

Brand Name: Zytiga

Generic Name: abiraterone acetate

Manufacturer¹: Janssen Biotech, Inc.

Drug Class^{1,2,3,4}: Antineoplastic agent, Antiandrogen

Uses:

Labeled^{1,2,3,4}: Metastatic castration-resistant prostate cancer (in combination with prednisone) in patients who have received prior chemotherapy containing docetaxel

Unlabeled: none

Mechanism of Action^{1,2,3,4}: Abiraterone (converted from abiraterone acetate) inhibits an enzyme required for androgen biosynthesis (CYP17). CYP17 is expressed in testicular, adrenal, and prostatic tumor tissues.

Pharmacokinetics:

Absorption:

T_{max}^5	2 hours
$V_d^{3,5}$	19,669 ±13,358 L
$t_{1/2}^{1,5}$	12 ± 5 hours
Clearance ⁹	803 L/ hour
Protein Binding ^{1,5}	>99%
Bioavailability ¹⁰	≤10% (fasting)

* Pharmacokinetic parameters are dose-proportional. Cmax and AUC increase significantly when abiraterone is administered with food (dependent on fat content).

Metabolism⁵: Abiraterone acetate is hydrolyzed to its active metabolite, abiraterone, after oral administration. This is likely the result of esterase activity rather than CYP mediated. Abiraterone sulphate (inactive) and N-oxide abiraterone sulphate (inactive) are the two primary metabolites of abiraterone via CYP 3A4 and SULT2A1.

Elimination⁵: After oral administration, approximately 88% of the administered dose is removed fecally. Abiraterone acetate and abiraterone are the main compounds found in feces (55% and 22% of the given dose, respectively). Approximately 5% is excreted renally (4.22% as N-oxide abiraterone sulfate).

Efficacy:

de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011 May 26;364(21):1995-2005.

Study Design: phase III, multinational, randomized, double-blind, placebo-controlled study

Description of Study: *METHODS:* Patients who had histologically or cytologically confirmed prostate cancer that had previously been treated with docetaxel, disease progression, and ongoing androgen deprivation were eligible for this study. This study was conducted at 147 sites in 13 countries. One-thousand one hundred and ninety-five patients were randomly assigned in a 2:1 ratio to receive prednisone 5 mg twice daily with either 1000 mg of abiraterone acetate (797) or placebo (398) orally once daily in 28-day cycles. Treatment was continued until disease progression. The primary endpoint was overall survival. Secondary endpoints included the PSA response rate, time to PSA progression, and radiographic evidence of progression-free survival. The score of the Functional Assessment of Cancer Therapy, the score for fatigue, and counts of circulating tumor cells were also measured. *OUTCOME RESULTS:* The median treatment duration was 8 months in the abiraterone group and 4 months in the placebo group. At the interim analysis, treatment with abiraterone caused a 35.4% risk reduction of death compared with placebo (HR 0.65; 95% CI 0.54 to 0.77; $p < 0.001$). Three hundred and thirty-three patients died in the abiraterone group and 219 patients died in the placebo group. The median overall survival was 14.8 months in the abiraterone group versus 10.9 months in the placebo group. The benefit of abiraterone on overall survival was consistent across all subgroups. Due to these results, the independent data and safety monitoring committee recommended unblinding and crossover for patients in the placebo group to the abiraterone group if they met certain criteria. Urinary tract infections were more common in the abiraterone group (12% vs 7%; $p = 0.02$). Treatment discontinuation from adverse events occurred with a similar frequency in both groups ($p = 0.09$). Fluid retention/edema, hypertension, hypokalemia, cardiac disorders, and liver-function test abnormalities were more common in the abiraterone group than in the placebo group (55% vs 43%; $p < 0.001$). There was no significant increase in fatal cardiac events in the abiraterone group. A smaller percentage of patients in the abiraterone group died as a result of adverse events than in the placebo group (12% vs 15%).

Limitations: This study was partially funded by Cougar Biotechnology, which later became Janssen Research and Development, the manufacturer of abiraterone. Additionally, many authors had financial and other affiliations with Cougar Biotechnology and various companies. This presents possible conflicts of interest and investigator bias. The authors did not report other medications taken by the participants at the time of the study. This information would be important as abiraterone has many drug interactions with multiple cytochrome P450 inducers, inhibitors, and substrates.

Conclusions: The results of this study showed that abiraterone acetate, when combined with prednisone, prolongs overall survival among patients with metastatic castration-resistant prostate cancer as compared to placebo plus prednisone. Additionally, the side effect profile is relatively safe and manageable.

