# *How I do it: Prescribing abiraterone acetate for metastatic castration resistant prostate cancer*

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*Abiraterone acetate (AA) is a selective irreversible inhibitor of CYP 17, a key enzyme in androgen biosynthesis. The efficacy and safety of AA in improving survival and quality of life in metastatic castration resistant prostate cancer (mCRPC) has been demonstrated in two landmark clinical trials (COU-AA-301 and COU-AA-302). This article will review the rationale, pharmacology, clinical indications and contraindications, administration, and adverse effects of AA administration in mCRPC.*

**Key Words:** abiraterone acetate, abiraterone, Zytiga, metastatic castrate resistant prostate cancer, mCRPC, CYP17, prostate cancer

## Abiraterone acetate

Abiraterone acetate (AA) is a novel therapeutic agent used in the treatment of metastatic castration resistant prostate cancer (mCRPC). AA is a selective irreversible inhibitor of cytochrome P450 isoform 17 (CYP17).[1] CYP17 has an important role in androgen biosynthesis through its 17α-hydroxylase and C17, 20-lyase activity.[1]

During treatment with androgen deprivation therapy (ADT), androgens can still be produced at low levels and at extragonadal sites—including the adrenal glands and intratumorally. Mean serum testosterone levels during ADT are 20 ng/dL (0.7 nmol/L) and can be as high as 50 ng/dL (1.7 nmol/L).[2] Other steroidal hormones such as androstenedione and dehydroepiandrosterone are also produced and activate the androgen receptor (AR).

Through its inhibition of gonadal and extragonadal CYP17, AA reduces the level of serum testosterone to 1-2 ng/dL (< 0.1 nmol/L) and also results in a significant reduction in the concentration of other androgens.[3] This results in reduced ligand binding to the AR—thereby reducing AR activation and downstream signaling. AA is generally administered with prednisone as this reduces CYP17 inhibition induced mineralocorticoid excess, Figure 1.

## A changing landscape in prostate cancer

Inhibition of AR signaling via castration was the main breakthrough in the treatment of metastatic prostate cancer in the 20th century. Castration, as initially described by Huggins and Hodges, provided a dramatic initial benefit in metastatic prostate cancer.[4] Nonetheless,

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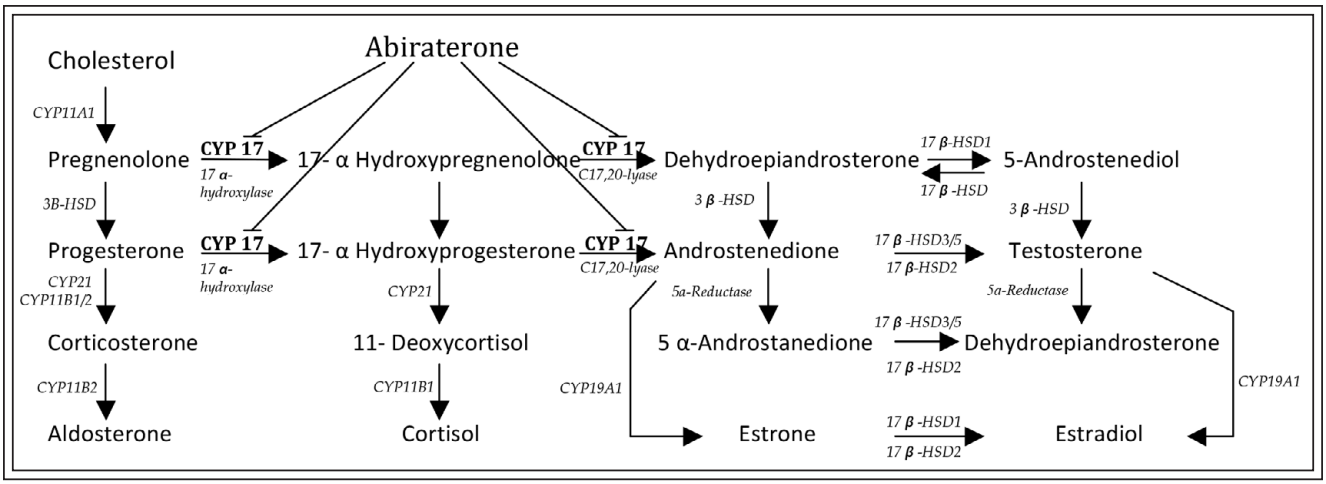


