ZYTIGA® (abiraterone acetate)
Use of ZYTIGA in Combination With Enzalutamide in Metastatic Castration-Resistant Prostate Cancer

SUMMARY

- In the ALLIANCE A031201 phase 3, randomized, multicenter study, the addition of ZYTIGA plus prednisone to enzalutamide therapy did not prolong survival in men with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) when compared to enzalutamide alone (N=1311). Median overall survival (OS) was 32.7 months (95% confidence interval [CI], 29.9-35.4 months) and 33.6 months (95% CI, 30.5-36.4 months), for the combination compared to single agent therapy, respectively, with two-sided *P*=0.53. The combination also resulted in more adverse events (AEs) than enzalutamide alone. Grade 3 to 5 AEs were reported in 68.8% for the combination group and 55.6% for the single agent group.[1]
- The open-label PLATO study evaluated treatment with enzalutamide once daily (N=509) followed by randomized treatment with ZYTIGA plus prednisone in combination with either enzalutamide or placebo in patients with mCRPC (n=251). The primary study endpoint, progression-free survival (PFS) was not met: median PFS was 5.7 months in the combination group and 5.6 months in the control group (hazard ratio [HR]=0.83; 95% CI, 0.61-1.12; *P*=0.22). There was no statistical difference in secondary end points. The two most common grade ≥3 AEs were hypertension (10% vs 2%) and increased alanine aminotransferase (ALT; 6% vs 2%) or aspartate aminotransferase (AST; 2% vs 0%) were more frequent in the combination group than the control group, respectively.[2]
- In a phase 2, open-label, single-center, interventional study of 60 patients with mCRPC and bone metastases, the use of ZYTIGA plus prednisone in combination with enzalutamide reported maximal prostate-specific antigen (PSA) decline of ≥30%, ≥50%, and ≥90% in 87%, 77%, and 48% of evaluable patients, respectively. A 23% decrease in the minimum blood plasma concentration (C_{min}) was achieved in the combination group versus ZYTIGA only group. Grade 3 AEs included hypertension (n=10), ALT increase (n=7), alkaline phosphatase (ALP) increase (n=3), arthralgia (n=3), AST increase (n=2), bone pain (n=2), lymphocyte count decrease (n=2), hypokalemia (n=2), and syncope (n=2). No grade 5 AEs or deaths were reported.[3]

CLINICAL DATA

Morris et al (2019)[1] evaluated the combination of ZYTIGA plus prednisone and enzalutamide versus enzalutamide alone in patients with chemotherapy naïve mCRPC (N=1311).

Study Design/Methods

- Phase 3, randomized, multicenter study (ALLIANCE A031201, NCT01949337)
- Patients were randomized 1:1 to receive either ZYTIGA plus prednisone and enzalutamide (n=654) or enzalutamide alone (n=657) at standard FDA-approved doses.
- Patients also maintained castration therapy.
- Men with progressive mCRPC by Prostate Cancer Working Group 2 criteria who had not previously received ZYTIGA nor enzalutamide were eligible. Exclusion criteria also included prior treatment with taxanes for mCRPC.
- Patients were stratified by prior chemotherapy and Halabi prognostic three risk groups.
- **Primary endpoint**: OS (defined as the date of randomization from date of death or last follow-up)
- **Secondary endpoints**: radiographic PFS (rPFS) and PSA declines during treatment
- **Exploratory endpoints**: imaging changes and changes in serum biomarkers such as androgens, angiokines, and circulating microRNA and RNA.

Results

Patient Characteristics

- Groups were well balanced between arms, including stratification variables: 15.6% of patients were high risk, 35.3% intermediate risk, and 48.1% low risk.

Efficacy

- Median OS was 32.7 months (95% CI, 29.9-35.4 months) and 33.6 months (95% CI, 30.5-36.4 months), for the combination compared to single agent therapy, respectively, with two-sided *P*=0.53.
- Fifty percent PSA decline rate was 76.5% in the combination group vs 80% in the single agent group.

Safety

- Grade 3 to 5 AEs were 68.8% for the combination group and 55.6% for the single agent group.
- Treatment discontinuation due to AEs occurred in 12% and 5%; patient withdrawal in 13% and 5%; and progression or death in 48% and 57% of patients in the combination group compared to the single agent group, respectively.

Attard et al (2018)[2] studied the combination of ZYTIGA plus prednisone with enzalutamide compared to ZYTIGA plus prednisone with placebo following enzalutamide therapy in patients with chemotherapy naïve mCRPC (n=251).

