ZYTIGA® (abiraterone acetate)
Sequencing of ZYTIGA with Enzalutamide in Metastatic Castration-Resistant Prostate Cancer

SUMMARY

- There are limited prospective, randomized clinical study data regarding optimal sequencing strategies for ZYTIGA plus prednisone and enzalutamide in the treatment of metastatic castration-resistant prostate cancer (mCRPC).
- A phase 2, randomized, multicenter, open-label study included patients with treatment-naïve mCRPC who received ZYTIGA plus prednisone (group A) or enzalutamide (group B) as first-line therapy, with crossover to the alternate therapy at prostate-specific antigen (PSA) progression (N=202). Primary endpoints were time to second PSA progression (TT2P) and PSA response (≥30% decline from baseline) for second-line therapy. At the time of data cutoff, 72% of patients in group A and 74% of patients in group B had crossed over. TT2P was longer in group A than in group B (median 19.3 months vs 15.2 months, respectively; hazard ratio [HR]=0.66; 95% confidence interval [CI], 0.45–0.97; *P*=0.036) with a median follow-up of 22.8 months. PSA responses to second-line therapy were seen in 26/73 (36%) patients for enzalutamide and 3/75 (4%) for ZYTIGA (X^2 $P<0.0001$).[1] There was no difference in time to quality of life (QoL) deterioration between the two treatment sequences based on Functional Assessment of Cancer Therapy-Prostate (FACT-P) scoring; however, enzalutamide was associated with worse physical well-being (PWB) QoL scores.[2] Baseline pathogenic circulating tumor (ct)DNA alterations in androgen receptor (AR), TP53, RB1, BRCA2, and ATM genes were also evaluated.[3, 4] The most common grade 3–4 adverse events (AEs) for the entire study were hypertension (27/101 [27%] patients in group A vs 18/101 [18%] patients in group B) and fatigue (6 [10%] vs 4 [4%], respectively). Serious AEs were reported in 15/101 (15%) patients in group A and 20/101 (20%) in group B. There were no treatment-related deaths.[1]
- A phase 2 study reported interim analysis results in patients with mCRPC evaluating the use of 3 consecutive treatment modules, each lasting 12 weeks: ZYTIGA plus prednisone; cabazitaxel plus carboplatin; enzalutamide plus radium-223 (in those with bone metastases).[5, 6]
- A phase 4 study reported the efficacy and safety of enzalutamide in patients with progressing mCRPC, who were previously treated with ZYTIGA plus prednisone.[7]

BACKGROUND

Although the mechanisms of action for abiraterone acetate and enzalutamide are different, cross-resistance has been hypothesized due to lower response rates reported in retrospective studies for either agent given in the third-line setting for mCRPC in patients who previously received docetaxel. Prospective, randomized clinical studies are needed to identify which patients may respond to either sequential therapy in this setting.[8, 9]

CLINICAL DATA

Phase 2 Crossover Study

Khalaf et al (2019)[1] prospectively evaluated sequencing of ZYTIGA plus prednisone vs enzalutamide, with crossover at PSA progression, for treatment-naïve patients with mCRPC (N=202).

Study Design/Methods

- Phase 2, randomized, multicenter, open-label, crossover study (NCT02125357).
- Patients were initially randomized 1:1 to 1 of 2 treatment arms. Patients in group A (n=101) received ZYTIGA 1,000 mg orally (PO) once daily plus prednisone 5 mg PO twice daily as first study treatment until confirmed PSA progression, wide-field radiotherapy of symptomatic bone metastases, unacceptable treatment-related toxicity, or withdrawal of consent. They then crossed over to receive enzalutamide 160 mg PO once daily until symptomatic or clinical progression, unacceptable treatment-related toxicity, or withdrawal of consent. Patients in group B (n=101) received the opposite sequence of initial enzalutamide followed by ZYTIGA plus prednisone. If a patient no longer met study eligibility criteria at crossover, he was removed from the study.
- All patients received a gonadotropin releasing hormone (GnRH) analog or had previous bilateral orchiectomy.
- FACT-P questionnaires were completed at baseline, crossover, and every 4 weeks on treatment for QoL assessment.[2]
- **Primary endpoints:** TT2P (defined as the time from start of first-line therapy to confirmed PSA progression on second-line therapy, or death from prostate cancer before crossover, whichever occurred first) and PSA response (defined as ≥30% decline from baseline) for second-line therapy
- **Secondary endpoints:** proportion of patients with PSA response on first-line therapy; time to PSA progression (TTPP) on first-line therapy; TTPP on second-line therapy; overall survival (OS); time on treatment for second-line therapy; time to clinical progression on second-line therapy; safety of second-line ZYTIGA plus prednisone and enzalutamide; change in Montreal Cognitive Assessment score while receiving first-line and second-line therapy; and correlation of cell-free DNA biomarkers with PSA response after first-line and second-line treatment.