**Figure 1.** Androgen biosynthesis pathway. Abiraterone the metabolite and active molecule of abiraterone acetate inhibits CYP17 activity thus inhibiting biosynthesis of downstream products including androgens and glucocorticoids. Decrease glucocorticoids cause increase in ACTH production which results in exaggerated production of precursor steroids with high mineralocorticoid activity (cortiosterone, deoxycorticosterone (not shown)).

patients with prostate cancer treated with castration inevitably developed disease recurrence and progression. This disease state, metastatic castration resistant prostate cancer (mCRPC), is highly morbid and ultimately fatal. Patients are classified as harboring mCRPC when they have metastases detectable clinically or by imaging and a serum testosterone in the castrate range by means of surgical orchiectomy or medical therapy.[5]

A number of therapeutic advances have been made in improving the morbidity and the mortality of patients with mCRPC in the last decade. This era began with the TAX-327[6] clinical trial in 2004 demonstrating a survival benefit using docetaxel in mCRPC. It was followed subsequently with landmark trials outlining the overall survival benefits of AA (COU-AA-301[7] and COU-AA-302[8]), enzalutamide (AFFIRM[9] and PREVAIL[10]), radium-223 (ALSYMPCA[11]), sipuleucel-T (IMPACT[12]), and cabazitaxel (TROPIC[13]). Novel agents for mCRPC can be classified as those that directly affect AR activity and those that do not, Table 1.

TABLE 1. **Mechanism of action and key clinical trial of novel treatments for CRPC**

| | Method of action | Indication | Clinical trial |
|---|---|---|---|
| **Abiraterone acetate** | CYP17 inhibitor (androgen synthesis inhibitor) | mCRPC (pre-[8] and post-[7] chemotherapy) | COU-AA-301[7] COU-AA-302[8] |
| **Enzalutamide** | AR inhibitor | mCRPC (pre-[10] and post-[9] chemotherapy) | AFFIRM[9] PREVAIL[10] |
| **Radium-223** | α-particle emitting radiopharmaceutical | mCRPC with symptomatic bone metastases with no known visceral metastatic disease | ALSYMPCA[11] |
| **Sipuleucel-T** | Autologous cellular immunotherapy | Minimally or asymptomatic mCRPC | IMPACT[12] |
| **Docetaxel** | Taxane chemotherapy (microtubule inhibitor) | mCRPC | TAX-327[6] |
| **Cabazitaxel** | Taxane chemotherapy (microtubule inhibitor) | mCRPC post docetaxel | TROPIC[13] |

mCRPC = metastatic castrate resistant prostate cancer; AR = androgen receptor

## Predecessors to abiraterone acetate

Manipulation of extragonadal androgen synthesis has long been a therapeutic target in mCRPC—namely with aminoglutethimide and ketoconazole. Aminoglutethimide inhibits the conversion of cholesterol to pregnenolone and ketoconazole is a weak nonspecific inhibitor of CYP 17.[14] Both of these agents result in PSA responses, but their use was limited by toxicities and the lack of a demonstrated survival benefit.[15] Neither are first line recommendations in recent American Urological Assocation (AUA)[15] or Canadian Urological Association (CUA)[5] guidelines.

## Metabolism of abiraterone acetate

Abiraterone acetate is a pro-drug which is rapidly hydrolyzed into abiraterone after ingestion.[1] The time to maximum plasma concentration after ingestion is 2 hours. Bioavailability data suggests significant variation based on the fat content of meals associated with AA intake. There is a 10- to 17-fold increase in plasma concentration when the medication is taken with a fatty meal.[16] The product monograph suggests that AA be taken on an empty stomach to avoid varying drug exposure. No solid or liquid food should be consumed for 2 hours and at least 1 hour after ingestion AA.[1]