Study Design/Methods

- Randomized, two-stage, open-label study (PLATO, NCT01995513)
- Patients received enzalutamide 160 mg once daily (period 1; N=509) followed by randomized treatment with ZYTIGA 1,000 mg plus prednisone 5 mg orally twice daily in combination with either enzalutamide or placebo (period 2; n=251).
- Men with no PSA increase from baseline at weeks 13 and 21 in period 1 continued treatment until PSA progression (defined as a ≥25% increase and ≥2 ng/mL above nadir that required confirmation by a second consecutive PSA assessment ≥3 weeks later) and then randomized 1:1 in period two to receive open-label ZYTIGA 1,000 mg orally once daily and prednisone 5 mg orally twice daily in combination with enzalutamide 160 mg daily (n=126) or placebo (n=125).
- Patients were stratified by PSA ≥30% decline at period one week 13 (0-29% vs ≥30%).
- **Primary endpoint:** PFS (defined as radiographic or unequivocal clinical progression or death during study)
- **Secondary endpoints:** time to PSA progression, PSA response of ≥50%, PSA response of ≥30%, rate of pain progression, objective response rate, time to first use of subsequent antineoplastic therapy, time to degradation of Functional Assessment of Cancer Therapy-Prostate (FACT-P) score, and safety (period 2)

Results

Patient Characteristics

- Period 2 key baseline and disease characteristics are described in Table: Baseline Patient and Disease Characteristics.

Baseline Patient and Disease Characteristics[2]

	Combination Group n=126	Control Group n=125
Age, median (years) IQR	72 67.0-77.0	71 65.0-77.0
ECOG PS, n (%)		
0	79 (63)	84 (67)
1	47 (37)	41 (33)
PSA, median (µg/L)	14.4	11.0
Testosterone, median (nmol/L)	1.2	1.2
Distribution of disease, n (%)		
Bone	113 (90)	112 (90)
Lymph node	52 (41)	56 (45)
Visceral disease, lung/liver	8 (6)	5 (4)
Other soft tissue	13 (10)	15 (12)
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PS, performance status; PSA, prostate-specific antigen.		

Efficacy

- Median treatment duration in period 2 was 5.6 months for both groups.
- Median PFS was 5.7 and 5.6 months for the combination and control groups, respectively (HR=0.83; 95% CI, 0.61-1.12; *P*=0.22).
- Because the primary endpoint of PFS was not met, all analyses of secondary endpoints were exploratory. There was no difference in the secondary endpoints:
  - Median time to PSA progression was 2.8 months for both groups (HR=0.87; 95% CI, 0.62-1.24; *P*=0.45).
  - One (1%) of 124 patients in the combination group and 3 (2%) of 122 patients in the control group had a confirmed reduction in baseline PSA of ≥50%.
  - There was no difference in median time to degradation of FACT-P score (4.6 months [95% CI, 3.7-6.5 months] for the combination group vs 6.4 months [95% CI,
    5.5-13.9 months] for the control group; HR=1.40; 95% CI, 0.97-2.03; *P*=0.07).
  - There was also no difference between the two groups with regard to rate of pain progression, objective response rate, or time to first use of subsequent antineoplastic therapy.

Safety

- In period 2, 102 (41%) of 249 patients had ≥1 grade ≥3 adverse event (56 [45%] in the combination group; 46 [37%] in the control group). The 2 most common grade ≥3 events were hypertension and a rise in ALT in 12 (10%) and 7 patients (6%) in the combination group, respectively, and in 2 (2%) and 3 patients (2%) in the control group respectively.
- Eleven patients (9%) in the combination group and 5 patients (4%) in the control group had an adverse event that was the primary reason for discontinuation of enzalutamide or placebo.
- Twelve patients (10%) receiving the combination and 4 patients (3%) in the control group had an AE that was the primary reason for discontinuation of ZYTIGA. Nineteen patients (8%) had an AE leading to ZYTIGA dose reduction (11 [9%] receiving the combination; 8 [6%] in the control group), and 60 patients (24%) had an AE leading to temporary interruption of ZYTIGA (37 [30%] receiving the combination; 23 [19%] in the control group).

Efstathiou et al (2020)[3] evaluated the effects of ZYTIGA plus prednisone in combination with enzalutamide in patients with bone mCRPC (N=60).

