ZYTIGA® (abiraterone acetate)
ZYTIGA - Comparison of ZYTIGA with Enzalutamide for the Treatment of Metastatic Castration-Resistant Prostate Cancer (mCRPC)

SUMMARY

- There are limited prospective, randomized, clinical study data comparing the efficacy and safety of ZYTIGA plus prednisone and enzalutamide for the treatment of mCRPC published to date.
- AQUARiUS was a phase 4, nonrandomized, prospective, multicenter, real-world, observational study that evaluated differences in patient reported outcomes (PROs), between patients with chemotherapy-naïve mCRPC newly initiated on ZYTIGA plus prednisone or enzalutamide (N=211). After treatment initiation, there were statistically significant differences between the ZYTIGA and enzalutamide groups for 18 PRO items (P<0.05). When assessed in a different approach (at least three consecutive periods [≥50%] needed to be significant), 9 of the 18 PRO items were statistically significant for the ZYTIGA group when compared to enzalutamide group, of which were related to cognition, fatigue, appetite loss, and nausea. The most common serious adverse events (AEs) were infections and infestations and renal and urinary disorders.[1]
- REAAcT was a phase 4, prospective, multicenter, open-label, real-world, observational study that evaluated differences in quality of life (QoL) and tolerability in patients with mCRPC treated with ZYTIGA plus prednisone or enzalutamide (N=100). The mean change from baseline for the Functional Assessment of Chronic Illness Therapy Fatigue subscale (FACIT-Fatigue) were -0.01 (95% confidence interval [CI], -2.40 to 2.38) and -4.00 (95% CI, -6.61 to -1.39) for the ZYTIGA and enzalutamide groups, respectively. Among patients that demonstrated change from baseline scores at or above the minimal clinically important differences (MCID) value, 26% and 30% of patients in the ZYTIGA group showed improvement on the FACIT-Fatigue and Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) assessments, respectively, compared to 14% and 15% of patients in the enzalutamide group. Grade 3/4 AEs and serious AEs were reported in 3 (6%) and 2 (4%) patients in the ZYTIGA and enzalutamide groups, respectively.[2]
- Real-world data from an international prostate cancer registry that evaluated patients with mCRPC receiving their first treatment have been reported.[3]
- Additional analyses have evaluated several different treatment outcomes in patients with mCRPC who have received ZYTIGA plus prednisone or enzalutamide.[4-7]

CLINICAL DATA

OBSERVATIONAL STUDIES

AQUARiUS Study

Thiery-Vuillemin et al (2020)[1] evaluated differences in PROs, such as health-related QoL, pain, fatigue, and cognitive function between patients with chemotherapy-naïve mCRPC newly initiated on ZYTIGA plus prednisone or enzalutamide (N=211).

Study Design/Methods

- Phase 4, nonrandomized, prospective, multicenter, real-world, observational study
- The decision to prescribe ZYTIGA plus prednisone or enzalutamide was made by the treating physician in accordance with their usual practice.
- **Key inclusion criteria:** patients aged ≥18 years; histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate, and with documented metastatic

disease and castration resistance; initiation of ZYTIGA plus prednisone or enzalutamide for asymptomatic or mildly symptomatic mCRPC after androgen deprivation therapy (ADT) failure
- **Key exclusion criteria:** prior chemotherapy to treat mCRPC; prior chemotherapy/cytotoxic agent to treat metastatic hormone-sensitive prostate cancer in the previous 12 months
- **Primary endpoints:** mean change from baseline in PRO scores and percentage of patients who showed clinically meaningful worsening (CMW) vs improvements/no change in PRO items.
- Medical records were utilized to capture clinical and demographic data. PRO data were collected prospectively using paper questionnaires completed by the patient at baseline and during routine visits to the clinic over 12 months. Questionnaires included the FACT-Cog, Brief Fatigue Inventory-Short Form (BFI-SF), Brief Pain Inventory-Short Form (BPI-SF), and European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30).

Results

Patient Characteristics

- Baseline characteristics were balanced between the ZYTIGA (n=105) and enzalutamide (n=106) groups. The median age was 76 years (ZYTIGA group: interquartile range [IQR], 10.0; enzalutamide group: IQR, 11.0) for both the ZYTIGA and enzalutamide groups. A total of 11 patients in the ZYTIGA group and 8 patients in the enzalutamide group had neurological abnormalities at baseline.
- The overall median completion rate for the 12-month period was 81%.
- The mean overall treatment duration was 38.3 weeks (standard deviation [SD], 17.2) and 38.7 weeks (SD, 18.2) in the ZYTIGA and enzalutamide groups, respectively.

