ZYTIGA® (abiraterone acetate)
ZYTIGA - Dosage and Administration – Lower Dosing

SUMMARY

- Johnson & Johnson cannot recommend any practices, procedures, or dosing modifications that deviate from product labeling and are not approved by regulatory agencies.
- High inter- and intra-patient variability in abiraterone pharmacokinetics (PK) have been reported in the published literature.[1] To control variations in dietary intake and minimize variations in bioavailability, abiraterone acetate has been administered in a fasting state in phase 3 studies.[2]
- Two phase 3, randomized, placebo-controlled, multicenter clinical trials (COU-AA-301 and COU-AA-302) enrolled patients who had metastatic castration-resistant prostate cancer (mCRPC) in which ZYTIGA was administered orally (PO) on an empty stomach at a dose of 1,000 mg daily in combination with prednisone 5 mg PO twice daily in the active treatment arms. Placebo plus prednisone 5 mg PO twice daily was given to patients on the control arm. A third phase 3, randomized, placebo-controlled, multicenter clinical trial (LATITUDE) enrolled patients who had metastatic high-risk castration-sensitive prostate cancer (CSPC) in which ZYTIGA was administered on an empty stomach at a dose of 1,000 mg daily in combination with prednisone 5 mg PO once daily. Placebos were administered to patients in the control arm.[3-5]
- In a phase 2 study evaluating the PK of a reduced-dose regimen in 72 patients with progressive castration-resistant prostate cancer (CRPC), administration of abiraterone acetate 250 mg PO once daily with a low-fat breakfast and in combination with prednisone 5 mg PO twice daily had similar effects on prostate-specific antigen (PSA) levels and PK parameters compared with abiraterone acetate 1,000 mg once-daily administered in a fasted state in combination with prednisone 5 mg PO twice daily. The primary study endpoint, log change in PSA using a noninferiority design, is not a clinically validated endpoint. Overall, adverse events (AEs) were consistent with prior studies and observed in ≥15% of patients in either arm, though there were numerically more patients with grade 3 or higher events in the reduced-dose group (32.4% vs 17.6%; *P*=0.26).[6]
- Another phase 2 study evaluated an initial dose of ZYTIGA 500 mg PO once daily for one month, followed by ZYTIGA 750 mg once daily, plus prednisone 5 mg PO daily in 26 patients ≥85 years old with locally advanced and/or metastatic CRPC (mCRPC). PSA response was observed in 18 (69.2%) patients, median time to PSA progression was 6.4 months (95% CI, 2.8-8.8 months) and median overall survival (OS) was 14.3 months (95% CI, 7.2-18.3 months). AEs related to mineralocorticoid excess were grade 1-2. Other grade 1-2 AEs included constipation, fatigue, back pain and bone pain. Cardiac disorders were reported in 3 (11.5%) patients.[7]
- A phase 1 study determined the PK of abiraterone acetate 500 mg once daily with a continental breakfast did not meet criteria for bioequivalence compared to 1,000 mg administered in a fasted state in 12 evaluable patients due to the large variability in PK of abiraterone within and between patients with metastatic prostate cancer. The prednisone dose was not specified. Due to this large variability in abiraterone exposure, the intake of abiraterone acetate with food could not be advised.[8]
- Additional study abstracts evaluating PSA response, quality of life, and/or safety of lower ZYTIGA dosing in patients with mCRPC have been published.[9-11]

BACKGROUND

Wide inter- and intra-patient variability in abiraterone PK have been reported in the published literature due to a multitude of factors, with potential for excess toxicity or sub-therapeutic levels inducing resistance and limiting therapeutic efficacy.[1] Variability in absorption dependent upon food intake has been observed, including increased abiraterone exposure in patients taking ZYTIGA with high-fat meals compared to low-fat meals.[12] Because fat content and composition of meals are variable and cannot be well controlled in an outpatient setting, current dosing recommendations are to take ZYTIGA on an empty stomach.[13] To control variation in diet and minimize variability in bioavailability, abiraterone acetate was administered in a fasting state in phase 3 studies.[2]

CLINICAL DATA

Phase 2 Studies

Szmulewitz et al (2018)[6] investigated the PK of a reduced-dose (250 mg) daily regimen of abiraterone acetate in combination with a low-fat breakfast in patients with progressive CRPC (N=72).

