UCSF Helen Diller Family Comprehensive Cancer Center

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A Phase II Study of Increased-Dose Abiraterone Acetate in Patients with Castration Resistant Prostate Cancer (CRPC)

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Protocol Signature Page

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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators" Brochure (or Manufacturer"s Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

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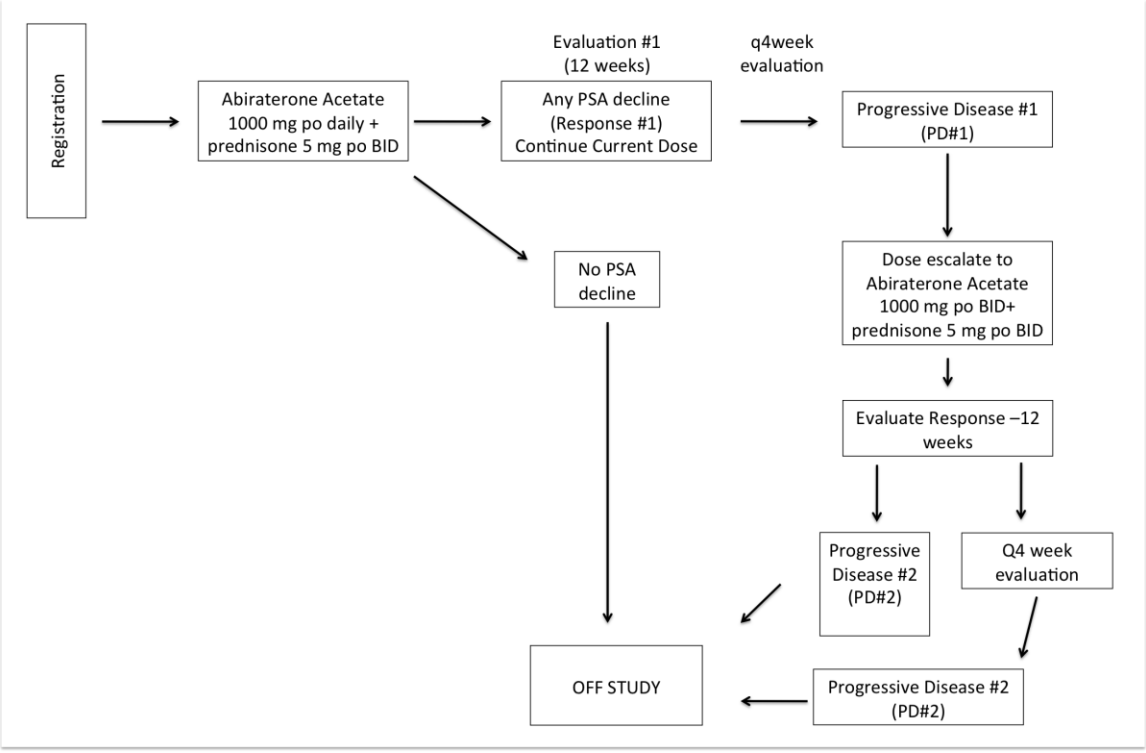
Study Schema



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1. BACKGROUND

1.1. Hormonal Therapy in Prostate Cancer

Prostate cancer is the second most common cancer in men representing approximately 30% of all cancers diagnosed in men. When confined to the prostate gland the disease is curable with local therapy. However approximately 50% of men fail local therapy and develop incurable metastatic disease. Androgen deprivation therapy (ADT) remains the mainstay of treatment, not only for advanced disease but also in the adjuvant and in certain neoadjuvant settings. ADT lowers circulating testosterone levels, induces a remission in 80 to 90% of patients with advanced disease, and results in a median progression-free survival of 12 to 33 months, at which time a castration resistant phenotype usually emerges. This accounts for the median overall survival of 23 to 37 months from the initiation of androgen deprivation.

1.2. Mechanisms of Prostate Cancer Growth Despite ADT

Androgen deprivation can be achieved surgically with orchiectomy, or by drug treatment. Current approaches to ADT utilize luteinizing hormone releasing hormone (LHRH) agonists. These act by continuous stimulation of the anterior pituitary resulting in inhibition of luteinizing hormone (LH) secretion, and hence a fall in testicular production of testosterone. Although ADT is clinically effective in the majority of patients, the adrenal cortex remains active and produces multiple androgens including dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS) and androstenedione. While not as potent as testosterone or dihydrotestosterone, these androgens nonetheless can function as weak agonists for the wild type AR and can stimulate mutant AR resulting in cell growth. Similarly, these androgens may be peripherally converted to dihydrotestosterone, a potent stimulator for AR, by the enzyme 5a reductase[1,2].

Studies have shown that adrenal androgens represent an important alternative source of stimulation in a significant proportion of prostate cancer patients. As much as 10% of baseline circulating testosterone remains in castrate men, due to the peripheral conversion of adrenal steroids to testosterone[3]. Increased levels of androgen receptor have been documented in CRPC cells and confer resistance to antiandrogens in prostate cancer xenograft models[4]. This amplification is hypothesized to result in amplified signal output from circulating low levels of adrenal androgens and suggests a role for agents that target the adrenal androgen synthesis pathway.

At the same time androgen production by tumor cells themselves has been postulated to lead to increased levels of androgens in the tumor microenvironment. CRPC cells express higher levels of enzymes responsible for androgen synthesis, and androgen levels are higher in metastatic CRPC biopsies than in circulation[5]. Using agents that target both this intracrine androgen production as well as systemic androgen production therefore have the potential to slow CRPC growth.

1.3. Adrenal Androgens in Prostate Cancer

Prior studies have shown that suppression of adrenal androgen synthesis can slow the growth of CRPC. Ketoconazole is an orally available azole antifungal agent that inhibits the side chain cleavage enzyme responsible for the conversion of cholesterol to pregnenolone, a necessary

step in the production of all androgens. Ketoconazole has been shown to suppress DHEA, DHEAS and androstenedione following one month of therapy, and has been shown to have modest antitumor activity in patients who have progressed on combined LHRH agonist and antiandrogen therapy[6]. Approximately 30% of patients enrolled on CALGB 9583, a randomized phase III trial of antiandrogen withdrawal (AAWD) alone versus high-dose ketoconazole/hydrocortisone experienced a 50% or greater PSA decline. A statistically significant (p=0.0001) increase in DHEAS and androstenedione was noted at the time of progression on ketoconazole suggesting that, over time, this drug loses its ability to inhibit adrenal androgen synthesis.

Another limitation of ketoconazole, however, is the fact that it is an unselective inhibitor of CYP450 enzymes. It inhibits cholesterol side chain cleavage and 11β-hydroxylation[7] as well as CYP17 activities. The result of this lack of specificity is an almost universal requirement for corticosteroid replacement in patients leading to increased cost, potential for morbidity and difficulty with compliance. Abiraterone Acetate was developed specifically to address this need.

1.3.1. The Adrenal Steroid Synthesis Pathway

The adrenal steroid synthesis pathway is shown below in Figure 1. The enzyme complexes inhibited by Abiraterone Acetate and ketoconazole, are shown. Ketoconazole"s principal mechanism of action is blockade of the cholesterol side chain cleavage enzyme as well as 11-beta hydroxylase, as shown, whereas Abiraterone Acetate inhibits the CYP 17A1 complex of enzymes, with dual c17 lyase and 17, 20 hydroxylase activity. As the figure demonstrates, the end result of inhibition is a reduction of adrenal androgen production.

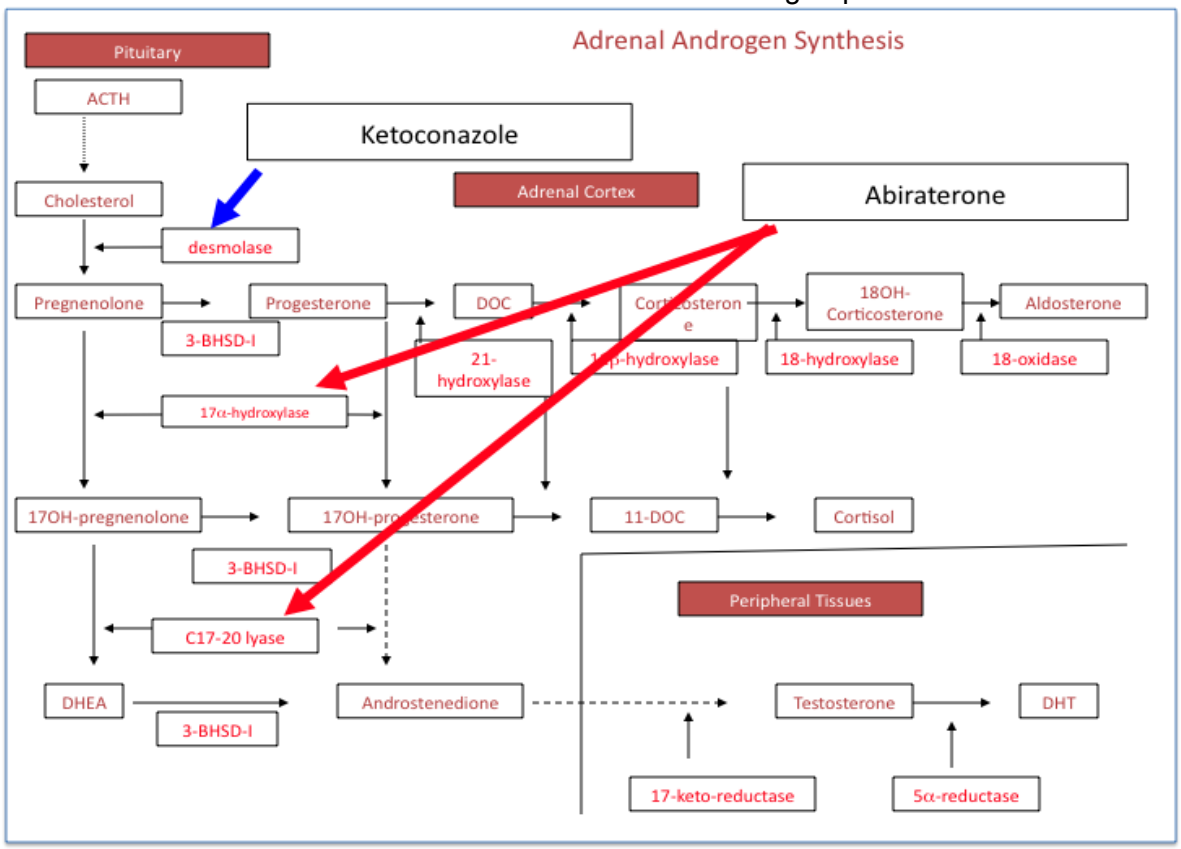


Figure 1: The adrenal steroid synthesis pathway

1.4. **Abiraterone Acetate** (JNJ212082).