Results

Patient Characteristics

- A summary of clinical characteristics is included in Table: Patient Clinical Characteristics at Baseline and Crossover.

Patient Clinical Characteristics at Baseline and Crossover[1]

	Baseline		Crossover	
	Group A (n=101)	**Group B (n=101)**	**Group A (n=73)**	**Group B (n=75)**
Median age, years (range)	72.9 (51.3-93.3)	77.6 (49.3-94.1)	73.8 (51.5-92.7)	78.0 (49.8-93.2)
Median PSA, ng/mL (range)	35.0 (2.2-2817.0)	37.0 (1.7-1060.0)	16.0 (0.8-991.0)	12.0 (0.20-1604.0)
Median alkaline phosphatase[a] (range)	0.82 (0.29-12.50)	0.75 (0.30-47.80)	0.88 (0.31-6.87)	0.75 (0.31-4.67)
Median lactate dehydrogenase[a,b] (range)	0.79 (0.37-4.00)	0.80 (0.31-12.90)	0.85 (0.22-4.69)	0.74 (0.38-2.46)
Hemoglobin, g/L	130 (89-155)	130 (89-165)	132 (87-152)	129 (79-157)
ECOG PS 0-1, n (%)	89 (88)	79 (78)	62 (85)	57 (76)
Prior docetaxel, n (%)	5 (5)	6 (6)	-	-
Bone metastases, n (%)	85 (84)	82 (81)	61 (84)	65 (87)
Lung metastases, n (%)	8 (8)	9 (9)	6 (8)	7 (9)
Liver metastases, n (%)	5 (5)	7 (7)	4 (5)	7 (9)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PSA, prostate-specific antigen; ULN, upper limit of normal.
Group A: ZYTIGA plus prednisone followed by enzalutamide.
Group B: enzalutamide followed by ZYTIGA plus prednisone.
[a]Relative to ULN.
[b]At crossover, median lactate dehydrogenase levels were higher in Group A than in Group B (*P*=0.0008; post-hoc analysis).

Efficacy

- The median follow-up after second-line therapy was 30.7 months. Outcomes are summarized in Table: Response to Second-line Therapy.
- At the time of data cutoff, 72% of patients from group A had crossed over to receive enzalutamide and 74% of patients from group B had crossed over to receive ZYTIGA plus prednisone; 142 patients had disease progression on second-line therapy or had died of prostate cancer before crossover.
- Seventeen (17%) patients in each group discontinued therapy without crossing over. No patients were lost to follow-up before crossover.
- A large proportion of patients had delayed crossover (79% of patients in each group), defined as initiation of second-line therapy >2 weeks from the date of confirmed progression; however, in a post-hoc analysis, times from progression to crossover did not differ significantly between groups (median 39 days vs 36 days; *P*=0.60).
- TT2P was longer in group A than in group B (median 19.3 months vs 15.2 months; HR=0.66; 95% CI, 0.45–0.97; *P*=0.036) with a median follow-up of 22.8 months. This difference between the groups was confirmed by the second primary endpoint: PSA responses to second-line therapy were seen in 26/73 (36%) patients in group A and 3/75 (4%) patients in group B (*P*<0.0001 as a post-hoc statistical analysis).
- Between trial start and data cutoff, there were 48 deaths in group A and 58 in group B. At a median follow-up for OS of 30.7 months, median OS was 28.8 months vs 24.7 months; HR=0.79, 95% CI, 0.54–1.16; *P*=0.23).
- For first-line therapy, PSA responses were seen in 68% of 101 patients who received ZYTIGA plus prednisone and 82% of 101 patients who received enzalutamide (χ^2 *P*=0.023). However, there was no significant difference between first-line ZYTIGA plus prednisone and first-line enzalutamide for TTPP (median 11.2 months vs 10.2 months; HR=0.95; 95% CI, 0.66–1.36; *P*=0.78) after a median follow-up of 21.6 months.
- In the patient population that crossed over to second-line therapy, second-line enzalutamide was better than second-line ZYTIGA plus prednisone for both TTPP on second-line therapy (median 3.5 months vs 1.7 months; HR=0.42; 95% CI, 0.28–0.65; *P*<0.0001) and time on second-line treatment (median 4.6 months vs 3.6 months; HR=0.66; 95% CI, 0.46–0.94, *P*=0.023). Median follow-up for these endpoints was 3.9 months and 19.4 months, respectively.
- The prespecified secondary endpoint of time to clinical progression on second-line treatment was not evaluated because full discretion was given to local study investigators to continue second-line treatment beyond PSA progression until there was no clinical benefit to continuation, per standard practice; therefore, the authors were concerned the endpoint was subject to individual physician decision-making variability.