Abiraterone is metabolized by the liver and excreted in the gastrointestinal tract.[1] The mean plasma half-life is 15 hours. AA can be used in those with mild hepatic insufficiency (Childs-Pugh class A) with no dose adjustment. AA should not be used in patients with pre-existing moderate or severe liver dysfunction (Childs-Pugh class B and C). Only 5% of AA is ultimately excreted in the urine, preventing the need for dose modifications in patients with renal dysfunction.[1]

Abiraterone is a substrate of the hepatic enzymes SULT2A1 and CYP3A4.[16] Co-administration with a strong CYP3A4 inducer (eg. phenytoin, carbamazepine, rifampicin, rifabutin, phenobarbital) should be avoided or dose modifications may be required. AA may also interact with other CYP450 hepatic enzymes therefore consultation with a pharmacist for patients receiving AA is advised. Co-administration of AA with St. John's wort, a CYP3A4 inducer, should also be avoided.[1]

AA does not appear to result in QTc prolongation.[1] Additionally, co-administration with mineralocorticoid receptor antagonists (spironolactone) should be avoided. Prior use of ketoconazole may lower AA response rates.[1]

## Clinical evidence

Two landmark clinical trials provide the rationale for using AA in patients with mCRPC, Table 2.

The COU-AA-301[3,7] trial was a double-blind, multicenter, randomized clinical trial. In this study, 1195 men with mCRPC and disease progression despite docetaxel were randomized to treatment with AA and prednisone versus placebo and prednisone. Treatment with AA resulted in an improvement in overall (15.8 months versus 11.2 months; HR, 0.74; 95% CI, 0.64-0.86; $p < 0.0001$). All secondary end points analyzed also supported use of AA including PSA response rate (29.5% versus 5.5%, $p < 0.0001$), time to PSA progression (8.5 months versus 6.6 months; HR, 0.63; $p < 0.0001$) and median progression-free survival (PFS) on the basis of radiographic evidence (5.6 months versus 3.6 months, $p < 0.0001$).[3,7]

The COU-AA-302[8] trial was a double-blind, multicenter, randomized clinical trial that evaluated the use of AA in mCRPC patients that had not received docetaxel. A total of 1088 patients were randomized to receive AA plus prednisone or placebo plus prednisone. Treatment with AA resulted in an improvement in OS (34.7 months versus 30.3 months; HR, 0.8 [95% CI, 0.70-0.93, $p = 0.0033$]). AA treatment also improved secondary end points including median time to opiate use, time to initiation of cytotoxic chemotherapy, PSA progression, and decline in performance status.[8]

## Indications and contraindications for treatment with abiraterone acetate

The Canadian product monograph lists two indications for AA treatment.[1] Treatment with AA is indicated for mCRPC patients who are asymptomatic or mildly symptomatic and have not received docetaxel chemotherapy. Treatment with AA is also indicated for patients that have received prior docetaxel chemotherapy. These indications for treatment with AA are based upon COU-AA-301[7] and COU-AA-302[8] and are consistent with guidelines from both the CUA[5] and AUA.[15]

The CUA and AUA guidelines differ slightly in their recommendations with regards to symptomatic patients that have not received docetaxel. The COU-AA-302[8] study did not include these patients. AA is a first-line option for the treatment of these patients in the AUA guidelines.[15] The authors justify this recommendation because of a plausible mechanism of action and extrapolation of ketoconazole data. In the CUA guidelines,[5] AA treatment is only considered first-line therapy for those symptomatic mCRPC patients that are unfit or refuse docetaxel. The CUA guideline