Reid AH, Attard G, Danila DC, et al. Significant and sustained antitumor activity in post-docetaxel, castration-resistant prostate cancer with the CYP17 inhibitor abiraterone acetate. J Clin Oncol. 2010 Mar 20;28(9):1489-95. Epub 2010 Feb 16.

Study Design: phase II, single-arm, open-label, two-stage study

Description of Study: *METHODS:* Castrate patients with an Eastern Cooperative Oncology Group ECOG performance status of 0 to 2 who had a histologic diagnosis of prostate adenocarcinoma, a PSA greater than 5 ng/mL, and progressive disease were eligible. Participants were required to have received prior docetaxel chemotherapy, a ≥ 4 week washout period after the use of prostate cancer therapy (except LHRH agonists), a ≥ 6 week washout period after the use of antiandrogens, a normal serum potassium, and adequate bone marrow, renal, and hepatic functions. The primary endpoint was achievement of PSA decline of $\geq 50\%$ in at least seven patients. In the first stage of the study, 20 patients were recruited; if at least three reached the primary endpoint, 13 additional patients would be recruited for the second stage. Secondary objectives included: PSA declines of $\geq 30\%$ and $\geq 90\%$, rate of RECIST (Response Evaluation Criteria in Solid Tumors) responses and duration on study, time to PSA progression, safety and tolerability, and circulating tumor cell (CTC) enumeration. A dose of 1000 mg of abiraterone acetate was administered once daily to patients in 28-day cycles. *OUTCOME RESULTS:* Forty-seven patients were enrolled from December 2006 to August 2007. Thirty patients had measurable disease via CT scan at baseline, and 45 had bony metastasis at baseline. Twenty-four patients (51%) had a PSA decline of $\geq 50\%$ at least once during the study. Thirty-two (68%) and seven (15%) patients had $\geq 30\%$ and $\geq 90\%$ decline in PSA, respectively. Eight (27%) patients met the criteria for partial response by RECIST. An improvement in performance status was observed during treatment in 11 patients. The median time to PSA progression was 169 days (95% CI 113 to 281 days). Seventeen of 27 patients (63%) had a decline in CTC count by $\geq 50\%$; 18 of 27 patients (67%) had a decline in CTC count by $\geq 30\%$ after starting treatment with abiraterone acetate. Hypokalemia, hypertension, and fluid retention occurred in 26 (55%), 8 (17%), and 7 (15%) patients. Additional adverse events included nausea, constipation, fatigue, anorexia, hyperglycemia, and headache. Three patients died during the study; two were not related to the study drug and one did not have a postmortem conducted.

Limitations: This study was sponsored by Cougar Biotechnology, which later became Janssen Research and Development, the manufacturer of abiraterone. Additionally, many investigators/authors were employees of or stockowners in Cougar Biotechnology.

These affiliations present potential conflicts of interest. This was a single-arm trial without a control present. Results were reported in numbers and percentages. Statistical tests were not completed. Additionally, this was an open-label study so bias could be present. Patients were permitted to be on stable low-dose steroids if they were required to maintain fitness for the study. However, the authors did not report the specific steroids, doses, or frequency of use in the study participants. This is a significant limitation as abiraterone is now indicated for use in combination with prednisone. In addition, other medications that patients were taking during the study were not reported. Lastly, the investigators did not assess patient adherence.

Conclusions: The results of this study showed that abiraterone acetate has significant antitumor activity in patients with late-stage metastatic castration-resistant prostate cancer who received docetaxel treatment. Additionally, adverse events were relatively benign and/or managed with a low-dose steroid (hypokalemia, hypertension, and edema). This study, among others, likely led to the indication with concomitant prednisone administration.

Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013 Jan 10;368(2):138-48. Epub 2012 Dec 10.

