 6.6 months	 0.58 (0.46-0.73) 0.63 (0.52-0.78)	 <0.001 <0.0001
Median rPFS (final analysis)[2]	5.6 months	3.6 months	0.66 (0.58-0.76)	<0.0001
Exploratory Endpoints				
ORR by RECIST IA[1] Updated analysis[2]	 14.0% 14.8%	 2.8% 3.3%	 - 	 <0.001 <0.0001
Median time to a skeletal event (IA)	9.9 months	4.9 months	-	-
Rate of pain palliation[c] (IA)	44%	27%	-	0.002

Abbreviations: CI, confidence interval; HR, hazard ratio; IA, interim analysis; ORR, objective response rate; OS, overall survival; PSA, prostate-specific antigen; PSAWG, Prostate-Specific Antigen Working Group; RECIST, Response Evaluation Criteria in Solid Tumors; rPFS, radiographic progression-free survival; TTPP, time to PSA progression.
[a]Proportion of patients with a PSA decline of 50% or higher according to PSAWG criteria.
[b]Calculated from date of randomization to date of PSA progression according to PSAWG criteria or date of radiographically documented disease progression or death.
[c]Rate of pain palliation among patients who had a baseline pain score ≥4 and ≥1 postbaseline score.

Safety

- All patients who received any study medication were included in the safety analysis (n=1185). 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), cardiac disorders, and liver function test abnormalities were deemed of special interest and more common in the ZYTIGA group vs the placebo group (55% vs 43%, respectively; *P*<0.001).

- The updated analysis revealed consistent results with the first interim analysis as summarized in Table: Adverse Events - Updated Analysis.[2]

Adverse Events - Updated Analysis[2]

	ZYTIGA Plus Prednisone (n=791)			Placebo Plus Prednisone (n=394)		
%	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Hematologic						
Anemia	25	7	1	28	7	2
Thrombocytopenia	4	1	<1	4	<1	<1
Neutropenia	1	<1	0	<1	<1	0
Febrile neutropenia	<1	0	<1	0	0	0
Nonhematologic						
Fatigue	47	9	<1	44	10	<1
Back pain	33	7	<1	36	10	<1
Nausea	33	2	<1	33	3	0
Arthralgia	30	5	0	24	4	0
Constipation	28	1	0	32	1	0
Bone pain	27	6	<1	30	7	1
Vomiting	24	3	<1	26	3	0
Diarrhea	20	1	<1	15	1	0
Pain in arm or leg	20	3	<1	21	5	0
Asthenia	15	3	0	14	2	<1
Dyspnea	15	2	<1	12	2	<1
Abdominal pain	13	2	0	12	2	0
UTI	13	2	0	7	<1	0
Pyrexia	10	<1	0	9	1	0
Hematuria	9	2	0	9	2	0
Pain	5	<1	0	5	2	<1
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; UTI, urinary tract infection.
[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

Ryan et al (2013 and 2015)[3, 4] 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 1000 mg PO once daily and prednisone 5 mg PO twice daily (n=546) or placebo and prednisone 5 mg PO twice daily (n=542)
  - ADT, GnRH analog, or prior orchiectomy was required in both arms.[7]

- Treatment continued until radiographic or clinical (cytotoxic chemotherapy, radiation or surgical treatment for cancer, pain requiring chronic opioids, or 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.[7]
- Select inclusion criteria: metastatic prostate adenocarcinoma (confirmed by positive bone scan or metastasis other than liver/visceral metastasis by imaging scan or lymph node metastasis ≥2 cm in diameter if the only evidence of metastasis); radiographic (modified Response Evaluation Criteria In Solid Tumors [RECIST]) or PSA disease progression (adapted Prostate Cancer Working Group 2 [PCWG2] criteria); none or mild symptoms; ECOG-PS 0 or 1; ongoing medical or surgical castration (serum testosterone <50 ng/dL); and prior anti-androgen use with disease progression after withdrawal.
- Select exclusion criteria: patients with moderate or severe pain, opiate use for cancer pain, ketoconazole treatment for prostate cancer, history of adrenal gland or pituitary disorder, or visceral organ metastases.
- **Co-primary endpoints:** OS and rPFS
- **Secondary endpoints:** time to opiate use (for cancer pain); time to initiation of chemotherapy; time to ECOG-PS deterioration; and TTPP based on PCWG2 criteria.
- **Exploratory endpoints:** rPFS as measured by investigators (rather than a blinded review); PSA response rate (≥50% decline in PSA level from baseline); objective response rate (according to RECIST criteria); health-related quality of life as measured by means of patients' reports of pain (increase in the baseline pain level by 30% or more measured by the average of the pain scores on the BPI-SF at 2 consecutive visits, without a decrease in analgesic use); and functional status (the time to a decline in functional status is defined as the months from randomization to the first date a patient has a decrease of ≥10 points in Functional Assessment of Cancer Therapy-Prostate [FACT-P] scores).[4,8]