TABLE 2. **Characteristics of COU-AA-301[1,3,7] and COU-AA-302[1,8,17]**

| | COU-AA-301 | COU-AA-302 |
|---|---|---|
| **Study design** | Multinational, double-blind, randomized, placebo controlled phase 3 trial | Multinational, double-blind, randomized, placebo controlled phase 3 trial |
| **Intervention and control** | Abiraterone (1000 mg once daily) + prednisone (5 mg twice daily) vs. placebo + prednisone (5 mg twice daily) | Abiraterone (1000 mg once daily + prednisone (5 mg twice daily) vs. placebo + prednisone (5 mg twice daily) |
| **Treatment setting** | Post chemotherapy | Chemotherapy-naive |
| **Number of patients** | 797 (intervention) vs. 398 (control) randomized 2:1 | 546 (intervention) vs. 542 (control) randomized 1:1 |
| **Outcomes** | Primary: overall survival<br>Secondary: time to PSA progression, radiographic progression-free survival, time to first skeletal-related event, PSA response rate (≥ 50% decline in PSA level from baseline) | Primary: overall survival, radiographic progression-free survival<br>Secondary: time to opiate use for cancer related pain, time to initiation of cytotoxic chemotherapy, time to a decline in ECOG performance status, time to PSA progression, PSA response rate (≥ 50% decline in PSA level from baseline), rate of objective response according to RECIST criteria, and health related quality of life (patient reports) |
| **Age (median) years old** | 69 (intervention) vs. 69 (control) | 71 (intervention) vs. 70 (control) |
| **ECOG performance status** | 0, 1 or 2 | 0 or 1 |
| **Gleason score (intervention vs. control group)** | ≤ 7 (49% vs. 46%)<br>≥ 8 (51% vs. 54%) | ≤ 7 (46% vs. 50%)<br>≥ 8 (54% vs. 50%) |
| **PSA level median (intervention vs. control group)** | PSA: 129 (ng/mL) vs. 138 (ng/mL) | PSA: 42 (ng/mL) vs. 38 (ng/mL) |
| **Median follow up** | 20.2 months | 49.2 months |
| **Results** | Median OS: 15.8 vs. 11.2 months<br>Median TTPP: 8.5 vs. 6.6 months<br>Median rPFS: 5.6 vs. 3.6 months<br>PSA response rate: 29.5% vs. 5.5%<br>Time to first skeletal-related event: 25 vs. 20.3 months<br>Grade 3 adverse event: 21% vs. 17%<br>Grade 4 adverse event: 3% vs. 3% | Median OS: 34.7 vs. 30.3 months<br>Median TTPP: 11.1 vs. 6.5 months<br>Median rPFS: 16.5 vs. 8.2 months<br>PSA response rate: 62% vs. 24%<br>Time to chemotherapy: 25 vs. 16.8 months<br>Time to increase in pain: 26.7 vs. 18.4 months<br>Time to decline in QoL: 12.7 vs. 8.3 months<br>At least Grade 3-4 adverse event: 54% vs. 44% |

OS = overall survival; TTPP = time to PSA progression; rPFS = radiographic progression-free survival

authors took this position because data for treatment with AA in these patients is not available—while there is level 1 evidence for use of docetaxel in this disease state. This indication is not included in the Canadian product monograph as it was not part of the AA Health Canada approval.[1]

Patients are classified as having mCRPC when they have metastases detectable clinically or by imaging and a serum testosterone in the castrate range by surgical orchiectomy or medical therapy.[5] Although a serum testosterone threshold of < 50 ng/dL (< 1.7 nmol/L) has been the historical castration standard, increasing evidence[2] supports a lower cut off (< 20-32 ng/dL, < 0.7-1.1 nmol/L). Generally metastases are detected by computed tomographic (CT) imaging or nuclear bone scintigraphy—which should be performed as a

staging investigation for patients appearing to progress clinically or biochemically on ADT.[5]

Patients on ADT who recur biochemically and have no demonstrable metastatic disease fall into the clinical state of nonmetastatic castration resistant prostate cancer.[5] This state is defined by the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) definition—a rising PSA that is greater than 2 ng/mL higher than the nadir, which is confirmed by further subsequent rises in PSA greater than 25% measured at least 3 weeks apart.[15] Patients must also have no radiographic evidence of metastatic disease.[15] Assessment for presence of metastases in these patients is key given that AA is not currently indicated in patients with no detectable metastases.