Study Design: randomized, multinational, double-blind, placebo-controlled study

Description of Study: *METHODS:* Patients 18 years or older with metastatic, histologically or cytologically confirmed adenocarcinoma of the prostate, PSA progression or radiographic progression in soft tissue of bone with or without PSA progression, ongoing androgen deprivation, an ECOG performance status grade of 0 or 1, no or mild symptoms (BPI-SF), and previous therapy with an antiandrogen were included in this study. Patients were randomly assigned in a 1:1 ratio to receive abiraterone (1 g daily) plus prednisone (546 patients) or placebo plus prednisone (542 patients). All patients received prednisone 5 mg orally twice daily. Safety and compliance were assessed at each study visit and at treatment discontinuation. The primary endpoints were radiographic progression-free survival (PFS) and overall survival (OS). The secondary endpoints were time to opiate use for cancer-related pain, time to initiation of cytotoxic chemotherapy, time to a decline in ECOG performance status, and time to PSA progression. Three interim analyses were planned. *OUTCOME RESULTS:* At the second interim analysis, the median time to PFS was 16.5 months in the abiraterone group and 8.3 months in the placebo group (HR 0.53; 95% CI 0.45 to 0.62; $p < 0.001$). This benefit was consistently positive across all subgroups. More deaths occurred in the placebo group than in the abiraterone group (34% vs 27%). There was a 25% decrease in the risk of death in the abiraterone group (HR 0.75; 95% CI 0.61 to 0.93; $p = 0.01$). However, this did not reach the prespecified level of significance ($p < 0.001$). The benefit of abiraterone on OS was favorable across all subgroups. Serious adverse events were reported in 33% and 26% of patients and adverse events resulting in death occurred in

4% and 2% of patients in the abiraterone and placebo groups, respectively. The frequency of adverse events resulting in treatment discontinuation was similar in both groups. Hypertension, hypokalemia, and fluid retention/edema were more common in the abiraterone group. The statistical significance of differences in adverse effects between the treatment groups was not determined.

Limitations: Janssen Research and Development, the manufacturer of abiraterone, funded this study. Additionally, multiple authors were affiliated with this company. These conflicts of interest present the potential for investigator bias. Statistical tests were not used to assess differences in adverse events between treatment groups. Medications unrelated to the study treatments were not reported. This is important because many drug interactions exist with abiraterone.

Conclusions: The results of this study showed that abiraterone plus low-dose prednisone prolonged PFS and improved OS in men with metastatic castration-resistant prostate cancer (without prior chemotherapy) as compared with placebo plus prednisone. Additionally, the safety profile of abiraterone was favorable. Abiraterone would prove useful when a nontoxic agent is required to maintain quality and duration of life and decrease morbidity and mortality associated with castration-resistant prostate cancer (CRPC). The results of this study may lead to an additional indication for abiraterone use in patients with CRPC without previous docetaxel treatment if further studies demonstrate superiority (or equality and improved side effect profile) of abiraterone as compared to docetaxel.

Contraindications¹⁻⁵:

Pregnancy: Abiraterone acetate is contraindicated in women who are or may become pregnant as it has the potential to cause fetal harm. It is a FDA pregnancy category X drug (all trimesters). Effective contraception should be used during treatment and for at least one week after discontinuation. It is unknown if abiraterone or its metabolites are present in human milk or semen.

**Abiraterone is not indicated for use in females.*

Precautions¹⁻⁵:

Adrenocortical insufficiency: Prednisone dose reduction/discontinuation, concurrent infection, and unusual stress (surgery) are associated with an increased risk. Monitoring is recommended. An increase in corticosteroid dose may be required.

Breastfeeding: It is unknown if abiraterone is excreted in human milk. Discontinue drug or stop nursing as it may be secreted in breast milk. Serious adverse effects could result in nursing infants.

Cardiovascular conditions (history of cardiovascular disease, heart failure, recent myocardial infarction, ventricular arrhythmia): Hypertension, hypokalemia, and fluid retention from mineralocorticoid excess can compromise underlying cardiovascular conditions. Monitoring is recommended.

Concomitant use of CYP2D6 substrates with narrow therapeutic index (thioridazine): Avoid; if unavoidable, use caution and consider reducing dose of CYP2D6 substrate.

Concomitant use of strong CYP3A4 inducers (phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital): Avoid; if clinically indicated, dose adjustment required.

Children, adolescents, infants, neonates: Safety and efficacy have not been established.

Food effect: C_{max} and AUC increase significantly when administered with a meal. Take on an empty stomach at least 2 hours before and 1 hour after administration.

Hepatic impairment: Avoid if severe (Child-Pugh class C); initiate at reduced dose if moderate (Child-Pugh class B)

Hepatotoxicity: Monitoring recommended. This generally occurs in the first three months of treatment.

Mineralocorticoid excess: May result in hypertension, hypokalemia, and fluid retention as a result of CYP17 inhibition. Incidence and severity are reduced with concomitant administration of corticosteroid. Monitoring is recommended.

Special handling: Abiraterone is a hazardous agent; appropriate precautions for handling and disposal should be used.