Abiraterone Acetate (JNJ212082, previously known as CB7630) is the 3-acetate and a prodrug of JNJ-589485 (previously known as CB7598) suitable for oral administration. Abiraterone Acetate [JNJ-589485, 17-(3-pyridyl) androsta-5,16-dien-3β-ol] was developed as a highly specific steroidal inhibitor of CYP17 (17a-hydroxylase/$C_{17,20}$-lyase), with two important enzymatic activities in the synthesis of testosterone, based on the observation that nonsteroidal 3-pyridyl esters had improved selectivity for inhibition of 17α-hydroxylase/$C_{17,20}$- lyase.[8] JNJ-589485 is a potent inhibitor with an apparent inhibition constant of 0.5 nM.

The chemical nomenclature of JNJ212082 is 3β-acetoxy-17-(3-pyridyl) androsta-5,16-diene; its empirical formula is $C_{26}H_{33}NO_2$. It has a molecular weight of 391.55. Once absorbed after oral administration, JNJ212082 is rapidly converted to the active form, JNJ-589485 (Figure 2). JNJ-589485 was the predominant, if not the only form of Abiraterone Acetate detected in blood both in preclinical studies and in previously conducted clinical studies.

Abiraterone Acetate (1000 mg) is FDA approved for use with prednisone for metastatic castration-resistant prostate cancer following docetaxel. It is used in patients whose disease has not gotten better with other chemotherapy or hormone therapy.

1.5. **Rationale For Using Abiraterone Acetate in Prostate Cancer**

The major limitation of therapy with ketoconazole is the development of resistance to the therapy over time, the high rate of intolerability due to gastrointestinal toxicities, and the multiple drug interactions that limit its use in patients with comorbidities. In addition, therapy with ketoconazole requires the administration of 6 ketoconazole tablets daily as well as three tablets of hydrocortisone daily for glucocorticoid replacement. As Abiraterone Acetate is administered as 4 tablets once daily and does not have significant drug-drug interactions, it represents a significant advance in the management of androgen independent prostate cancer and a desirable alternative to ketoconazole.

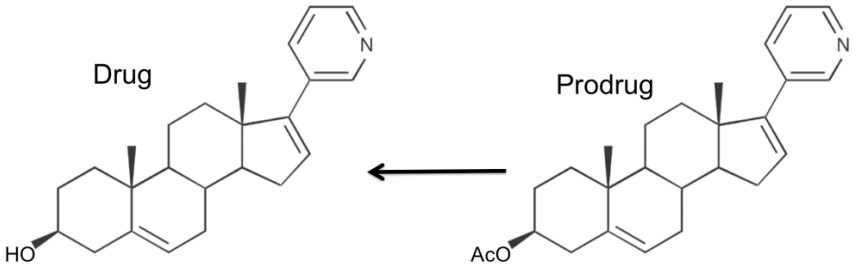


Figure 2. Prodrug Abiraterone Acetate is converted to Abiraterone after absorption.

1.6. **Clinical Data with Abiraterone Acetate.**

To determine if inhibition of 17-alpha-hydroxylase/$C_{17,20}$ lyase could indeed suppress adrenal testosterone production in human as predicted from mechanism of action and animal models, Phase 1 exploratory studies of JNJ212082 were conducted in castrated or noncastrated patients with prostate cancer. An overview of the three initial Phase 1 studies is provided as well as an overview of subsequent studies. In the first series of phase 1 studies a total of 26 patients were

treated with doses ranging from 10 to 800 mg/d. Overall, the results of these studies showed that JNJ212082 was safe and well tolerated. At 500 and 800 mg/d either as single dose or as consecutive daily doses, significant decreases in circulating testosterone were observed. The effects of JNJ212082 on glucocorticoid and mineralocorticoid levels were also investigated especially in patients receiving 12-day continuous dosing at 500 and 800 mg/d. There were no clear clinical signs of mineralocorticoid excess or glucocorticoid insufficiency. In this multiple-dose study, basal levels of cortisol were within normal limits, but short Synacthen tests with standard doses of adrenocorticotropic hormone (ACTH) on Day 11 showed diminished peak cortisol levels at 30 minutes when compared with those in pretreatment test. However, the peak responses that were below the 500 nmol/L (18 µg/dL) normal threshold were observed only in five of the six patients (two at 500 and three at 800 mg/d dose levels). The clinical relevance of abnormal ACTH stimulation test in patients receiving JNJ212082 is unknown. Results from these Phase 1 studies were published in the British Journal of Cancer[9].

A second Phase 1/2 was then performed in which a total of 21 patients were treated with in a dose escalation fashion ranging from 250 to 2000 mg/d[10]. A total of 3 patients were treated at the maximum dose of 2,000 mg/d and no treatment related grade 3 or 4 toxicities were observed in any patient. Two patients at the 2,000 mg/d dose experienced Grade 1-2 hypertension, two experienced Grade 1-2 hyperkalemia, and one experienced Grade 1-2 peripheral edema. Because a plateau of endocrine effects was seen at 750 mg/d, the 1000 mg/d dose was chosen as the recommended phase 2 dose. An expansion to a phase II study was then performed at the 1,000 mg/d dose in an additional 33 men. A PSA decline of ≥ 50% was observed in 28 (67%) of 42 Phase I/II patients treated at 1,000 mg/d. Radiographic partial responses by RECIST criteria were seen in 9 (37.5%) of 24 phase II patients with measurable disease. Importantly, the addition of dexamethasone at disease progression reversed resistance in 33% of patients regardless of prior treatment with dexamethasone.

Abiraterone Acetate was evaluated in a subsequent Phase I study in men with chemotherapy naïve CRPC[11]. A total of 33 men were enrolled, including 19 (58%) who had received prior ketoconazole. Fasted or fed cohorts were treated with Abiraterone Acetate doses of 250, 500, 750, or 1,000 mg daily and single-dose pharmacokinetic analyses were performed before continuous daily dosing. Confirmed ≥ 50% PSA declines at week 12 were seen in 18 (55%) of 33 patients, including nine (47%) of 19 patients with prior ketoconazole therapy and nine (64%) of 14 patients without prior ketoconazole therapy. Substantial declines in circulating androgens and increases in mineralocorticoids were seen with all doses. No dose-limiting toxicities were observed. Hypertension (grade 3, 12%) and hypokalemia (grade 3, 6%; grade 4, 3%) were the most frequent serious toxicities and responded to medical management. On the basis of evidence of clinical responses across several doses, maximization of the intended endocrinologic effects, and the favorable safety, dose escalation was ceased at 1,000 mg daily.

A series of phase II study then evaluated Abiraterone Acetate in men with CRPC. In one study 33 patients received Abiraterone Acetate 1,000 mg daily with prednisone 5 mg twice daily in continuous 28-day cycles[12]. Prednisone was added to mitigate mineralocorticoid excess which resulted in the hypokalemia and hypertension observed in the Phase I studies. A ≥50% PSA decline at week 12 was confirmed in 22/33 (67%) patients. PSA declines of ≥50% were seen in 26/33 (79%) patients. PSA declines of any magnitude at 12 weeks were observed in 85% of patients. Undetectable PSA levels (≤0.1 ng/mL) occurred in two patients. Median time on therapy and time to PSA progression were 63 weeks and 16.3 months, respectively. Adverse events were typically grade 1/2 and consistent with prior published Abiraterone Acetate reports.

A second phase II study of 58 men with progressive metastatic CRPC who experienced treatment failure with docetaxel-based chemotherapy received Abiraterone Acetate 1,000 mg daily with prednisone 5 mg twice daily[13]. Twenty-seven (47%) patients had received prior ketoconazole. A ≥50% decline in PSA was confirmed in 22 (36%) patients, including 14 (45%) of 31 ketoconazole-naïve and seven (26%) of 27 ketoconazole-pretreated patients. Partial responses were seen in four (18%) of 22 patients with RECIST-evaluable target lesions. Improved ECOG PS was seen in 28% of patients. Median time to PSA progression was 169 days (95% CI, 82 to 200 days). The majority of adverse events were grade 1 to 2, and no Abiraterone Acetate-related grade 4 events were seen.