Results

Patient Characteristics

- The following patient demographics were balanced between the treatment arms: median age, 70 years; ECOG-PS 0 (76%) and 1 (24%); baseline pain assessment was 0-1 (asymptomatic, 66%) and 2-3 (mildly symptomatic, 32%), as defined by the BPI-SF (worst pain over the last 24 hours).

Efficacy

- There were 3 planned interim analyses and a final analysis conducted at 13%, 43%, 56%, and 96% survival events.
- ZYTIGA plus prednisone prolonged median rPFS, based on blinded central radiographic review at the first interim analysis (IA1), as compared to placebo plus prednisone (median not reached vs median of 8.3 months, respectively; HR, 0.43; 95% CI, 0.35-0.52; $P<0.001$).[4]
- With a median follow-up of 49.2 months at final analysis after 741 deaths were observed, ZYTIGA plus prednisone significantly prolonged OS vs placebo plus prednisone (median OS, 34.7 months vs 30.3 months, respectively; HR, 0.81; 95% CI, 0.70-0.93; $P=0.0033$).[3]
- At final analysis, 67% of patients treated with ZYTIGA plus prednisone and 80% with placebo plus prednisone received subsequent therapies with 1 or more agents at final analysis: cabazitaxel, docetaxel, enzalutamide, ketoconazole (not a regulatory agency-approved use), radium-223, and sipuleucel-T. Of note, 44% of patients included in the placebo plus prednisone treatment arm received subsequent ZYTIGA.[3]

- The secondary and exploratory endpoints are described in the Table: Secondary and Exploratory Endpoints.

Secondary and Exploratory Endpoints[3, 4,8]

	ZYTIGA Plus Prednisone (n=546)	Placebo Plus Prednisone (n=542)	HR (95% CI)	*P* Value
Secondary Endpoints[a]				
Median time to opiate use (final analysis)[3]	33.4 mo	23.4 mo	0.72 (0.61-0.85)	0.0001
Median time to chemotherapy	26.5 mo	16.8 mo	0.61 (0.51-0.72)	<0.0001
Median time to ECOG-PS deterioration	12.3 mo	10.9 mo	0.83 (0.72-0.94)	0.005
Median TTPP	11.1 mo	5.6 mo	0.50 (0.43-0.58)	<0.0001
Exploratory Endpoints[a]				
PSA decline ≥50% (IA2)[4]	68%	29%	2.59 (2.19-3.05)[b]	<0.001
ORR (IA2)[c,4]	36%	16%	2.27 (1.59-3.25)[b]	<0.001
Mean time to pain interference progression	10.3 mo	7.4 mo	0.80 (0.68-0.93)	0.005
Median time to FACT-P degradation	12.7 mo	8.3 mo	0.79 (0.67-0.93)	0.005

Abbreviations: CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HR, hazard ratio; IA, interim analysis; mo, month; ORR, objective response rate; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria In Solid Tumors; TTPP, time to PSA progression.
[a]IA3[9] unless otherwise noted.
[b]Relative risk (95% CI).
[c]Based on RECIST criteria in patients with measurable disease at baseline: n=220 in the ZYTIGA plus prednisone group and n=218 in the placebo plus prednisone group.

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).[5]
- Grade 3 or 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.[3] 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.[5] AEs 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)			
%	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
Fluid retention[b]	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 increase	9	5	<1	0	4	<1	<1	0
AST increase	12	3	0	0	4	<1	0	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]Prior to crossover.
[b]And edema.

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 09 June 2023. Summarized in this response are relevant data from the pivotal phase 3, randomized studies. Post-hoc and other analyses not prespecified in the study protocols were excluded.

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