Adverse Effects²:

Occurring in >10% of patients:

Cardiovascular

Edema (25% to 27%)

Hypertension (9% to 22%; grades 3/4: 1% to 4%)

Central Nervous System

Fatigue (39%)

Insomnia (14%)

Dermatologic

Bruising (13%)

Endocrine and Metabolic

Triglycerides increased (63%)

Hyperglycemia (57%)

Hypernatremia (33%)

Hypokalemia (17% to 28%; grades 3/4: 2% to 3%)

Hypophosphatemia (24%; grades 3/4: 7%)

Hot flush (19% to 22%)

Gastrointestinal

Constipation (23%)

Diarrhea (18% to 22%)

Dyspepsia (6% to 11%)

Vomiting ($\geq 10\%$)

Genitourinary

Urinary tract infection (12%)

Hematologic

Anemia ($>20\%$)

Lymphopenia (38%; grades 3/4: 9%)

Hepatic

ALT increased (11% to 42%; grades 3/4: 1% to 6%)

AST increased (31% to 37%; grades 3/4: 2% to 3%)

Neuromuscular and Skeletal

Joint swelling/discomfort (30%)

Muscle discomfort (26%)

Respiratory

Cough (11% to 17%)

Upper respiratory infection (5% to 13%)

Dyspnea (12%)

Nasopharyngitis (11%)

Occurring in $>1\%$ to $<10\%$ of patients:

Cardiovascular

Arrhythmia (7%)

Chest pain/discomfort (4%)

Heart failure (2%)

Central Nervous System

Fever (9%)

Dermatologic

Rash (8%)

Genitourinary

Hematuria 10%)

Polyuria (7%)

Nocturia (6%)

Hepatic

Bilirubin increased (7%; grades 3/4: $<1\%$)

Neuromuscular and Skeletal

Groin pain (7%)

Falling (6%)

Fractures (6%)

Drug Interactions^{1,2}:

Abiraterone is a CYP3A4 substrate (major) and inhibitor of CYP1A2 (weak), CYP2C19 (moderate), CYP2C8 (strong), CYP2C9 (moderate), CYP2D6 (moderate), CYP3A4 (moderate), and p-glycoprotein².

**Major/moderate/weak classification based on clinically relevant drug interaction potential.*

CYP3A4 Inhibitors

Abiraterone is a CYP3A4 substrate. Exposure to abiraterone, and subsequently adverse effects, may be increased when coadministered with a CYP3A4 inhibitor.

Examples: ketoconazole¹, itraconazole¹, clarithromycin¹, atazanavir¹, nefazodone¹, saquinavir¹, St. John's Wort¹, telithromycin¹, ritonavir¹, indinavir¹, nelfinavir¹, voriconazole¹

CYP3A4 Inducers

Abiraterone is a CYP3A4 substrate. Exposure to abiraterone may be decreased when coadministered with a CYP3A4 inducer.

Examples: phenytoin¹, carbamazepine¹, rifampin¹, rifabutin¹, rifapentine¹, phenobarbital¹

CYP1A2 Substrates

Abiraterone is a CYP1A2 inhibitor. Exposure to CYP1A2 substrates, and subsequently adverse effects, may be increased when coadministered with abiraterone.

Examples: clozapine, pomalidomide

CYP2C19 Substrates

Abiraterone is a CYP2C19 inhibitor. Exposure to CYP2C19 substrates, and subsequently adverse effects, may be increased when coadministered with abiraterone.

Examples: citalopram, clopidogrel

CYP2C8 Substrates

Abiraterone is a CYP2C8 inhibitor. Exposure to CYP2C8 substrates, and subsequently adverse effects, may be increased when coadministered with abiraterone.

Examples: Amodiaquine², enzalutamide¹, repaglinide², rosiglitazone², loperamide², naproxen², pioglitazone², pitavastatin²

CYP2C9 Substrates

Abiraterone is a CYP2C9 inhibitor. Exposure to CYP2C9 substrates, and subsequently adverse effects, may be increased when coadministered with abiraterone.

Examples: diclofenac, ospemifene, rosiglitazone, carvedilol

CYP2D6 Substrates

Abiraterone is a CYP2D6 inhibitor. Exposure to CYP2D6 substrates, and subsequently adverse effects, may be increased when coadministered with abiraterone. Avoid concomitant administration of abiraterone and CYP2D6 substrates with narrow therapeutic indexes (thioridazine). Abiraterone inhibits the conversion of prodrugs, such as codeine and tamoxifen, to active metabolites.