A third phase II study evaluated Abiraterone Acetate in 42 patients who previously received docetaxel. PSA declines of ≥ 30%, ≥ 50% and ≥ 90% were seen in 68% (32 of 47), 51% (24 of 47), and 15% (seven of 47) of patients, respectively. Partial responses (by RECIST) were reported in eight (27%) of 30 patients with measurable disease. Median time to PSA progression was 169 days (95% CI, 113 to 281 days). The median number of weeks on study was 24, and 12 (25.5%) of 47 patients remained on study ≥ 48 weeks.

Abiraterone Acetate was subsequently evaluated in COU-AA-301, a multicentered randomized, double-blind placebo controlled Phase 3 study[14]. In total 1195 men with CRPC who had previously received docetaxel were randomly assigned in a 2:1 fashion to received prednisone 5mg twice daily plus either 1000 mg of Abiraterone Acetate (797 patients) or placebo (398 patients). The primary end point was overall survival. After a median follow-up of 12.8 months, overall survival was longer in the Abiraterone Acetate–prednisone group than in the placebo–prednisone group (14.8 months vs. 10.9 months; hazard ratio, 0.65; 95% confidence interval, 0.54 to 0.77; P<0.001). Data were unblinded at the interim analysis, since these results exceeded the preplanned criteria for study termination. All secondary end points, including time to PSA progression (10.2 vs. 6.6 months; P<0.001), progression-free survival (5.6 months vs. 3.6 months; P<0.001), and PSA response rate (29% vs. 6%, P<0.001), favored the treatment group.

On the basis of this study, in April 28th, 2011 the United States Food and Drug Administration approved abiraterone acetate for use in combination with prednisone for the treatment of patients with metastatic CRPC who have received prior chemotherapy containing docetaxel.

A second multicentered randomized double-blind placebo-controlled Phase III study, COU-AA-302, is testing the effect of Abiraterone Acetate 1000mg daily plus prednisone 5mg bid in men with CRPC who have not yet received chemotherapy, with progression-free and overall survival as co-primary endpoints. This study is currently ongoing.

1.7. **Clinical Safety Data**

Over 1400 men with CRPC have been treated in the aforementioned studies, with the vast majority of patients having received the 1,000 mg/d dose. Overall the most common adverse events (≥5%, all grades) observed in clinical studies were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection. In that phase III study common adverse events in both groups were back pain (30% in the Abiraterone Acetate group and 33% in the placebo group), nausea (30% and 32%, respectively), constipation (26% and 31%), bone pain (25% and 28%), and arthralgia (27% and 23%). Most of these events were grade 1 or 2. Urinary tract infection was more frequent in the Abiraterone Acetate group (12%, vs. 7% in the placebo group; P=0.02); these infections were

also primarily grade 1 or 2 events. Adverse events resulting in treatment discontinuation occurred with similar frequency in the Abiraterone Acetate and placebo groups (19% and 23%, respectively; P=0.09). The incidence of adverse events leading to dose modification or interruption was also similar in the two groups. Adverse events associated with elevated mineralocorticoid levels due to CYP17 blockade (fluid retention and edema, hypokalemia, and hypertension) were observed in the phase I and II studies and were treated with aldosterone antagonists, potassium supplementation, and concurrent administration of corticosteroids (see section 1.9). In the phase III study the incidence of fluid retention and edema was higher in the Abiraterone Acetate group (31%, vs. 22% in the placebo group; P=0.04). Grade 1 or 2 peripheral edema accounted for most of these events. Hypokalemia also occurred in a higher proportion of patients in the Abiraterone Acetate group (17%, vs. 8% in the placebo group; P<0.001).

In the phase III study cardiac events (primarily grade 1 or 2) occurred at a higher rate in the Abiraterone Acetate group than in the placebo group (13% vs. 11%, P=0.14), but the difference was not significant. The most frequently reported cardiac events were tachycardia (3% in the Abiraterone Acetate group and 2% in the placebo group, P=0.22) and atrial fibrillation (2% and 1%, respectively; P=0.29). All tachycardia events were grade 1 or 2; atrial fibrillation events were grade 3 or lower. Despite the slightly higher incidence of cardiac events in the Abiraterone Acetate group than in the placebo group, there was no significant increase in fatal cardiac events in the Abiraterone Acetate group (1.1%, vs. 1.3% in the placebo group). One death associated with arrythmia and one patient with sudden death were observed on the Abiraterone Acetate arm, while none were observed on the placebo arm.

In the phase III study a grade 4 elevation in an aminotransferase level early in the study led to a protocol amendment specifying more frequent monitoring with liver-function tests during the first 12 weeks of treatment. Overall, however, abnormalities in liver-function tests occurred at a similar frequency in the Abiraterone Acetate and placebo groups, including changes of any grade in liver-function tests (10% and 8%, respectively), grade 3 or 4 changes in liver-function tests (3.5% and 3.0%), grade 3 or 4 elevations in aspartate aminotransferase levels (1.4% and 1.6%), grade 3 or 4 elevations in alanine aminotransferase levels (1.0% and 1.1%), and grade 4 elevations in aminotransferase levels (0.3% and 0.5%). Across all studies elevations hepatotoxicity was observed in 2.3% of patients typically during the first 3 months of treatment. Elevations in AST/ALT returned to normal upon drug discontinuation.

Overall in the Phase III study grade 3-4 events were rare; compared to placebo-treated patients, patients on the Phase III studied treated with Abiraterone Acetate were more likely to experience Grade 3-4 hypertension (1.3% vs. 0.3%), edema (1.9% vs. 0.8%), urinary tract infection (2.1% vs. 0.5%), cardiac failure (1.9% vs. 0.3%), elevated AST (2.1% vs 1.5%), hypokalemia (5.3% vs 1%), hypophosphatemia (7.2% vs 5.8%) and elevated ALT (1.4% vs 0.8%). No individual grade 4 adverse events occurred in 2% or more of patients in either treatment group.

In the Phase III study a total of 11% of patients in the Abiraterone Acetate group and 13% of patients in the placebo group died within 30 days after the last dose of study medication, primarily as a result of disease progression. A lower proportion of patients in the Abiraterone Acetate group than in the placebo group had an adverse event that resulted in death (12% vs. 15%).

1.8. **Clinical Pharmacokinetics**

Blood specimens from phase 1 studies were analyzed for JNJ-589485. The pharmacokinetic parameters all show considerable variability between patients and are presented in Table 1. The

mean T_{max} was 2.70 hours (± Std Dev 2.71) with a mean elimination half-life of 27.6 hours (± Std Dev 20.17). A range of up to 10-fold in AUC was seen for a given dose. The level of interpatient variability made analysis of dose-dependent pharmacokinetic relationships difficult. Further investigation is required in clinical trials. Adrenal metabolite analysis showed inhibition of CPY17 even at low doses of Abiraterone Acetate and a compensatory increase of corticosterone was apparent at all dose levels tested.

When administered with food that had high-fat content, drug exposure was significantly increased (by 4.4-fold) compared with fasting administration (P=0.049; Fig 3D). The variability between fed patients was comparable to that observed between fasted patients. There was no significant increase in Cmax, but absorption was significantly extended after food. Based on these results and for consistency in absorption, in all subsequent studies of Abiraterone Acetate patients have been instructed to take orally at least 2 hours after a meal or 1 hour before a meal any time up to 10 pm every day.

The maximum dose of abiraterone acetate used in pharmacokinetic studies is 2,000 mg/d. Up to 2.5 fold variations in AUC were observed at 750 mg/d and 2,000 mg/d cohorts. Figure 3 demonstrates that despite interpatient variability overall both the AUC and Cmax appear to increase with increasing dose of abiraterone acetate. The terminal half life of the 1000mg dose of abiraterone acetate is 14.4 hours.

Table 1: Summary of Pharmacokinetic Data for JNJ212082 Measured as JNJ-589485 in Plasma

Patient	Dose (mg/m^2)	AUC μM.h	C_{max} μM	T_{max} H	$T_{1/2\alpha}$ h	$T_{1/2\beta}$ h	K_{abs} H
1	10	ND	ND	ND	ND	ND	ND
2	10	ND	0.001	2	ND	ND	ND
3	10	ND	0.018	11	ND	ND	ND
4	30	ND	ND	ND	ND	ND	ND
5	30	ND	0.004	4	ND	ND	ND
6	30	ND	0.006	1	ND	ND	ND
7	100	0.15	0.012	13	6.5	ND	6.5
8	100	0.09	0.011	0.16	0.97	26.5	0.03
9	100	0.12	0.019	3.7	2.0	28	1.8
10	200	0.39	0.061	2.8	1.59	25.8	3.87
11	500	0.25	0.063	0.8	0.28	29	0.01
12	500	1.68	0.139	3.7	1.83	21	1.8
13	500	0.73	0.06	3.6	1.73	74	1.71
14	500	0.67	0.066	4	1.43	18	1.41
15	500	0.42	0.077	2	0.29	13.4	1.00
16	500	1.38	0.167	2.7	0.05	13.3	1.15
17	200	0.23	0.037	0.69	1.49	28	0.03
18	500	1.23	0.054	1.7	0.19	14.6	0.3
19	500	1.101	0.183	1.51	0.71	14	0.7
20	500	2.08	0.30	1.41	1.59	24	0.12
21	500	3.54	0.62	1.70	1.07	23.2	0.82
22	500	0.34	0.07	2.30	0.79	12.0	0.80
23	500	NE	NE	NE	NE	NE	NE
24	800	11.66	1.19	3.02	1.32	87	1.34
25	800	2.32	0.43	1.20	0.45	19.9	0.45
26	800	2.84	0.18	3.10	1.73	26.2	1.82

Details of patients: PT 1 - 16: single dose study in castrate males
PT 17 - 20: single dose in non-castrate males
PT 21 - 26: multi-dose study in non-castrate males

Abbreviations:
NE: Not evaluated due to problems with the assay; ND: Not detectable, plasma concentrations too allow to permit estimation of the pharmacokinetic behaviour of the drug; AUC: Area under the concentration time curve; C_{max}: maximum concentration; T_{max}: time to maximum concentration, $T_{1/2\alpha}$: Initial half-life, $T_{1/2\beta}$: terminal half life; K_{abs}: absorption rate constant.