Study Design/Methods

- Phase 2, randomized, international study
- Patients received either 250 mg ZYTIGA PO once daily with a low-fat breakfast (LOW arm, n=36) or 1,000 mg ZYTIGA PO once daily while fasting (STD arm, n=36); all patients received prednisone 5 mg PO twice daily.
- PSA was assessed monthly; PK samples were collected on day 8 and monthly for the first 4 months.
- **Primary endpoint:** log change in serum PSA as a biomarker for efficacy from baseline to week 12 using a noninferiority design (not a clinically validated endpoint)
- **Secondary endpoints:** comparison of PK, PSA response rate (defined as a ≥50% reduction in PSA after 12 weeks of therapy), change in androgen levels, progression-free survival (PFS), and safety

Results

- Baseline characteristics were well balanced between arms, though the LOW arm had a higher percentage of patients who self-identified as African American (31% vs 14% in the STD arm).
- Noninferiority of the primary endpoint at 12 weeks was established.
  - Mean log change in PSA at 12 weeks (LOW vs STD, respectively): −1.59 vs −1.19
- There were higher drug concentrations (trough and C_{max}) and higher PK variability in the STD arm compared with the LOW arm. There was no clear association within this study between drug concentration and efficacy.
- The PSA response rate was 58% in the LOW arm vs 50% in STD arm, and the median PFS was 8.6 months in both arms (P=0.38). Androgen levels decreased similarly in both arms.
- Overall, AEs were consistent with prior studies and observed in ≥15% of patients in either arm, though there were numerically more patients with grade 3 or higher events in the LOW arm (32.4% vs 17.6%; P=0.26).

Petrioli et al (2015)[7] evaluated the use of ZYTIGA 750 mg once daily plus prednisone 5 mg PO daily in patients ≥85 years old with locally advanced and/or mCRPC (N=26).

Study Design/Methods

- Phase 2 study conducted at 2 centers in Italy
- Patients initiated treatment with ZYTIGA 500 mg PO once daily for one month and then received ZYTIGA 750 mg PO once daily. Prednisone 5 mg PO daily was co-administered.
- Treatment continued until disease progression (serum PSA, radiographic imaging, and clinical findings).
- **Primary endpoint:** PSA response (defined as the proportion of patients with ≥50% decrease in PSA concentration from baseline, confirmed after ≥4 weeks).
- **Secondary endpoints:** time to PSA progression (defined as an increase from nadir of ≥25% and ≥2 ng/mL), OS, and pain response.

Results

- 26 patients were enrolled; median age: 88 years (range, 85-93 years).
- Eastern Cooperative Performance Status (ECOG) performance status (PS) was 0-1 (n=17) and 2 (n=9); 21 patients had bone metastases.
- Patient comorbidities included: cardiovascular, n=18 (69.2%); respiratory, n=9 (34.6%); diabetes mellitus, n=7 (26.9%), dyslipidemia, n=7 (26.9%), and genitourinary issues, n=4 (15.3%).
- Primary and secondary outcomes are described in Table: Outcomes Summary.
- The median duration of treatment was 32 weeks. One patient received only one month of ZYTIGA for treatment-unrelated reasons and one patient was lost to follow-up after 4 months from the start of treatment. All patients were included in the overall intent-to-treat analysis.
    - Twenty-three of 25 patients treated for >2 months escalated dosing to the planned 750 mg daily after the first month of treatment: 2 patients (90 and 92 years) interrupted the treatment for 10 and 15 days due to transitory liver function test (LFT) abnormalities and urinary infection, respectively, after the first months of treatment. Both patients were maintained on 500 mg daily dosing.
    - In another two patients, dosing interruption occurred for about one week because of atrial fibrillation and tachycardia episodes, which occurred after 7 and 9 months of treatment, and in these cases ZYTIGA was restarted at 500 mg once daily.

Outcomes Summary[7]

Efficacy Parameter	ITT Population (n=26)	Prior Docetaxel (n=12)	No Prior Docetaxel (n=14)
Palliative response, n (%)[a]	15 (78.9%)	NR	NR
Median duration of palliative response, months (95% CI)[a]	4.6 (1.5-7.6)	NR	NR
PSA decline ≥50%, n (%)	18 (69.2%)	8 (66.6%)	10 (71.4%)
Median time to PSA progression, months (95% CI)	6.4 (2.8-8.8)	5.5 (2.2-7.9)	7.9 (4.8-9.1)
Median OS, months (95% CI)	14.3 (7.2-18.3)	12.8 (6.4-15.7)	16.4 (8.9-17.4)
[a]n=19 Abbreviations: CI, confidence interval; ITT, intent-to-treat; NR, not reported; PSA, prostate-specific antigen; OS, overall survival			

- AEs related to mineralocorticoid excess were grade 1-2 and cardiac disorders were reported in 3 (11.5%) patients as described in Table: Most Frequent Adverse Events. Other grade 1-2 AEs included constipation, back pain and bone pain.