Efficacy

- There were no statistically significant differences between the groups in baseline PRO scores for each item, except for pain interference (BPI-SF), although the difference was not clinically meaningful.
- After treatment initiation, there were statistically significant differences between the ZYTIGA and enzalutamide groups for 18 PRO items ($P<0.05$). When assessed in a different approach (at least three consecutive periods [≥50%] needed to be significant), 9 of the 18 PRO items were statistically significant for the ZYTIGA group when compared to enzalutamide group, of which included: cognitive functioning, fatigue, nausea and vomiting, appetite loss, fatigue right now, usual level of fatigue, worst level of fatigue, perceived cognitive impairments, and comments from others.
    - Of the 9 significant PRO items, significantly fewer patients in the ZYTIGA group vs the enzalutamide group experienced at least one episode of CMW in the following (ZYTIGA group vs enzalutamide group): "perceived cognitive impairments" (49% vs 76%; OR, 0.31; 95% CI, 0.14-0.70; $P=0.005$), "comments from others" (32% vs 62%; OR, 0.14; 95% CI, 0.05-0.39; $P<0.001$]; FACT-Cog), "worst level of fatigue" (53% vs 79%; OR, 0.33; 95% CI, 0.15-0.75; $P=0.008$; BFI-SF), "fatigue" (45% vs 74%; OR, 0.29; 95% CI, 0.14-0.62; $P=0.001$), and "appetite loss" (36% vs 60%; OR, 0.38; 95% CI, 0.17-0.88; $P=0.023$; QLQ-C30).

Safety

- Overall, 69% and 77% of patients in the ZYTIGA and enzalutamide groups, respectively, experienced at least one AE over 12 months.

- At least one serious AE occurred in 23% of patients in the ZYTIGA group and 26% of patients in the enzalutamide group, with 5% and 11% of patients, respectively, with an AE leading to treatment or study termination.
- The most common serious AEs (ZYTIGA group vs enzalutamide group) were: infections and infestations (7% vs 9%) and renal and urinary disorders (5% vs 7%).
- AEs leading to hospitalization occurred in 22% and 24% of patients in the ZYTIGA and enzalutamide groups, respectively.
- Five deaths occurred in the ZYTIGA group and 7 in the enzalutamide group, however, they were not deemed related to treatment.

REAAcT Study

Shore et al (2019)[2] evaluated differences in QoL and tolerability in patients with mCRPC treated with ZYTIGA plus prednisone or enzalutamide (N=100).

Study Design/Methods

- Phase 4, prospective, multicenter, open-label, real-world, observational study
- **Key inclusion criteria:** patients aged ≥18 years; confirmed metastatic adenocarcinoma of the prostate; Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; initiation of ZYTIGA plus prednisone or enzalutamide for mCRPC at the recommended dose per the respective prescribing information
- **Key exclusion criteria:** prior chemotherapy; seizure disorders; dementia; known alcohol or substance abuse; routinely taking medications that cause sedation or confusion
- **Primary endpoints:** change from baseline to month 2 in the Cogstate test, EORTC-QLQ-C30, FACIT-Fatigue, and FACT-Cog; participant or caregiver observational questionnaire at baseline and at month 2[8]
- **Secondary endpoint:** safety[8]

Results

Patient Characteristics

- Patient baseline characteristics were similar in both groups (n=50 each group). The median age was 75 years (range, 61-94) and 74 years (range, 58-92) for the ZYTIGA and enzalutamide groups, respectively. At baseline, approximately 20% of patients in each arm had mild cognitive impairment compared with age-matched controls.
- Almost all patients received prior medication for prostate cancer, with the most commonly reported being endocrine therapy (84% and 96% in the ZYTIGA and enzalutamide groups, respectively).
- The median treatment duration was 2.04 months for patients treated with ZYTIGA plus prednisone and 2.10 months for patients treated with enzalutamide.[9]

Efficacy

- The mean change in FACT total score was 0.22 and -3.34 for the ZYTIGA and enzalutamide groups, respectively.
- The mean changes from baseline for the Cogstate tests, EORTC-QLQ-C30 assessments, and FACT-Cog assessments were similar for both groups and showed no meaningful change over the 2-month period.
- FACIT-Fatigue baseline scores were similar between the groups were similar; however, the mean change from baseline was -0.01 (95% CI, -2.40 to 2.38) and -4.00 (95% CI, -6.61 to -1.39) for the ZYTIGA and enzalutamide groups, respectively, indicating a statistically significant worsening of fatigue with enzalutamide.