Figure 3: Additional Pharmacokinetic Data for JNJ212082 Measured as JNJ-589485 in Plasma

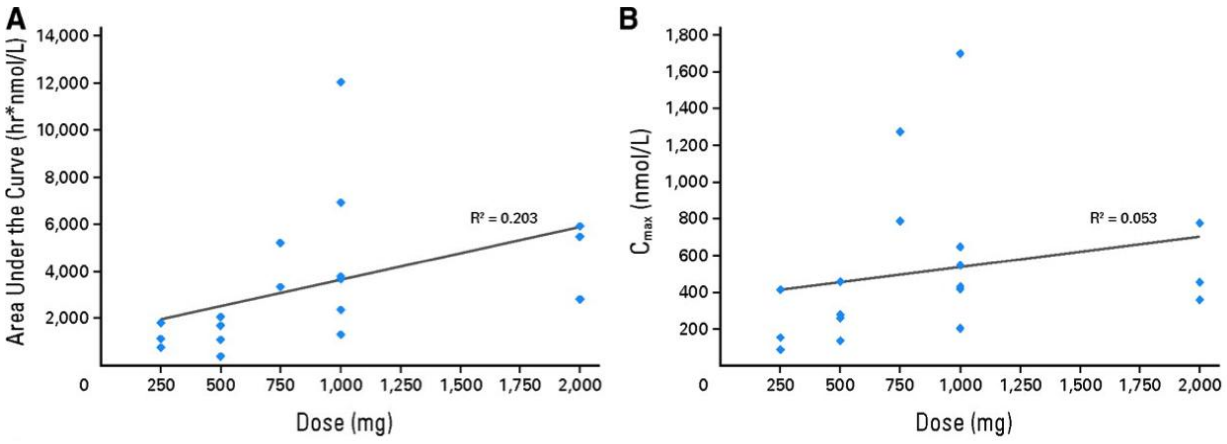


Figure 3: Pharmacokinetics of Abiraterone Acetate. (A) Area under the concentration-time curve versus dose in fasted patients; (B) maximum concentration (C_{max}) versus dose in fasted patients

1.9. Concurrent Prednisone

Reduced cortisol levels induced by blockade of CYP17A1 lead to a compensatory ACTH surge and thereby result in the hypertension, hypokalemia, and fluid retention observed in the Phase 1 and 2 studies. These side-effects were readily managed with potassium supplementation, eplerenone (selective mineralocorticoid antagonist), antihypertensive agents, and low dose corticosteroids. Grade 1-2 fatigue was observed in some patients and was associated with discontinuation of corticosteroids as required per Phase 2 protocol entry criteria and extended duration of treatment with Abiraterone Acetate. Although there was no evidence of a dose-response relationship, administration of low-dose corticosteroids improved symptoms of fatigue and tolerability of Abiraterone Acetate in Phase 2 studies, including symptoms of mineralocorticosteroid excess. The improved tolerability of Abiraterone Acetate after concomitant administration of low-dose corticosteroids was associated with suppression of ACTH surge and upstream adrenal steroids, suggesting that this combination may be a better tolerated and safer regimen in this older and frail patient population. Prednisone was selected over other corticosteroids because it is commonly used as standard of care in combination with approved chemotherapy agents or as a monotherapy for palliation of symptoms. The use of concurrently administered prednisone was evaluated in the COU-AA-301 phase III study and was determined to be safe and effective as discussed in section 1.7.

1.10. Hypotheses regarding resistance to adrenal targeted therapies

Resistance to Abiraterone Acetate is hypothesized to develop due to an inability over time of Abiraterone Acetate to suppress androgen synthesis, resulting in increasing levels of androgens within tumors and disease progression. This hypothesis is supported by multiple lines of evidence. First, pretreatment androgen levels are associated with the likelihood of response to Abiraterone Acetate[15], suggesting that CRPC tumors rely on androgen signaling for growth and survival. Second, molecular analysis of CRPC tumors has shown that enzymes regulating androgen synthesis are upregulated compared to benign tissue, and that intratumoral androgen levels are elevated[16], suggesting that suppressing both systemic and local androgen production

in the tumor microenvironment may be necessary to induce a clinical response. Third, circulating androgen levels are known to rise at the time of clinical progression on ketoconazole, an agent similar to Abiraterone Acetate, suggesting that increases in androgen signaling may lead to progression of disease.[17] Fourth, the addition of dexamethasone at the time of disease progression on Abiraterone Acetate has been shown to induce second responses[10], suggesting possibly that manipulation of the hormonal milieu even at the time of disease progression on Abiraterone Acetate has the potential to reverse Abiraterone Acetate resistance. Lastly, while a pharmacodynamic study of Abiraterone Acetate in men with CRPC did not show consistent rises in circulating androgen levels and the time of disease progression[18], intratumor androgen levels were not assayed and therefore androgen levels within CRPC tumors at the time of progression on Abiraterone Acetate are unknown. Similarly, the small total number of patients (n=14) and the 4 different dosing schedules investigated in this initial pharmacodynamic study greatly limits the statistical power of this observation. Taken together this evidence suggests that further reduction in androgen synthesis has the potential to slow tumor growth and result in a second response to Abiraterone Acetate therapy.

1.11. Rationale for using dose increased Abiraterone Acetate at the time of clinical progression

Intratumoral androgen levels are hypothesized to increase at the time of clinical progression, and pharmacokinetic studies suggest that an increased dose of Abiraterone Acetate can result in a higher exposure of CRPC to drug.

Elevated dose therapy is given at disease progression as opposed the outset of therapy for a number of reasons:

- Standard dose Abiraterone Acetate appears to be an effective therapy for the vast majority of men with CRPC not yet treated with chemotherapy, with close to 80% response rate and a median time to progression of 11.5 months in phase 2 testing. Therefore most subjects men stand to benefit clinically from a standard dose „run-in" period.

- Dose increase at the time of resistance to standard dose therapy will allow for better characterization of the biology of Abiraterone Acetate resistance both by analysis of hormone levels at the time of initial resistance, and characterization of hormone and PSA responses to increased dose.

- While safe and well tolerated at all dosing levels in phase 1 testing, increased dose Abiraterone Acetate has not been tested in large numbers of subjects, and therefore increased dose at the time of initial therapy could place some subjects at risk of unnecessary toxicity.

- As the terminal half-life of the 1000mg daily dose is 14.4 hours, a dose of 1000mg BID (q12 hours) is chosen, as this dose is likely to result in consistently higher abiraterone levels. 4 x 250mg tablets BID is also expected to be easier to take than 8 x 250mg tablets at once.

1.12. Rationale for using PSA response as the primary endpoint

PSA response defined as a ≥30% PSA decline from baseline after 12 weeks of elevated dose therapy will be used as a primary endpoint in this study. Although PSA is not a surrogate for survival[19], there exists no better biomarker that is easily measured, widely used in clinical practice, and not subject to interobserver bias. Moreover, while objective measures (bone scan, CT scan) have been used to define disease progression in Phase III clinical studies of Abiraterone Acetate, it is likely that treatment resistance develops long before disease progression is radiographically apparent, and in the majority of cases resistance is heralded by a rise in the PSA. Similarly, it is expected that most clinicians will use PSA response to make decisions about when to stop treating patients with Abiraterone Acetate. Lastly, PSA response endpoints, as described in this study, have been recently endorsed as suggested outcome measures by the Prostate Cancer Clinical Trials Working Group[20]. Therefore PSA response will be used in this study as an endpoint.

1.13. Rationale for this study

Determination of the mechanisms of resistance to standard-dose Abiraterone Acetate is important in this patient population. Observational data suggests that increased androgen levels may allow CRPC to grow despite androgen synthesis inhibitor therapy. This study will aid in the understanding of resistance to Abiraterone Acetate, and simultaneously test whether resistance may be overcome via an increased dose. The study will also allow for a pharmacokinetic and pharmacodynamic understanding of resistance and may aid in allowing clinicians to risk-stratify patients for appropriately dosed therapy.

This is an investigator initiated study. Janssen Services will be supporting the study by supplying Abiraterone Acetate and study funding.

1.14. Mechanisms of Resistance

1.14.1. Circulating Tumor Cell and Metastatic Biopsy, and Pharmacogenetic Analysis

Resistance to Abiraterone Acetate is hypothesized to be due to a failure over time of abiraterone to inhibit androgen synthesis leading to a rise in intratumoral androgen levels and progression of disease. Mechanisms of increased synthesis include amplification of CYP17A1 and other genes in the androgen synthesis pathway, changes in CYP17A1 gene methylation leading to increased expression, or point mutations impairing the ability of Abiraterone Acetate to bind to its CYP17A1 substrate. Other mechanisms include AR amplification, over-expression, or loss of negative regulators of AR.