Most Frequent Adverse Events[7]

Adverse Event, n (%)	Grade 1	Grade 2
Hypokalemia	2 (7.6)	0
Peripheral edema	3 (11.5)	1 (3.8)
Hypertension	2 (7.6)	2 (7.6)
Cardiac disorders	2 (7.6)	1 (3.8)
Fatigue	3 (11.5)	2 (7.6)

Phase 1 Crossover Study

Van Erp et al (2019)[8] evaluated the PK of abiraterone acetate 1,000 mg daily (fasting) followed by 500 mg with a continental breakfast in a crossover study in patients with metastatic prostate cancer (N=14).

Study Design/Methods

- Phase 1, multi-center, crossover study
- Patients received ZYTIGA 1,000 mg daily in a fasted state, followed by 500 mg daily taken with a continental breakfast. The prednisone dose was not specified.
- Abiraterone plasma exposure was measured after both dosing periods of 14 days.

Results

- 12 patients were eligible for PK analysis.
- Geometric mean ration (GMR) for fed/fasted $AUC_{0\text{-}24h}$ was 0.88 (90% CI, 0.73-1.07), GMR C_{max} was 1.03 (90% CI, 0.79-1.34) and the GMR C_{trough} was 0.81 (90% CI, 0.60-1.10).
- The criteria for bioequivalence could not be met due to the large variability in PK of abiraterone within and between patients.
- The intake of abiraterone acetate with food could not be advised by the authors based on the results presented.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File databases (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 20 February 2024. Summarized in this response are relevant data from prospective studies.

REFERENCES

1. Arasaratnam M, Crumbaker M, Bhatnagar A, et al. Inter- and intra-patient variability in pharmacokinetics of abiraterone acetate in metastatic prostate cancer. *Cancer Chemother Pharmacol*. 2019;84(1):139-146.

2. Acharya M, Bernard A, Griffin T, et al. A phase 1 study to determine the effect of food on the pharmacokinetics of abiraterone acetate (AA) in healthy male subjects. Poster presented at: American Association of Pharmaceutical Scientists (AAPS) Annual Meeting; October 23-27, 2011; Washington, DC.

3. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.

4. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138-148.

5. Fizazi K, Tran NP, Fein L, et al. Protocol for: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352-360.

6. Szmulewitz RZ, Peer CJ, Ibraheem A, et al. Prospective international randomized phase II study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer. *J Clin Oncol*. 2018;36(14):1389-1395.

7. Petrioli R, Francini E, Fiaschi A, et al. Reduced dose of abiraterone acetate with concomitant low-dose prednisone in the treatment of ≥85 year-old patients with advanced castrate-resistant prostate cancer. *Anticancer Res*. 2015;35(5):3097-3102.

8. Erp NPV, Benoist GE, Gerritsen WR, et al. Does a food intervention makes abiraterone treatment affordable? *J Clin Oncol*. 2019;37(Suppl.15):e16523-e16523.

9. Makphanchareonkit K, Dejthevaporn TS, Muntham D, et al. The study of the treatment efficacy in metastatic castration-resistant prostate cancer of low dose abiraterone with food. *J Clin Oncol*. 2020;38(Suppl.15):e17571-e17571.

10. Acharya S. Low dose abiraterone in prostate cancer - safety, efficacy and pharmacoeconomic implications [abstract]. *Cancer Res*. 2023;83(Suppl. 11):A083.

11. Shaherose S, Charu GK, Santa A, et al. Low-dose abiraterone with fatty food versus standard dose abiraterone in metastatic castration-resistant prostate cancer [abstract]. *Ann Oncol*. 2022;33(Suppl. 9):S1496. Abstract 159MO.

12. Chi KN, Spratlin J, Kollmannsberger C, et al. Food effects on abiraterone pharmacokinetics in healthy subjects and patients with metastatic castration-resistant prostate cancer. *J Clin Pharmacol*. 2015;55(12):1406-1414.

13. Bryce A, Ryan CJ. Development and clinical utility of abiraterone acetate as an androgen synthesis inhibitor. *Clin Pharmacol Ther*. 2012;91(1):101-108.