- Among patients that demonstrated change from baseline scores at or above the MCID value, 26% and 30% of patients in the ZYTIGA group showed improvement on the FACIT-Fatigue and FACT-Cog assessments, respectively, compared to 14% and 15% of patients in the enzalutamide group. In both groups, 23% of patients had improved scores on EORTC-QLQ-C30 global health assessment.
- A total of 25 and 21 caregivers of patients in the ZYTIGA and enzalutamide groups completed questionnaires, respectively, and there were no major changes observed between baseline and end of the study.

Safety

- AEs were reported in 18 (36%) patients and 26 (52%) patients in the ZYTIGA and enzalutamide groups, respectively.
- Fatigue occurred more frequently in the enzalutamide group vs the ZYTIGA group (26% vs 8%, respectively).
- Dose reductions due to AEs occurred in 6% of patients in the ZYTIGA group and 16% of patients in the enzalutamide group. Dose interruptions due to AEs occurred in 3 patients in each group and drug discontinuations due to AEs occurred in 2 patients in the ZYTIGA group and 1 patient in the enzalutamide group.
- Grade 3/4 AEs and serious AEs were reported in 3 (6%) patients in the ZYTIGA group and 2 (4%) patients in the enzalutamide group.
- Treatment-emergent AEs that occurred in ≥4% of patients in the ZYTIGA group included: fatigue, constipation, decreased appetite, muscular weakness, dizziness, hot flush, hypokalemia, liver function test increased, hyperglycemia, hyponatremia, and dyspnea.
- Cardiorespiratory arrest leading to death was reported in the ZYTIGA group, however, it was not considered drug related.

Additional Analyses

Kvorning Ternov et al (2021)[4] conducted an exploratory analysis of a phase 4 trial (HEAT) that randomized men with mCRPC 1:1 to enzalutamide 160 mg orally daily or ZYTIGA 1000 mg plus prednisone 10 mg orally daily. Patients were grouped according to baseline testosterone levels above, less than, or equal to mean. A total of 166 patients (82 in the enzalutamide group and 84 in the ZYTIGA plus prednisone group) were included in these analyses, and the mean baseline testosterone was 0.35 nmol/L with a median follow-up of 22.3 months. No interaction was found between treatment subgroups in the PSA progression-free survival (PFS) endpoint (P=0.635). Men with baseline testosterone above the mean had a significantly greater PSA response rate compared to men with lower testosterone (≤0.35 nmol/L) in the ZYTIGA plus prednisone subgroup (90% [26/29] vs 64% [35/55], respectively; P=0.011). There was no significant difference observed in PSA response rate in men with baseline testosterone above the mean compared to lower testosterone in the enzalutamide subgroup (92% [34/37] vs 87% [39/45], respectively; P=0.503). Safety results were not reported in this exploratory analysis. **Kvorning Ternov et al (2021)**[7] also evaluated the treatment differences in fatigue and QoL assessed by the FACIT-Fatigue and FACT–Prostate Cancer total scores, respectively. The mean treatment difference in changes between enzalutamide vs ZYTIGA plus prednisone for fatigue and QoL was 3.4 (95% CI, 1.2-5.6; P=0.003) and 4.0 (95% CI, 0.3-7.8; P=0.034), respectively. Metabolic changes were also evaluated, which reported a higher incidence of type 2 diabetes mellitus, a greater increase in HbA1c, weight, and visceral fat mass in patients treated with ZYTIGA than enzalutamide. An additional analysis was conducted evaluating the treatment changes in serum androgens for the HEAT study.[5]

Dearden et al (2019)[6] also reported qualitative and quantitative data related to fatigue, treatment satisfaction, and health-related quality of life in patients with mCRPC receiving treatment with ZYTIGA plus prednisone or enzalutamide (N=152). Patients in the ZYTIGA group (n=78) had a mean BFI score of 2.9 compared to a mean score of 3.6 in the enzalutamide group (n=74). A total of 26 (33%) patients in the ZYTIGA group and 41 (55%) patients in the enzalutamide group reported feeling unusually tired or fatigued in the last week (*P*=0.006). Cancer Therapy Satisfaction Questionnaire domain scores were similar between the two groups. No statistically significant differences between the ZYTIGA and enzalutamide groups in the EuroQol-5-Dimensions 5-Levels (EQ-5D-5L) Utility (*P*=0.253) and visual analog scale (VAS) scores (*P*=0.366) between treatment groups were found. Patients in the ZYTIGA group had a trend towards higher self-reported utility scores and health status (mean scores: 0.84; SD, 0.20 and 70.3; SD, 15.3, respectively) compared to the enzalutamide group (mean scores: 0.80; SD, 0.23 and 67.9; SD, 17.3, respectively). Safety data were not 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 19 September 2023. Summarized in this response are data limited to prospective trials. Indirect comparison studies, retrospective analyses, and meta-analyses have been excluded.

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