Study Design/Methods

- Phase 2, open-label, single-center, interventional study.
- Patients in the study had progressive bone mCRPC and castrate level serum testosterone (≤50 ng/dL).
- Patients received ZYTIGA 1000 mg orally (PO) once daily plus prednisone 5 mg PO twice daily in combination with enzalutamide 160 mg PO once daily.
- Patients underwent disease evaluations with bone marrow biopsy or bone marrow aspirate performed every 3 cycles. Optional pharmacokinetic blood draws for ZYTIGA were performed on cycle (C) 1 on day (D) 4 and C2D1 whereas blood draws were performed on C3D1 for enzalutamide.
- Immunohistochemistry and liquid chromatography mass spectrometry (blood and bone marrow) were used to classify patient tumors and assess metabolite concentrations.
- **Primary endpoint:** safety and tolerability
- **Secondary endpoints:** PSA decline from baseline (≥30%, ≥50%, and ≥90%) and PFS (time from treatment initiation until progression, study withdrawal, or death), changes in AR signaling.
- **Exploratory endpoints:** drug-drug interactions based on plasma concentrations of enzalutamide, the M2 metabolite of enzalutamide, and ZYTIGA; nuclear expression of AR as well as other biomarkers.

Results

Patient Characteristics

- Median age: 66 years (range, 40-82 years)
- Eastern Cooperative Oncology Group performance status: 0 (35%), 1 (58.3%), and 2 (6.7%)
- Median baseline PSA: 20.7 ng/mL (range, 1-670.2 ng/mL)
- Gleason score at initial diagnosis: ≤7 (23.3%), 8-10 (65%)
- Disease distribution at screening: 60 patients (100%) had bone lesions, 10 patients (16.7%) had lymph node lesions, and 6 patients (10%) had visceral metastases.

Safety

- The most commonly occurring any-grade AEs (≥40% incidence) were fatigue (72%), hyperglycemia (67%), increased ALP (53%), and hot flush (43%).
- Grade 3 AEs that occurred in more than one patient included hypertension (n=10), ALT increase (n=7), ALP increase (n=3), arthralgia (n=3), AST increase (n=2), bone pain (n=2), lymphocyte count decrease (n=2), hypokalemia (n=2), and syncope (n=2).
- There were no grade 5 AEs or deaths reported.
- Median time to treatment discontinuation was 312 days (95% CI, 196.0-483.0; range, 0-1134 days).
- A total of 49 patients discontinued treatment due to progressive disease (n=41), PSA progression (n=3), AE (n=1), and other (n=3).[4]

Efficacy

Median PFS and Changes in PSA Levels

- Median PFS was 251 days (95% CI, 147-337 days).
- Data on evaluable patients; PSA changes for 60 patients:
  - Maximum PSA decline ≥30%: 87% (n=52)
  - Maximum PSA decline ≥50%: 77% (n=46)

- Maximum PSA decline ≥90%: 48% (n=29)
- PSA levels did not decrease in 6 (10%) patients.

Changes in Plasma and Bone Marrow Testosterone and Androstenedione

- Baseline and week 9 outcomes for testosterone and androstenedione plasma and bone marrow levels are reported in Table: Testosterone and Androstenedione Plasma and Bone Marrow Concentrations at Baseline and Week 9.

Testosterone and Androstenedione Plasma and Bone Marrow Concentrations at Baseline and Week 9[3]

Parameter	Testosterone (n=60)		Androstenedione (n=60)	
	Baseline	Week 9	Baseline	Week 9
Median plasma level, pg/mL (range)	17.8 (1.0-382.4)	1.0 (1.0-8.1)	29.6 (1.0-185.3)	1.0 (0.4-13.1)
Median bone marrow level, pg/mL (range)	14.1 (1.0-473.2)	1.0 (1.0-4.9)	31.9 (1.0-290.4)	1.0 (1.0-494.1)

Pharmacokinetics

- The least squares mean C_{min} for ZYTIGA in the enzalutamide plus ZYTIGA group was 37.9 ng/mL (range, 14.09-200.5 ng/mL) at steady state on C2D1 compared to 48.8 ng/mL (range, 14.39-172.22 ng/mL) when ZYTIGA was administered alone on C1D4 demonstrating a 23% decrease in the ZYTIGA C_{min} for the combination group.

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 14 March 2025. Summarized in this response are relevant data from prospective studies evaluating the combination of enzalutamide and ZYTIGA in mCRPC. Case reports, observational studies, and review articles have been excluded.

REFERENCES

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3. Efstathiou E, Titus M, Wen S, et al. Enzalutamide in combination with abiraterone acetate in bone metastatic castration-resistant prostate cancer patients. *Eur Urol Oncol*. 2020;3(1):119-127.

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