In order to discover the genetic events associated with treatment resistance, genomic analysis of circulating tumor cells (CTCs) and metastatic CRPC biopsies are techniques which offer the ability to analyze in real-time genomic changes in pathways associated with resistance. Quantitative CTC counting has demonstrated promise as a biomarker of response in men with CRPC treated with abiraterone and with chemotherapy, and qualitative analysis of CTCs offers the potential to interrogate genomic changes occurring in the androgen synthesis pathway in men treated with abiraterone.

Because CTC analysis is exploratory, biopsy of metastatic tissue offers a similar potential to evaluate changes in methylation as well as in the expression of CYP17A1 and other androgen synthesis genes, the androgen receptor (AR) and coregulators,

and other genes implicated in resistance to Abiraterone. Experience in CRPC has demonstrated that it is possible and feasible to collect metastatic biopsies prior to and on therapy. Currently, based on a Phase II trial that uses microarray-results from radiologically-guided therapies to determine AR activity so as to guide therapy, the technical success rate over the past 35 biopsy procedures is 74%. Thus, for the proposed trial, a similar if not improved success rate is anticipated. Microarray analysis of biopsies, in combination with exploratory CTC analysis, therefore has the potential to generate a wealth of data and allow for the discovery of both hypothesized and novel mechanisms of resistance to Abiraterone.

1.14.2. **Pharmacogenetic Analysis**

Signaling mediated by steroid hormone activation of the AR is suspected to be not only a pivotal event leading to the initial development of prostate cancer, but also critical in the progression of disease despite androgen deprivation. The CYP17A1 gene is located on chromosome 10q24.3 and encodes the cytochrome P450c17a, which is responsible for 17 –alpha-hydroxylase and 17-20 lyase enzymatic activity, key steps in the development of androgens (**See Fig 1**). Several benign conditions associated with androgen excess including male pattern baldness and polycystic ovaries in women have been associated with a variant allele of CYP17A1, A2. The CYP17A1 A2 allele polymorphism results from a single base pair substitution (-34T>G) located in the 5‟ untranslated region upstream of the initiation site. The net effect of this polymorphism is the creation of an additional Sp-1 type promoter site, which is hypothesized to result in increased transcription of the CYP17A1 gene leading to higher androgen levels. The A2 allele is present in approximately 56% of the Caucasian population, and 13-15% are homozygous for the A2 allele[21].

A series of studies have associated polymorphisms of CYP17A1 with risk of prostate cancer incidence and mortality. Stanford and colleagues, in a population-based study of incident prostate cancer, demonstrated that men with a family history of prostate cancer who are homozygous for the A2 allele of CYP17A1 have a 19-fold increased risk of prostate cancer[22]. Subsequently, Hamada and colleagues demonstrated that the presence of a polymorphism in the promoter region of the CYP17A1 gene is associated with survival in patients with CRPC regardless of the therapy given. In this analysis, the median survival from the time of diagnosis in patients with the variant allele (n=126) was 8.9 years versus 6.7 years in the patients with the A1 (reference) allele (P=0.04).[23] Although potentially contaminated by lead-time bias, these results collectively suggest that CYP17A1 polymorphisms deserve further study in the CRPC setting, in particular because CYP17A1 is now receiving considerable interest as a drug target. Interestingly, the two studies diverge somewhat in their conclusions suggesting that the onset of the disease may be *increased* by the presence of the SNP (potentially due to tumor promotion by higher androgen levels) yet in patients with prostate cancer the SNP may be protective (due to the effectiveness of androgen deprivation therapy compared to other approaches). Regardless, these studies did not incorporate specific CYP17A1 inhibitors and did not report differences in androgen levels.

Analysis of germline CYP17A1 polymorphisms may therefore aid both in the understanding of primary resistance to adrenal androgen targeted therapies such as Abiraterone Acetate, as well as in the understanding of mechanisms of treatment

resistance in men who have experienced a response to Abiraterone Acetate followed by disease progression.

2. OBJECTIVES

2.1. Primary Objective

To determine the efficacy of increased dose Abiraterone Acetate for patients who experienced disease progression following standard dose abiraterone acetate therapy. Primary endpoint is PSA response of at least 30% decline by 12 weeks.

2.2. Secondary Objectives

- To evaluate the overall safety and tolerability of therapy with increased-dose Abiraterone Acetate.
- To determine the time to PSA progression and progression free survival (PFS) for patients treated with increased dose Abiraterone Acetate.
- To measure the pharmacokinetics of Abiraterone Acetate at the initiation of standard dose therapy, at the time of initial disease progression, after the initiation of increased-dose Abiraterone Acetate, and at the time of disease progression on increased-dose therapy.
- Relationship of circulating androgen levels to increased dose Abiraterone Acetate and PSA decline.

2.3. Exploratory Objectives

- To evaluate the association between single-nucleotide polymorphisms within enzymes inhibited by Abiraterone Acetate and response to standard-dose and elevated-dose therapy.
- To evaluate whether resistance to Abiraterone Acetate is mediated by increased AR signaling, by measuring changes in the androgen receptor (AR) expression signature from metastatic biopsies at the initiation of standard dose therapy and at the time of initial progression.
- To evaluate whether resistance to Abiraterone Acetate is mediated by increased intratumoral androgen synthesis, by measuring CYP17A1 and androgen synthesis methylation status in metastatic biopsies and in circulating tumor cells (CTCs) taken at the initiation of standard dose therapy and at the time of initial progression.

3. STUDY DESIGN

3.1. Study Design

This is a phase II multicenter trial of Abiraterone Acetate in patients with progressive prostate cancer despite androgen deprivation with a particular focus on the pharmacokinetic, pharmacodynamic, and pharmacogenomic events occurring at the time of apparent drug resistance. All eligible patients will have baseline (prior to taking the first dose of Abiraterone Acetate 1000mg/daily) measures of routine clinical variables along with measurements of baseline and treatment related changes in testosterone, androgen, and endocrine levels, genotyping of SNPs in the selected enzymes known to be directly inhibited by Abiraterone Acetate, and collection of circulating tumor cells. All patients will be requested to consent for

biopsies which will be performed prior to treatment and at the time of disease progression on standard dose Abiraterone Acetate therapy. These biopsies will be analyzed for expression of an AR-signature as well as for microarray analysis to explore changes in methylation, and expression of CYP17A1 and other androgen synthesis genes.

Subjects will then begin daily oral therapy with Abiraterone Acetate 1000mg po daily with physiologic prednisone 5mg BID replacement. No food should be consumed for at least 2 hours before the dose of Abiraterone Acetate and for at least 1 hour after the dose of Abiraterone Acetate is taken. PSA will be followed monthly. Abiraterone Acetate will be supplied by Janssen Services. At the end of the first month, the third month, and then every three months thereafter, Abiraterone Acetate, testosterone, and androgen levels will be followed. Subjects whose disease is not sensitive to Abiraterone Acetate and do not achieve any PSA decline at 12 weeks will be taken off study. At the time of progression (defined by RECIST criteria OR by the Prostate Cancer Working Group 2 (PCWG) criteria as a 25% increase in PSA above the nadir and an increase in the absolute value PSA of at least 2ng/dl or back to baseline confirmed at least 2 weeks afterward) for subjects who achieved any initial PSA decline (referred to as Progressive Disease (PD) #1), **subjects will begin taking Abiraterone Acetate 1000 mg po BID (q12 hours).** Patients will continue to take prednisone 5mg BID and will continue taking the combination of elevated-dose abiraterone and prednisone for at least 12 weeks, which will be the first point at which evaluation for PD#2 will be made. If PD#2 occurs at 12 weeks or at any point thereafter subjects will be withdrawn from the study. While 1000 mg po BID is not the FDA recommended dose, it is the dose to be investigated in this study.

3.2. Rationale for Selection of this Patient Population

Patients with progressive prostate cancer despite castrate levels of testosterone in whom chemotherapy is not felt to be indicated yet are selected for this trial. There are few effective options for this population; these include, among others, ketoconazole, diethylstilbestrol, and antiandrogens. None of these options are curative, and only ~20-30% of men will have any significant clinical response to agents. Most men who experience PSA progression after a trial of these agents will require treatment with chemotherapy, which notably brings risks of myelosuppression, neurologic toxicity, and impairments in quality of life.

Abiraterone Acetate with corticosteroid replacement has been shown to be clinically effective in multiple phase II studies in men with chemotherapy-naïve CRPC, with PSA progression free survival ranging from 24-63 weeks. It prolongs survival in men with CRPC previously treated with chemotherapy, and currently a multinational randomized placebo controlled Phase III study is evaluating the potential benefit of Abiraterone Acetate in men with CRPC who have not received chemotherapy. This patient population therefore has the potential to derive benefit from treatment with Abiraterone Acetate.

Increasing the dose of Abiraterone Acetate at the time of disease progression is expected to “rescue” a proportion of men failing standard dose Abiraterone Acetate therapy, and thus will spare these patients the toxicities that come with most chemotherapeutic regimens.

Only patients with metastatic progressive castration resistant disease (as evidenced by RECIST criteria or by Prostate Cancer Working Group 2 criteria[20]) for bony disease will be included in this study to render the population uniform. It will also potentially allow for a higher yield in terms of tumor biopsy and CTC collection.

3.3 Population Base and Recruitment:

Patients will be recruited through the Urologic Oncology Program. Members of all ethnic groups are eligible for this trial. The following table summarizes the ethnicity of the Bay Area prostate cancer incidence and the ethnic breakdown of new prostate cancer cases seen at UCSF in 2006.

