ZYTIGA® (abiraterone acetate)
ZYTIGA - Use of ZYTIGA in Combination with Docetaxel for the Treatment of Metastatic Castration-Resistant Prostate Cancer (mCRPC)

SUMMARY

- A phase 2, randomized, 2-stage, open-label study of ZYTIGA 1,000 mg orally daily plus prednisone 5 mg twice daily (BID) in combination with docetaxel 75 mg/m^2 intravenously (IV) every three weeks (Q3W; arm A) vs docetaxel monotherapy plus prednisone (arm B) for the treatment of chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (mCRPC) progressing after ZYTIGA plus prednisone therapy noted no statistically significant differences in efficacy outcomes (n=88). Median radiographic progression-free survival (rPFS), the primary study endpoint, was 11.4 months vs 10.5 months in arms A and B, respectively. The most common grade 3-4 toxicities in arms A and B, respectively, included: neutropenia (57% vs 29%; *P*=0.027), febrile neutropenia (17% vs 10%), diarrhea (9% vs 7%), and asthenia (11% vs 10%).[1, 2]
- A phase 1b, open-label, dose-escalation study evaluated the maximum safe dose combination of ZYTIGA plus prednisone and docetaxel in chemotherapy-naïve patients with mCRPC (N=22). The recommended phase 2 dose was found to be docetaxel 75 mg/m^2 IV plus ZYTIGA 1,000 mg daily plus prednisone 10 mg daily. Dose-limiting toxicities (DLTs) observed with this dose combination included grade 3 hematuria and neutropenia with fever identified in one patient (who had preexisting hematuria) of the 6 included in this cohort. Efficacy outcomes were pooled (n=21). A decline from baseline in prostate-specific antigen (PSA) of ≥50% and ≥90% was observed for 85.7% and 66.7% of patients, respectively. At a median follow-up of 14.5 months, 8 patients had PSA progression and 6 had radiographic progression or died. Systemic exposure was comparable for docetaxel and ZYTIGA when given alone or in combination.[3]

CLINICAL DATA

Phase 2 Study

Duran et al (2020)[1] **and Puente et al (2018)**[2] evaluated the safety and efficacy of ZYTIGA plus prednisone in combination with docetaxel vs docetaxel plus prednisone for the treatment of chemotherapy-naïve patients with mCRPC progressing after ZYTIGA plus prednisone (N=148).

Study Design/Methods

- Phase 2, randomized, open-label, multicenter study in Spain (ABIDO-SOGUG trial; NCT02036060)
- Study consists of 2 stages:
  - Stage 1: patients received ZYTIGA 1,000 mg daily plus prednisone 5 mg BID until radiological or unequivocal clinical progression.[2]
  - Stage 2: upon progression, patients were randomized to receive docetaxel 75 mg/m^2 IV Q3W in combination with ZYTIGA 1,000 mg daily plus prednisone (arm A) or without ZYTIGA (arm B)
- **Primary endpoint:** rPFS
- **Secondary endpoints:** radiological response (RR), overall survival (OS), PSA response, PSA-PFS, and safety
- Inclusion criteria: chemotherapy-naïve mCRPC; no visceral metastases; Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1; serum testosterone <50 ng/dL; and adequate hematologic, hepatic, and renal function.[2]

Results

Patient Characteristics

- Stage 2 included 88 randomized patients (arm A, n=46 and arm B, n=42) who were evaluable for efficacy and safety.
- Median age was 69 years and ECOG PS was 0 in 43% of patients.
- Metastases included: bone (91%), liver (11%), and lung (5%).

Efficacy

- No statistically significant differences were noted in efficacy evaluations. Median rPFS was 11.4 months vs 10.5 months; and 12 month rPFS was 43% vs 45% in arms A and B, respectively.
- Median PSA-PFS was 6.2 months vs 5.5 months and median OS was 17.3 months vs 16.9 months in arms A and B, respectively.
- Twenty-four (52%) patients in arm A and 19 (46%) patients in arm B achieved a ≥50% PSA response.
- RR was achieved in 15% vs 7% of patients in arms A and B, respectively; and disease control rate was 74% in both arms.