Response to Second-line Therapy[1]

Response Measure	Group A	Group B	*P*-Value	HR (95% CI)
Primary Endpoints				
TT2P, months	19.3	15.2	0.036	0.66 (0.45-0.97)
PSA response, n/N (%)	26/73 (36)	3/75 (4)	<0.0001	NR
Key Secondary Endpoints				
Median TTPP, months	3.5	1.7	<0.0001	0.42 (0.28-0.65)

Median OS, months	28.8	24.7	0.23	0.79 (0.54-1.16)

Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; PSA, prostate-specific antigen; TT2P, time to second PSA progression; TTPP, time to PSA progression.
Group A: ZYTIGA plus prednisone followed by enzalutamide.
Group B: enzalutamide followed by ZYTIGA plus prednisone.

Post-Hoc and Uni/Multivariate Analyses

- After a median follow-up of 16.5 months, a post-hoc analysis showed that time to progression of second-line therapy for patients who crossed over was longer for those who received second-line enzalutamide than second-line ZYTIGA plus prednisone (median 2.7 months vs 1.7 months; HR=0.43; 95% CI, 0.20–0.61, *P*<0.0001).[1]
- After a median follow-up of 27.2 months, another post-hoc analysis of time to any progression on first-line therapy showed no difference between groups A and B (7.9 months vs 7.3 months; HR=0.95; 95% CI, 0.70-1.29, *P*=0.74).[1]
- In an additional post-hoc analysis, the time from start of first-line therapy to progression of any kind with second-line therapy was longer in group A than in group B (median 15.0 months vs 10.3 months; HR=0.69; 95% CI, 0.50–0.96; *P*=0.029).[1]
- The proportion of patients with QoL deterioration for total FACT-P score and FACT-P subscores from baseline to week 12 of 1st and 2nd line treatment was compared between arms using the χ^2 test. There was no difference in time to QoL deterioration between the two treatment sequences based on FACT-P scoring (for the entire sequence group A vs B: 10.5 months vs 10.8 months; *P*=0.74); however, enzalutamide was associated with worse PWB QoL scores. PWB scores for first-line group A vs group B: 26 vs 40; *P*=0.036; PWB scores for second-line group A vs group B: 45 vs 29; *P*=0.030).[2]
- Baseline (first-line) pathogenic ctDNA alterations in androgen receptor (AR), *TP53*, *RB1*, *BRCA2*, and *ATM* genes were associated with a shorter TTPP as described in Table: Univariate Analysis of ctDNA Biomarkers: First-line Therapy.[3]

Univariate Analysis of ctDNA Biomarkers: First-line Therapy[3]

ctDNA	Altered vs Not Altered TTPP HR (95% CI)	*P*-Value
DNA repair[a]	4.13 (2.55-6.68)	<0.001
TP53[b]	2.84 (1.90-4.23)	<0.001
AR	2.04 (1.39-3.00)	<0.001
RB1	1.96 (1.28-3.00)	0.002

Abbreviations: AR, androgen receptor; CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; TTPP, time to PSA progression.
[a]*BRCA2/ATM* alterations remained significant, HR=2.68 (95% CI, 1.58-4.54).
[b]*TP53* alterations remained significant, HR=2.54 (95% CI, 1.55-4.19).