Table 2

	All Races	**White/Non-Hispanic**	**Black**	**Hispanic**	**Asian/ Pacific Is.**	**Other/ Unknown**
***Bay Area Population Males Only (2006)**	2,142,518 (100%)	1,010,225 (47%)	170,506 (8%)	451,505 (21%)	444,944 (21%)	8,077 (0.41%)
***Bay Area Prostate Cancer Incidence (2006)**	2,872 (100%)	1,845 (64%)	322 (11%)	233 (8%)	358 (12%)	114 (4%)
UCSF Prostate Cancer (New Cases Seen in 2006)	807 (100%)	636 (79%)	45 (6%)	26 (3%)	56 (7%)	44 (5%)
UCSF new prostate cancer pts. enrolled on a clinical trial (2006)	100 (100%)	85 (85%)	5 (5%)	5 (5%)	4 (4%)	1 (1%)

***Bay Area Population Estimate numbers are listed for the 5 Bay Area Counties of San Francisco, San Mateo, Marin, Contra Costa and Alameda.**

3.4 Inclusion Criteria.

Each patient must meet the following criteria to be enrolled in this study:

3.4.1 Have signed an informed consent document indicating that the subjects understands the purpose of and procedures required for the study and are willing to participate in the study

3.4.2 Be willing/able to adhere to the prohibitions and restrictions specified in this protocol

3.4.3 Written Authorization for Use and Release of Health and Research Study Information has been obtained

3.4.4 Male aged 18 years and above

3.4.5 Able to swallow the study drug whole as a tablet

3.4.6 Willing to take abiraterone acetate on an empty stomach; no food should be consumed at least two hours before and for at least one hour after the dose of abiraterone acetate is taken

3.4.7 Patients who have partners of childbearing potential must be willing to use a method of birth control with adequate barrier protection as determined to be acceptable by the

principal investigator and sponsor during the study and for 1 week after last study drug administration.

3.4.8 Have a baseline serum potassium of ≥ 3.5 mEq/L

3.4.9 Have aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin levels < 1.5 x ULN

3.4.10 Have a serum albumin of ≥ 3.0 g/dL

3.4.11 Total bilirubin ≤ 1.5 x ULN (In patients with known Gilbert Syndrome, a total bilirubin ≤ 3.0 x ULN, with direct bilirubin ≤ 1.5 x ULN is acceptable)

3.4.12 Have a platelet count of ≥ 100,000/μL

3.4.13 Have an absolute neutrophil count of > 1500 cell/mm^3

3.4.14 Have a hemoglobin of ≥ 9.0 g/dL

3.4.15 Have histologically confirmed adenocarcinoma of the prostate.

3.4.16 No prior therapy with chemotherapy for metastatic prostate cancer.

3.4.17 Have metastatic disease based on a positive bone scan or objective imaging on CT scan.

3.4.18 Have ongoing gonadal androgen deprivation therapy with LHRH analogues or orchiectomy. Patients who have not had an orchiectomy must be maintained on effective LHRH analogue therapy for the duration of the trial.

3.4.19 Testosterone < 50 ng/dL.

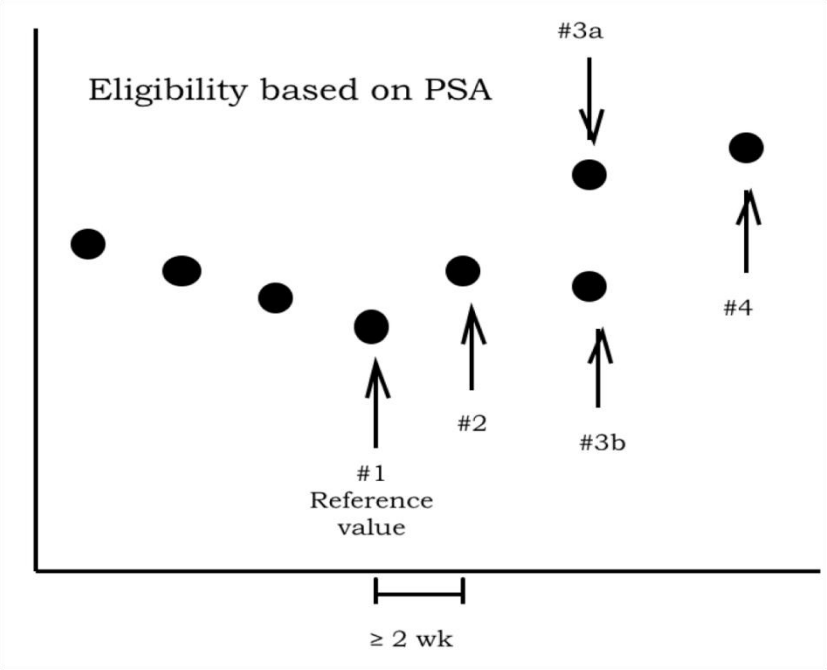
3.4.20 Progressive disease after androgen deprivation, defined as either :

-Objective radiographic progression as defined by RECIST or PCWG2 criteria

OR

-PSA evidence for progressive prostate cancer which consists of a PSA level of at least 2 ng/ml which has risen on at least 2 successive occasions, at least 2 weeks apart (Fig 4 #2 & #3a). If the confirmatory PSA value is less (Fig 4 #3b) than the screening PSA (Fig 4 #2) value, then an additional test for rising PSA (Fig 4 #4) will be required to document progression

Figure 4: Eligibility based on PSA



3.4.21 Antiandrogen Withdrawal

Patients who are receiving an antiandrogen as part of primary androgen ablation must demonstrate disease progression following discontinuation of antiandrogen.

3.4.21.1 Disease progression after antiandrogen withdrawal is defined as 2 consecutive rising PSA values, obtained at least 2 weeks apart, or documented osseous or soft tissue progression.

3.4.21.2 For patients receiving flutamide, at least one of the PSA values must be obtained 4 weeks or more after flutamide discontinuation.

3.4.21.3 For patients receiving bicalutamide or nilutamide, at least one of the PSA values must be obtained 6 weeks or more after antiandrogen discontinuation.

3.4.21.4 No antiandrogen withdrawal response is expected in patients in whom antiandrogen therapy did NOT result in a decline in PSA or in those patients in whom the response to antiandrogens was <3 months. Therefore, it is not necessary to wait for AAWD in pts without PSA decline on an anti-androgen or in those in whom a PSA response lasted <3 months.

3.4.22 ECOG Performance Status 0-1

3.4.23 Life expectancy of ≥12 weeks.

3.5 **Exclusion Criteria.**
Patients who meet any of the following criteria will be excluded from the study:

3.5.1 Active infection or other medical condition that would make prednisone/prednisolone (corticosteroid) use contraindicated

3.5.2 Known brain metastasis

3.5.3 Uncontrolled hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 95 mmHg) Patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment.

3.5.4 Active or symptomatic viral hepatitis or chronic liver disease

3.5.5 History of pituitary or adrenal dysfunction

3.5.6 Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart disease or known cardiac ejection fraction measurement of <50 % at baseline. No echocardiogram or MUGA scan is required for study entry.

3.5.7 Administration of an investigational therapeutic within 30 days of screening

3.5.8 Have poorly controlled diabetes

3.5.9 Have a history of gastrointestinal disorders (medical disorders or extensive surgery) that may interfere with the absorption of the study agents

3.5.10 Have a pre-existing condition that warrants long-term corticosteroid use in excess of study dose

3.5.11 Have known allergies, hypersensitivity, or intolerance to abiraterone acetate or prednisone or their excipients

3.5.12 Any condition which, in the opinion of the investigator, would preclude participation in this trial.

3.5.13 Pure small cell carcinoma of the prostate or any mixed histology cancer of the prostate (eg: neuroendocrine) which contains <50% adenocarcinoma.

3.5.14 Therapy with other hormonal therapy, including any dose of megestrol acetate (Megace), finasteride (Proscar), dutasteride (Avodart) any herbal product known to decrease PSA levels (e.g., Saw Palmetto and PC-SPES), or any systemic corticosteroid within 4 weeks prior to first dose of study drug.

3.5.15 Prior therapy with Abiraterone Acetate or other CYP17 inhibitor(s) including TAK-700 or TOK-001, or second-generation agent(s) targeting the androgen receptor including MDV-3100, ARN-509 for metastatic prostate cancer.

3.5.16 Prior therapy with ketoconazole for >2 weeks for prostate cancer.

3.5.17 Therapy with supplements or complementary medicines/botanicals not known to decrease PSA must be discontinued prior to the first dose of study drug, except for any combination of the following which may be continued while on study treatment:

- Conventional multivitamin supplements
- Selenium
- Lycopene
- Soy supplements

3.5.18 Prior radiation therapy completed < 4 weeks prior to enrollment

3.5.19 Prior chemotherapy for castration resistant prostate cancer. Patients who have received chemotherapy for early stage prostate cancer (e.g. as part of a neoadjuvant or adjuvant trial) or for other malignancies are eligible provided that >1 year has passed since the administration of the last chemotherapy dose.

3.5.20 Any “currently active” second malignancy, other than non-melanoma skin cancer. Patients are not considered to have a "currently active” malignancy, if they have completed therapy and are considered by their physician to be at least less than 30% risk of relapse over next year.

3.5.21 Active psychiatric illnesses/social situations that would limit compliance with protocol requirements.

3.5.22 Patients in whom urgent chemotherapy, in the opinion of the treating physician, is indicated should not be enrolled in this study.