Safety

- The median dose intensity for docetaxel was 86% and 90% for arms A and B, respectively, and 91% for ZYTIGA.
- Eleven patients discontinued treatment due to non-hematological toxicity (arm A, n=5 and arm B, n=6).
- The most common grade 3-4 toxicities in arms A and B, respectively, included: neutropenia (57% vs 29%; *P*=0.027), febrile neutropenia (17% vs 10%), diarrhea (9% vs 7%), and asthenia (11% vs 10%).

Phase 1b Study

Tagawa et al (2016)[3] conducted a study to determine the safe dose combination of docetaxel and ZYTIGA plus prednisone in 3 cohorts of patients with chemotherapy-naïve mCRPC (N=22).

Study Design/Methods

- Phase 1b, open-label, dose-escalation study (COU-AA-206)
- Patients ≥18 years of age were eligible for enrollment if they had the following:
  - Histologically or cytologically confirmed prostate cancer
  - PSA progression according to Prostate Cancer Working Group 2 criteria or objective radiographic progression according to modified Response Evaluation Criteria in Solid Tumors (RECIST) or bone scans
  - ECOG PS ≤2
  - Adequate hematologic and biochemical indices
  - Medical or surgical castration (testosterone <50 ng/dL)
- Up to 4 cohorts could receive escalating doses of the combination therapy.
  - Cohort 1: docetaxel 60 mg/m^2 plus ZYTIGA 500 mg
  - Cohort 2: docetaxel 75 mg/m^2 plus ZYTIGA 500 mg
  - Cohort 3: docetaxel 75 mg/m^2 plus ZYTIGA 1,000 mg
  - Cohort 4 (if necessary): docetaxel 60 mg/m^2 plus ZYTIGA 1,000 mg
  - Docetaxel was administered every 3 weeks along with prednisone 5 mg orally twice daily; ZYTIGA was initiated 1 week following study initiation.

- **Primary endpoint:** proportion of patients with a DLT between weeks 2 and 7, defined as follows:
  - Nonhematologic toxicity ≥grade 3
  - Grade 4 neutropenia for greater than 7 days (or febrile neutropenia)
  - Grade 4 thrombocytopenia
  - Other intolerable toxicity
- Patients were permitted to discontinue docetaxel (due to toxicity or at investigator discretion) following DLT assessment and continue ZYTIGA plus prednisone until disease progression.
- The recommended phase 2 dose was the highest dose of ZYTIGA plus prednisone and docetaxel at which ≤2 of 6 patients experienced a DLT.
- Concentration-time data were used to estimate pharmacokinetic parameters.
- **Secondary endpoints:** best change from baseline in PSA; time to PSA progression; best overall response; objective response rate (ORR); time to rPFS; assessment of the effect of steady-state abiraterone acetate on docetaxel pharmacokinetics and vice versa

Results

Patient Characteristics

- Data have been published for cohorts 1 (n=7), 2 (n=8), and 3 (n=7). See Table: Baseline Characteristics for Patients in Cohorts 1, 2, and 3.
- During the first week, 2 patients were replaced due to docetaxel toxicity.

Baseline Characteristics for Patients in Cohorts 1, 2, and 3[3]

Baseline Characteristic	Cohort 1 (n=7)	Cohort 2 (n=8)	Cohort 3 (n=7)
ECOG PS, n (%) 0 1 2	 4 (57.1) 2 (28.6) 1 (14.3)	 2 (25.0) 6 (75.0) 0	 2 (28.6) 4 (57.1) 1 (14.3)
PSA, µg/mL, median (IQR)	85.2 (8.2-141.63)	33.0 (10.1-50.9)	10.0 (2.5-98.9)
Gleason score ≥8, n (%)	2 of 6 (33.3)	6 of 8 (75.0)	5 of 7 (71.4)
Bone lesions, n (%)	7 (100)	7 (87.5)	6 (85.7)
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; PSA, prostate-specific antigen.			