- On multivariate analysis including clinical factors, *TP53* and *BRCA2/ATM* alterations remained significant (HR=2.54; 95% CI, 1.55-4.19 and HR=2.68; 95% CI, 1.58-4.54). Patients with a PSA increase as best response were enriched for alterations in DNA repair (*P*<0.001), *TP53* (*P*=0.005), *RB1* (*P*=0.04), and in 1 patient, a genomically truncated AR.[3]
- On multivariate analysis, factors associated with TT2P were bone metastases (HR=2.22; 95% CI, 1.08-4.54), liver metastases (HR=3.18; 95% CI, 1.21-8.41), and treatment group A vs B (HR=0.27; 95% CI, 0.17-0.40). At progression, *AR* gene copy number increased in 14% of evaluable patients (7/49) and *AR* L702H/T878A(S) mutations were present in 8% of patients.[4]

Safety

- The most common grade 3-4 AEs for the entire study were hypertension (27% of 101 patients in group A vs 18% of 101 patients in group B) and fatigue (6 [10%] vs 4 [4%], respectively).
- Serious AEs were reported in 15% of 101 patients in group A and 20% of 101 patients in group B. There were no treatment-related deaths.
- For first-line therapy, 6% of 101 patients required a dose reduction for ZYTIGA compared to 18% of 101 for enzalutamide. For second-line therapy, 14/73 (19%) patients required a dose reduction for enzalutamide compared with 4/75 (5%) patients for ZYTIGA.

Prospective, Single-Arm Studies

Liaw et al (2021)[5, 6] conducted a phase 2, open-label study (NCT02903160) to evaluate the use of 3 consecutive treatment modules in patients with mCRPC, each lasting 12 weeks (N=31): ZYTIGA 1000 mg PO once daily plus prednisone 5 mg PO twice daily; cabazitaxel 20 mg/m^2 intravenously (IV) plus carboplatin AUC 4 IV every 3 weeks; enzalutamide 160 mg PO once daily plus radium-223 55 kBq/kg IV every 4 weeks (in those with bone metastases). Upon completion of the 9-month study regimen, patients continued ADT alone. The primary endpoint was time to progression. Secondary endpoints were PSA response (>90%, >50%) with each module and changes to alkaline phosphatase (ALP) levels.

In the interim analysis of the efficacy endpoints, the median follow-up time was 20.7 months and the median TTPP was 3.8 months (95% CI, 2.1-6.3). Of the patients with bone metastasis and elevated ALP levels at baseline (9/31), 78% had normalization of ALP upon completion of study regimen. Five of 31 patients (16%) were able to be maintained on ADT alone for over a year during the post-study surveillance period: 3 patients were subsequently restarted on a mCRPC agent at time of disease progression, 2 patients demonstrate sustained disease control and remain on ADT alone. Baseline clinical features shared by the 5 patients included PSA of <10 ng/mL and normal ALP levels (<126 IU/L). PSA response rate results are provided in Table: PSA Response Rates Compared to Baseline by Treatment Module.

PSA Response Rates Compared to Baseline by Treatment Module[5]

	Module 1 ZYTIGA	Module 2 Cabazitaxel + Carboplatin	Module 3 Enzalutamide + Radium-223
>90% PSA Reduction	35.5%	41.9%	58.1%
>50% PSA Reduction	83.9%	87.1%	96.8%
Stable Disease	9.7%	9.7%	0%
Progression	6.5%	3.2%	3.2%
Abbreviation: PSA, prostate-specific antigen.			

De Bono et al (2017)[7] evaluated the efficacy and safety of enzalutamide in patients with progressing mCRPC, who were previously treated with ZYTIGA plus prednisone in a phase 4, multicenter, open-label study (N=215; NCT02116582). The primary endpoint was radiographic progression-free survival (rPFS), and secondary endpoints were OS, PSA response, and TTPP. The median duration of ZYTIGA therapy was 54 weeks, and the median duration of enzalutamide therapy was 5.7 months. Median rPFS was 8.1 months (95% CI, 6.1-8.3) and median OS was not reached in the total population. The most common treatment-emergent AEs included fatigue (32%), decreased appetite (25%), asthenia (18%), back pain (17%), and arthralgia (16%).

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 24 May 2023. Summarized in this response are relevant data limited to prospective clinical trials.

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