4.0 DRUG INFORMATION

4.1 DOSAGE AND ADMINISTRATION

Treatment will be administered on an outpatient basis and will consist of 28-day cycles.

Initial therapy will consist of Abiraterone Acetate, 1000 mg per day, plus prednisone 5 mg po bid. Abiraterone Acetate will be taken once daily in the form of four 250 mg-tablets. Abiraterone Acetate will be administered on an empty stomach. **No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken**. Patients should be instructed to take Abiraterone Acetate at the same time each day.

Participants will keep a drug diary to record each dose of study drug taken (see Appendix D). Any missed doses should be recorded on the dosing diary. Subjects will be required to bring the dosing diary to every visit unless instructed otherwise.

Because short-term rises in PSA after the initiation of Abiraterone Acetate therapy may be followed by meaningful response, the PSA at 12 weeks will be the first value requiring action. Patients who do not experience any decline in PSA while on Abiraterone Acetate at the 12 week

evaluation time point will be withdrawn from the study, Abiraterone Acetate will be stopped, and prednisone tapered off. Patients continuing Abiraterone Acetate/prednisone off-study OR those planning to receive subsequent chemotherapy do not need to taper prednisone. Patients coming off study at this point will have off study labs, CTCs, and optional metastatic biopsy (see Section 5.1.3).

In patients in whom a decline in PSA of any magnitude is achieved by week 12, Abiraterone Acetate and prednisone therapy will continue until progressive disease (PD#1) defined is documented. **Progressive disease** is defined by either RECIST criteria (as defined in Appendix B) OR by PSAWG2 criteria (as defined in Appendix C) – requiring a 25% increase in PSA above the nadir and an increase in the absolute-value PSA levels back to baseline or by 2ng/ml, confirmed at least 2 weeks afterwards, or by PCWG2 bone scan criteria. At time of progression (referred to as PD #1), Androstenedione, DHEA and DHEAS and Abiraterone Acetate levels will be measured and prednisone will be continued. Abiraterone Acetate 1000 mg by mouth BID (q12 hours) will be initiated **after Abiraterone and hormone levels are measured.** ACTH, PSA, and an electrolyte and liver function panel ("serum chemistries") will be measured. They will be measured again 2 weeks later and then again at the beginning of the next cycle with other hormone and laboratory levels as specified in Table 3.

Patients receiving Abiraterone Acetate 1000 mg BID plus prednisone 5 mg po BID, who are tolerating therapy well, will continue on therapy for 12 weeks, which will be the first point at which criteria for progressive disease #2 (as defined by PCWG2 and/or RECIST criteria) may be determined. This includes patients who do not achieve any PSA decline in response to increased-dose therapy. Once PCWG2 criteria for progressive disease is met the patients will come off study. This will be considered PD#2**.**

DURATION OF TREATMENT

Patients will continue on therapy until any one of the following events occurs:

- No evidence of any PSA decline at evaluation #1, after 12 weeks of treatment
- Progressive disease #2, determined after 12 weeks of increased-dose therapy.
- Any unacceptable treatment-related toxicity
- Patient"s withdrawal of consent
- Discretion of Principal Investigator

Adverse events and Dose Reductions

Reported adverse events and toxicity are described in Section 5.7

Dose reductions in response to toxicity are detailed in Section 5.7

4.2 Prednisone

Prednisone is an analogue of cortisol is believed to be the principal hormone secreted by the adrenal cortex. Naturally occurring glucocorticoids (prednisone and cortisone) have salt-retaining properties and are used as replacement therapy in adrenocortical deficiency states. They have potent anti-inflammatory effects and modify the body"s immune response to adverse stimuli.

Availability - Prednisone is commercially available in 5mg tablets.

Administration - Prednisone is administered orally with food at 5mg every morning and 5mg at bedtime.

Storage - Prednisone should be stored in well-closed containers at a temperature less than 40^0C, preferable 15-30^0C.

Toxicities - Prednisone may cause fluid and electrolyte disturbances, especially sodium retention and potassium loss; muscle weakness; peptic ulcer; impaired wound healing; thin fragile skin; petechiae and ecchymoses; psychic disturbances; manifestation of latent diabetes mellitus; hypertension; cataracts; weight gain; and nausea.

Precautions - Patients who have been on prednisone for longer than 4 weeks should have the drug gradually tapered rather than abruptly stopped. If the patient is subjected to unusual physiologic stress, increased dosage before, during, and after the stressful situation is indicated. It is recommended that hydrocortisone (an analogue of prednisone) 100mg administered intravenously every 8 hours be utilized until the physiologic stress has ended, at which point the normal replacement dosage of prednisone (see above) is resumed.

4.3 Abiraterone Acetate

Abiraterone Acetate 250-mg tablets are oval, white to off-white and contain Abiraterone Acetate and compendial (USP/NF/EP) grade lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and purified water, in descending order of concentration (the water is removed during tabletting).

Availability – Abiraterone Acetate will be supplied by Janssen Services in 250mg tablets.

Administration – Patients will be instructed to take 4 tablets (1000mg) orally (PO) once or twice daily (BID). No food should be consumed for at least two hours before the dose of abiraterone acetate is taken **and** for at least one hour after the dose of abiraterone acetate is taken.

Storage –Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)

Toxicities - Abiraterone Acetate may cause fluid and electrolyte disturbances, edema, hypertension, liver function abnormalities, muscle discomfort, back pain, hot flushes, diarrhea, urinary tract infections, cough, arrythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection.

Precautions - Mineralocorticoid excess: Use Abiraterone Acetate with caution in patients with a history of cardiovascular disease. The safety of Abiraterone Acetate in patients with LVEF < 50% or NYHA Class III or IV heart failure is not established. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention is recommended at least monthly. Adrenocortical insufficiency: Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations. (5.2) Hepatotoxicity: Increases in liver enzymes have led to drug interruption, dose modification and/or discontinuation. Monitor liver function and modify, interrupt, or discontinue Abiraterone Acetate dosing as recommended. Food Effect: Abiraterone Acetate must be taken on an empty stomach. Exposure (area under the curve) of Abiraterone Acetate increases when Abiraterone Acetate is taken with meals.

Drug Interactions – Based on in vitro data, Abiraterone Acetate is a substrate of CYP3A4. In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer,

decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during Abiraterone Acetate treatment. If a strong CYP3A4 inducer must be co-administered, increase the Abiraterone Acetate dosing frequency. In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

Effects of Abiraterone on Drug Metabolizing Enzymes
Abiraterone Acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.

In vitro, Abiraterone Acetate inhibits CYP2C8. There are no clinical data on the use of Abiraterone Acetate with drugs that are substrates of CYP2C8. However, patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

Pregnancy - Abiraterone Acetate may cause fetal harm when administered to a pregnant woman. Men who are sexually active with a pregnant women must use a condom during and for one week after treatment with Abiraterone Acetate. If their sexual partner may become pregnant, a condom and another form of birth control must be used during and for one week after treatment with Abiraterone Acetate. Pregnant women or women who may be pregnant should not handle abiraterone acetate.

Handling Abiraterone Acetate Tablets - This medicine may cause harm to the unborn child if taken by women who are pregnant. It should not be taken by women who are breast-feeding. Women who are pregnant or who may be pregnant should wear gloves if they need to touch abiraterone acetate tablets. Study staff and caregivers should be notified of this information, to ensure the appropriate precautions are taken.

5 STUDY PROCEDURES AND OBSERVATIONS

5.1 Schedule of Procedures and Observations

The study-specific assessments are detailed below and are outlined in Table 3, Schedule of Study Procedures and Assessments, Screening assessments must be performed within 28 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed a window of ± 3 days unless otherwise noted.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the consent form will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

5.1.1 SCREENING ASSESSMENTS

Clinical:
Required **within 28 days** before the first cycle:
- Signed informed consent
- History and physical examination, including height, weight, and vital signs and review of systems
- ECOG performance status
- Concomitant Medication review

Laboratory / Diagnostic: required **within 28 days** before the first cycle.
- CBC, platelet count, and automated differential
- Serum chemistries: includes BUN, Creatinine, ALT, AST, glucose, alkaline phosphatase, total bilirubin, electrolytes (K+, CL-, Na+, CO2, Mg, Ca+, Phos)
- Prostate Specific Antigen (PSA)
- LDH
- Urinalysis
- ECG
- Endocrine analysis
- Adrenal Androgen Levels - Testosterone, Dihydrotestosterone, Androstenedione, DHEAS, DHEA
- HPA Axis Hormones - FSH and LH
- Correlative studies
- Circulating tumor cells
- Genotyping
- Metastatic Biopsy – optional

Imaging/Diagnostic: Must be performed within **45 days** before starting the first cycle:
- CT Abdomen/Pelvis or MRI Abdomen/Pelvis.
- Bone Scan. Bone scan may be either a Technetium-99 bone scan or a sodium-fluoride PET scan. All subsequent bone imaging should be done with the same type of scan used at study entry.

5.1.2 TREATMENT PERIOD

The following assessments will be performed monthly during the treatment period unless otherwise noted.