Safety

- The median duration of docetaxel treatment exposure was 8 cycles (range, 4-12), 9.5 cycles (range, 1-12), and 6.1 cycles (range, 1-9) for cohorts 1, 2, and 3, respectively.
- The median duration of ZYTIGA plus prednisone treatment exposure was 14.6 months (range, 7.8-23.2), 15.5 months (range, 3.0-19.1), and 4.7 months (range, 1.4-7.6) for cohorts 1, 2, and 3, respectively.
- At data cutoff, 12 patients (55%) remained on treatment.
- Of the 22 treated patients, 18 were evaluable for DLT assessment.
- DLTs observed included the following: syncope and hypertension in cohort 1; grade 4 neutropenia in 1 patient in cohort 2; and grade 3 hematuria during admission for elective cystolitholapaxy for preexisting hematuria with subsequent fever during neutropenia in 1 patient in cohort 3.
- The combination dose received by cohort 3 (docetaxel 75 mg/m^2 plus ZYTIGA 1,000 mg plus prednisone 10 mg) was found to be the recommended phase 2 dose, and, therefore, cohort 4 was not enrolled.

- Grade 3-4 adverse events (AEs) were reported in 21 (95.5%) of the 22 treated patients.
- Based on investigator assessment, of these 21 patients, all had AEs related to docetaxel, 11 (52.3%) had AEs related to ZYTIGA plus prednisone, and 18 (85.7%) had AEs related to prednisone.
- The most common grade 3-4 AEs included neutropenia (77.2%), leukopenia (45.5%), febrile neutropenia (31.8%), back pain (9.1%), and hypertension (9.1%).
- Of the 13 patients that experienced serious AEs, 11 had drug-related serious AEs (6 were related to ZYTIGA plus prednisone; 3 related to prednisone; and 10 related to docetaxel).

Efficacy

- In the pooled population of patients (from cohorts 1, 2, and 3) with postbaseline PSA data (n=21), 66.7% (n=14) of patients had ≥90% PSA decline from baseline and 85.7% (n=18) of patients had ≥50% PSA decline from baseline.
- With a median follow-up of 14.5 months and 8 (38.1%) PSA progression events, the median time to PSA progression was 22.87 months (95% CI: 7.95-22.87).
- Of the 10 patients with measurable disease at baseline, 6 had an objective tumor response based on RECIST (all were partial); 3 had stable disease; and 1 had progressive disease.
- Median rPFS was not reached.

Pharmacokinetics

- Systemic exposure to docetaxel, as assessed by mean maximum plasma concentration (C_{max}) and area under the curve from time 0 to infinity (AUC_{∞}), was comparable when administered alone or in combination with abiraterone acetate plus prednisone. C_{max} and AUC_{∞} for abiraterone acetate were also comparable when abiraterone acetate plus prednisone was administered alone and in combination with docetaxel.

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 22 September 2023. Summarized in this response are relevant data from phase 1 and 2 studies of this doublet combination in men with mCRPC.

REFERENCES

1. Duran MAC, Font A, Duran I, et al. Randomized phase II study of docetaxel (D) + abiraterone acetate (AA) versus D after disease progression to first-line AA in metastatic castration-resistant prostate cancer (mCRPC): ABIDO-SOGUG Trial [abstract]. *J Clin Oncol*. 2020;38 (suppl 6): Abstract 95.
2. Puente J, Mendez Vidal MJ, Saez MI, et al. Preliminary safety results of the randomized phase II ABIDO-SOGUG trial: toxicity profile of concomitant abiraterone acetate + docetaxel treatment in comparison to docetaxel [abstract]. *Ann Oncol*. 2018;29(suppl 8):Abstract 822P.
3. Tagawa ST, Posadas EM, Bruce J, et al. Phase 1b study of abiraterone acetate plus prednisone and docetaxel in patients with metastatic castration-resistant prostate cancer. *Eur Urol*. 2016;70(5):718-721.