Contraindications to treatment with AA include hypersensitivity to the drug or any ingredient in the formulation or component of the container.[1] AA should also not be used in moderate and severe hepatic impairment (Childs-Pugh Class B and C).[1]

## Administering abiraterone acetate

In addition to an assessment of the appropriate indications for AA, patients should receive a comprehensive baseline evaluation prior to AA treatment. These patients may also be candidates for treatment with enzalutamide, docetaxel, denosumab, zoledronic acid, radium-223, or cabazitaxel and a comprehensive discussion on all options is needed prior to initiation of therapy.[5,15]

A decision to begin AA treatment should begin with a comprehensive history. The patient's prostate cancer course should be documented, including previously received therapies, laboratory values, and imaging results. A thorough review of systems should be performed—patients with mCRPC are at risk of developing a number of cancer related complications including obstructive uropathy, pathologic fractures and and spinal cord compression. Early prevention and treatment may reduce the morbidity of these complications. Patients that are candidates for treatment with AA should be continued on their ADT during the course of treatment.[5] Patients should also be assessed with regards to bone health including the results of any recent dual energy x-ray absorptiometry screening (DEXA). Patients should be treated with calcium, vitamin D, and bone targeted therapy with zoledronic acid or denosumab as indicated.[5,15] Finally, patients treated with AA have often been on long term ADT and should be assessed for its metabolic complications to ensure that these are being adequately screened for and managed.

A comprehensive physical examination is also important prior to initiation of AA. Assessing for complications of mCRPC—including spinal cord compression and pathologic fractures—is critical in preserving quality of life during AA treatment. Blood pressure and degree of peripheral edema should be assessed at a baseline and documented—as this can increase during AA treatment.[1]

Baseline laboratory values should be performed including serum potassium, liver function tests, and bilirubin.[1] Biochemical screening for anemia, hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, and obstructive uropathy may also be prudent. Baseline serum testosterone and PSA should be assessed and documented. During treatment for mCRPC, PSA levels along with other biochemical and radiographic imaging modalities are employed to assess response. A number of laboratory values including serum lactate dehydrogenase (LDH), hemoglobin, and alkaline phosphatase (ALP) have significant prognostic value with respect to overall survival. Imaging with CT scan of the chest, abdomen, and pelvis and nuclear bone scintigraphy should also be performed at a baseline and in follow up to assess disease burden and response to treatment.

Abiraterone acetate is prescribed at a dose of 1000 mg daily with co-administration of prednisone 5 mg twice a day or 10 mg daily.[1]

## Following patients on abiraterone acetate

Follow up visits for patients on AA are scheduled every two weeks initially for 3 months, although they may be decreased to monthly once patients demonstrate response without significant toxicity. A comprehensive history and physical examination should be performed at each visit to assess for mCRPC related complications. Assessment of performance status is integral to follow up as this remains a significant predictor of survival. Special attention should be paid to blood pressure and peripheral edema as these may increase during treatment with AA. Myopathy, rhabdomyolysis, and allergic alveolitis have also been reported with AA treatment and should be screened for clinically.[1]

From a biochemical standpoint, liver function tests and bilirubin should be monitored every 2 weeks for the first 3 months then monthly thereafter.[1] Serum potassium should be monitored monthly. If prednisone is withdrawn during treatment, patients should be monitored biochemically for signs and symptoms of mineralocorticoid excess.[1] We also monitor complete blood count (ADT and disease progression may cause anemia), creatinine level for

obstructive uropathy, HbA1c and lipid testing for the metabolic syndrome, and serum calcium as we generally administer concurrent bone targeted agents in most patients on AA.

Monitoring for response or progression with AA is complicated by the fact that PSA does not always correlate with disease status.[8] Assessing response to treatment is not standardized—a combination of radiographic, biochemical, and clinical factors should gauge response. In our practice, we assess PSA, hemoglobin, LDH and ALP levels monthly. At 3-6 month intervals, we perform CT scans of the chest, abdomen and pelvis and nuclear bone scintigraphy. The frequency and need for imaging in the setting of low and stable PSA can, however, be questioned on an individual basis. Patients are also assessed for clinical progression during their history and physical examination. Disease progression can be rapid when patients do not respond or fail AA therapy—and this is best detected by a vigilant approach and frequent assessments.

## Adverse effects of abiraterone acetate

Abiraterone acetate has a low rate of drug discontinuation or dose reduction secondary to toxicities. The most common adverse events (AE) seen in COU-AA-301[8] and COU-AA-302[3] were fatigue, back pain, nausea, bone pain, and arthralgia. These were generally low grade AEs and occurred at a similar rate in the placebo group.