Examples: dextromethorphan², thioridazine¹, amitriptyline, brinzolamide, fluoxetine, meclizine, metoprolol, tamoxifen, codeine

CYP3A4 Substrates

Abiraterone is a CYP3A4 inhibitor. Exposure to CYP3A4 substrates, and subsequently adverse effects, may be increased when coadministered with abiraterone.

Examples: amlodipine, amiodarone, fentanyl, lomitapide, lurasidone, ospemifene, paclitaxel, repaglinide, tamsulosin, vardenafil, aripiprazole, avanafil, bosutinib, budesonide, colchicine

P-glycoprotein Substrates

Abiraterone is a P-gp inhibitor and may increase exposure to P-gp substrates and subsequently adverse effects.

Examples: afatinib, nilotinib, pomalidomide, romidepsin, bosutinib, dabigatran

**Major¹; Moderate² (1)*

Dosing/Administration^{1,2,3}:

Usual dose (adults)

1000 mg orally once daily (in combination with prednisone 5 mg orally twice daily)

Geriatric dose

1000 mg orally once daily

Pediatric dose

Safety and efficacy have not been established.

Hepatic Impairment

Mild (Child-Pugh Class A): No dosage adjustment necessary.

Moderate (Class B): Reduce dose to 250 mg orally once daily. Use with caution as no clinical data exists. Discontinue and do not reinitiate therapy if ALT/AST increases >5 times the normal limits or total bilirubin increases >3 times the normal limit.

Severe (Class C): Do not use.

Hepatotoxicity: If patients' ALT/AST increases >5 times the normal limits or total bilirubin increases >3 times the normal limit, discontinue therapy. Resume at 750 mg orally once daily when LFTs return to baseline or AST/ALT \leq 2.5 times the normal limits and total bilirubin \leq 1.5 times the normal limit. If hepatotoxicity recurs, repeat approach and then resume at 500 mg orally once daily. If hepatotoxicity recurs, discontinue.

Renal Impairment

No dosage adjustment is required.

Administration

No food should be consumed for at least 2 hours prior to administration and for at least one hour after.

Use in Special Circumstances¹⁻⁵:

Overdose: There is no specific antidote for abiraterone; stop the drug and initiate supportive measures and monitoring. In clinical studies, there were no reported overdoses.

Pregnancy: Abiraterone is a FDA pregnancy category X drug as it may cause fetal harm when taken by a pregnant woman. It is contraindicated for use by women who are or may become pregnant. Women should be advised not to become pregnant if taking abiraterone. Abiraterone is not indicated for use in women. Abiraterone should not be handled by females who are or might be pregnant without protection. Men taking abiraterone should use a condom if having intercourse with a pregnant woman. Additionally, an effective method of birth control should be used if having sex with a woman of child-bearing age. It is unclear if abiraterone or its metabolites are present in

semen; therefore, these cautionary measures are necessary during and one week post-treatment with abiraterone.

Breastfeeding: It is unclear if abiraterone acetate is excreted in human milk. Discontinue abiraterone or discontinue nursing because of the potential for severe adverse reactions in nursing infants from this drug.

Administration: Abiraterone should be administered on an empty stomach at least 2 hours before or 1 hour after eating. When administered with food, C_{max} increases 7 to 17-fold and AUC increases 5 to 10-fold, depending on the fat content. For this reason (highly variable systemic exposure), abiraterone should be taken on an empty stomach.

Hepatic Impairment: The half-life of abiraterone is extended to 18 hours with mild impairment and 19 hours with moderate impairment.

NYHA Class III or IV Heart Failure (LVEF < 50%): The safety of abiraterone has not been established.

Conclusion: Abiraterone is a novel drug that inhibits androgen synthesis by blocking CYP17. This medication, plus low-dose prednisone, improves survival in patients with metastatic castration-resistant prostate cancer who have previously been treated with docetaxel. Abiraterone has shown promising results in these patients who have not received prior chemotherapy; this may lead to additional FDA-approved indication(s) in the future if head-to-head studies with docetaxel show superiority or equality with an improved adverse effect profile. Abiraterone's safety profile is favorable. The main adverse effects include hypokalemia, hypertension, and fluid retention, which can be managed with low-dose glucocorticoids. Therefore, one main advantage to this drug is that it maintains quality of life while preventing morbidity and mortality associated with prostate cancer. Unfortunately, abiraterone has many drug interactions due to its activity with cytochrome P450 enzymes.

Recommended References:

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