Specific AEs in COU-AA-301[3] thought to be related to treatment with AA include those associated with mineralocorticoid excess (hypokalemia, hypertension and fluid retention) as well as cardiac disorders and liver function test abnormalities. These were seen more frequently in the COU-AA-301[3] treatment group (55% versus 43%, $p < 0.001$). The incidence of fluid retention and edema was higher with AA treatment (31% versus 22%, $p = 0.04$). Hypokalemia was also seen more commonly with AA treatment (17% versus 8%, $p < 0.001$). Post-hoc subgroup analysis of the COU-AA-301[3] and 302[8] data evaluating patients older than 75 years old, a subgroup postulated to be more susceptible to the mineralocorticoid excess, showed no difference in adverse events compared to the younger cohort (less than 75 year old).[18]

Although treatment with AA has been known to increase liver function tests, significant differences between the treatment and placebo groups were not seen in COU-AA-301.[3] In COU-AA-302,[8] treatment with AA resulted in a significant increase in aminotransferase levels (8% versus 3%) but no hepatotoxicity related deaths were recorded.

Although initially hypothesized, mineralocorticoid excess did not significantly increase cardiac AEs (tachycardia, atrial fibrillation or fatal cardiac events).[3] Rare cases of myopathy and rhabdomyolysis occurred within the first month of treatment and resolved following drug discontinuation.[1]

The dose of prednisone administered with AA is low and is associated with few adverse effects. Pooled retrospective data from COU-AA- 301 and 302 showed that the most common corticosteroid associated AEs were weight gain and hyperglycemia.[19] No trend could be observed with the length of treatment duration with low dose corticosteroid and the frequency of corticosteroid associated AE's.[19] Nonetheless, though risk is low patients treated with AA and prednisone should be advised about prednisone related AEs and patients should be monitored for these.

## Dose adjustments

No dose adjustments are required for mild (Childs-Pugh Class A) hepatic impairment or renal insufficiency.[1] For patients who develop hepatotoxicity (AST or ALT increase 5 times above the upper limit of normal [ULN] or bilirubin rise 3 times the ULN) treatment should be withheld until liver function tests normalized. AA related hepatotoxicity is generally reversible on discontinuation of the drug. After normalization of hepatic enzymes, treatment may be resumed at a reduced dose of 500 mg daily. If patients develop severe hepatoxicity (ALT > 20 times ULN) AA should be discontinued permanently.[1] Myopathy, rhabdomyolysis or confirmed pneumonitis or allergic alveolitis should also prompt permanent discontinuation of the medication.

## Resistance to abiraterone acetate

Resistance to AA is inevitable and patients will ultimately progress on therapy. Multiple androgen receptor (AR) dependent and independent mechanisms have been identified to explain AA resistance. AA treatment may permit glucocorticoid or progesterone AR agonism.[20] In a small study evaluating one such mutation, it was found that 3/18 patients with mCRPC had developed mutations that allowed for more non-selective AR activation.[21] Furthermore, the identification of AR7 splice variant confers increased resistance to molecules targeting AR signaling including AA and enzalutamide.[22] AR independent mechanisms for AA resistance include glucocorticoid receptor overexpression that may cause downstream utilization of the AR transcriptome. Large genomic studies and epigenomic studies are underway to evaluate the tumor biology that drives AA resistance.

## Progression after abiraterone acetate

A number of options are available for patients who progress on AA.[5,15] The optimal sequencing of novel CRPC agents is currently unknown. In our practice, patients progressing on AA are generally considered for docetaxel or enzalutamide. Symptomatic patients with a good performance status are referred for docetaxel or radium-223 in the setting of significant burden of bone disease. In those, with poor performance status (thus not eligible for docetaxel) enzalutamide may be considered following progression on abiraterone. We also continue ADT, monitor for mCRPC complications, and consider institution of palliative care when patients progress on AA.

## Conclusion

Abiraterone acetate is a CYP17 inhibitor that improves overall survival and quality of life in metastatic castration resistant prostate cancer. AA is well tolerated and side effects are primarily those of mineralocorticoid excess—including hypokalemia, hypertension, and peripheral edema. AA may rarely be associated with hepatotoxicity and liver function testing during therapy is essential. Disease progression on AA is inevitable and patients need to be closely followed such that timely referral can be made for subsequent therapies. □

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