Clinical Assessments
- Physical examination (including weight) and vital signs
- ECOG Performance Status
- Adverse Events
- Concomitant Medication review

Laboratory Evaluation - Within 72 hours prior to visit the following blood tests will be performed:

- PSA
- CBC, platelet count, and automated differential
- Serum chemistries: include BUN, creatinine, ALT,AST, glucose, alkaline phosphatase, total bilirubin, electrolytes (Na+, K+, Cl-, Na+, CO2, MG, CA+, Phos). These will be checked every 2 weeks during the first 3 cycles of treatment (ie cycle 1 day 1, cycle 1 day 15, cycle 2 day 1, cycle 2 day 15, cycle 3 day 1, cycle 3 day 15) for a total of 6 evaluations, then at the beginning of each cycle thereafter.
- LDH
- Abiraterone Acetate level – Patients should hold abiraterone on these days until the level is drawn. For patients taking the elevated dose, the AM dose should be held on these days. These levels should be drawn at the same time of day for each patient, ideally between 8AM and noon at the following visits:
    - the 1st study visit after patient begins taking standard dose Abiraterone Acetate (1000 mg daily)
    - the time of disease progression #1
    - the 1st study visit after the initiation of elevated-dose therapy
    - disease progression #2
- Endocrine analysis – evaluated every 2 cycles
    - Adrenal Androgen Levels - Testosterone, Dihydrotestosterone, Androstenedione, DHEAS, DHEA
    - HPA Axis Hormone Levels - FSH, LH, and ACTH
- ECG – evaluated every 3 cycles

Imaging/Diagnostics - evaluated at the completion of every 3 cycles

- CT Abdomen/Pelvis or MRI Abdomen/Pelvis
- Bone Scan or NaF-PET

Patients with bone-only disease at baseline are unlikely to develop new soft tissue disease if responding by PSA to Abiraterone Acetate and do **not** need to have serial imaging of the abdomen/pelvis with CT or MRI **until** the time of disease progression #1 (PD#1). If soft-tissue disease is found then these patients will undergo q3cycle bone scan and CT or MRI of the abdomen and pelvis. If no soft-tissue disease is found at PD#1 then patients do not need to have another CT or MRI until PD#2.

Patients with soft tissue-only disease at baseline are unlikely to develop new bony lesions if responding by PSA to Abiraterone Acetate and do **not** need to have serial imaging with bone scans **until** the time of disease progression #1 (PD#1). If bony disease is found then these patients will undergo q3cycle bone scan and CT or MRI of the abdomen and pelvis. If no bony disease is found at PD#1 then patients do not need to have another bone scan until PD#2.

If new soft-tissue or bone disease is discovered on a radiologic exam performed for non-study reasons then patients should be evaluated with the appropriate (bone scan or CT or MRI of the abdomen and pelvis) q3cycle imaging of the lesion. Repeat imaging does not need to occur if the last scan was within 8 weeks; if this is the case the next scan should occur at the next regularly scheduled assessment (ie if a scan done to confirm PD#1 is obtained during cycle 6, the next scan should be at cycle 10)

5.1.3 Study procedures at the time of progression (PD#1)

A critical aim of this study is to determine the endocrinologic and pharmacokinetic state of patients at the time of clinical progression. Thus, it is required that hormone and Abiraterone

Acetate levels be obtained from patients at the time of progression but prior to the Abiraterone Acetate dose increase. At the time of clinical progression, the following evaluations will be performed.

Clinical Assessments
- Physical examination (including weight) and vital signs
- ECOG Performance Status
- Adverse Events
- Concomitant Medication review
- ECG

Laboratory Evaluation
- CBC, platelet count, and automated differential
- Serum chemistries
- Circulating tumor cells
- *The following must be obtained prior to Abiraterone Acetate dose increase:*
  - PSA
  - Abiraterone Acetate level
  - Endocrine analysis
    - Adrenal Androgen Levels - Testosterone, Dihydrotestosterone, Androstenedione, DHEAS, DHEA
    - HPA Axis Hormone Levels - FSH, LH, and ACTH

    If progression occurs during a period between visits (e.g. due to imaging done to evaluate pain) every effort should be made to continue therapy until such time as the above named blood tests can be obtained.

Metastatic Biopsy – optional

Imaging/Diagnostics – if performed within previous 8 weeks, will not need to be repeated.
- CT Abdomen/Pelvis or MRI Abdomen/Pelvis
- Bone Scan or NaF-PET

5.1.4 Study procedures at the time of dose increase

After starting dose-increased Abiraterone Acetate (1000 mg BID), patients will continue to be monitored monthly as described in section 5.1.2, Treatment Period, until the time of second disease progression according to PSAWG 2 criteria (see Appendix C). The following additional laboratory evaluations will be performed

2 weeks after dose-increased Abiraterone Acetate

Clinical Assessments
- ECG
- Blood pressure check

Laboratory Evaluation
- An Abiraterone Acetate level will be drawn
- ACTH, PSA, and Electrolyte and liver function panels (serum chemistries) will be drawn

4 weeks after dose-increased Abiraterone Acetate

Clinical Assessments

- ECG

Laboratory Evaluation

- Adrenal Androgen Levels - Testosterone, Dihydrotestosterone, Androstenedione, DHEAS, DHEA
- HPA Axis Hormone Levels - FSH, LH, and ACTH
- PSA, and Electrolyte and liver function panels (serum chemistries) will be drawn 4 weeks after dose-increased Abiraterone Acetate (at the first monthly visit)
- Note that adrenal androgen and HPA axis hormone levels should continue to be drawn every 2 cycles (ie every "odd" cycle – C1, 3, 5, 7, 9….) regardless of the timing of PD#1.

5.1.5 Study procedures at the time of second progression (PD#2) / End of Study Visit

An end-of-study evaluation will be performed within 2 weeks of the last dose. This includes subjects who did not experience an initial decline in PSA to standard-dose Abiraterone Acetate. The end of study visit will include the following:

Clinical Assessments

- Physical examination (including weight) and vital signs
- ECOG Performance Status
- Adverse Events
- Concomitant Medication review
- ECG

Laboratory Evaluation

- PSA
- CBC, platelet count, and automated differential
- Serum chemistries: include BUN, creatinine, ALT,AST, glucose, alkaline phosphatase, total bilirubin, electrolytes (Na+, K+, Cl-, Na+, CO2, MG, CA+, Phos).
- LDH
- Abiraterone Acetate level
- Endocrine analysis – evaluated every 2 cycles
  - Adrenal Androgen Levels - Testosterone, Dihydrotestosterone, Androstenedione, DHEAS, DHEA
  - HPA Axis Hormone Levels – FSH and LH
- Circulating tumor cells

Imaging/Diagnostics - if performed within previous 8 weeks, will not need to be repeated.

- CT Abdomen/Pelvis or MRI Abdomen/Pelvis
- Bone Scan or NaF-PET

Metastatic Biopsy – optional

5.2 Abiraterone Acetate Levels

Abiraterone Acetate levels to be drawn four (4) times during study, as described above and in Table 3**.** Abiraterone Acetate levels to be drawn in separate serum chemistry test tube, then stored and shipped to the UCSF Drug Studies unit for evaluation per drug study unit protocol.

5.3 **Genotype Analysis**

- Eighteen mls of whole blood in 2 plastic EDTA tubes and 1 serum tube will be collected from patients during their first study visit and freshly frozen at -80 degrees centigrade in the UCSF Cancer Center.
- Batched germline DNA will be isolated from peripheral whole blood mononuclear cells by the UCSF genomics core facility in standardized aliquots according to the UCSF DNA bank protocol, with an estimated yield of ~1 microgram of DNA per sample.
- DNA samples will be de-identified and transported on ice to the Kroetz laboratory at UCSF Mission Bay for SNP analysis.
- Samples will be genotyped for the rs743572 SNP as well as other SNPs in the CYP17A1 gene in the Kroetz laboratory at UCSF using a commercially available Applied Biosystems (ABI) SNPlex™ Genotyping System according the manufacturer"s instructions.
- Samples will be used for this study only. Any remaining germline blood samples will be destroyed at the end of the study.

5.4 Circulating tumor cells

Blood for circulating tumor cell studies will be drawn 3 times during subject"s participation in this study:

  - prior to the first dose of Abiraterone Acetate
  - at PD#1 (prior to Abiraterone Acetate dose increase for patients who experienced a decline in PSA on standard dose Abiraterone Acetate. CTCs should also be collected at the off study visit for patients who do not experience any PSA decline)
  - at PD#2. Cells may be taken before discontinuation of Abiraterone Acetate (preferred) or after the discontinuation of Abiraterone Acetate.

- 40ml of peripheral blood will be drawn in sodium or lithium heparin coated tubes, deidentified to protect patient privacy, and delivered freshly to the Paris Lab at UCSF. This can be done at any time after PD#1 has been documented and prior to the first dose of Abiraterone Acetate 1000mg BID.
- A additional 10ml of peripheral blood will be drawn (total 50ml including CTCs to be sent to Paris lab) will take place simulatenously into blood collection tubes containing preservative provided by Epic Sciences and will be shipped directly to the Epic Sciences processing facility. These should be placed into ambient blood shipping containers provided and shipped on the same day of the blood draw with the goal of arrival within 48 hours of blood draw.
- An additional optional 7.5ml of peripheral blood will be collected for CTC cell counting (enumeration only) using the Veridex Cell Search® System. This will be shipped to Veridex and analyzed per a standardized protocol. Samples will be destroyed after Veridex CTC enumeration.
- Blood drawn for circulating tumor cells will be de-identified, transported on ice to, and any residual cells will be banked at the UCSF HDFCCC Tissue Core for up to 10 years for future genetic studies. These studies could potentially include immunohistochemical analysis of androgen receptor levels, CYP17A1 levels, or levels of other enzymes involved in androgen biosynthesis. Other potential studies include SNP studies to correlate single base mutations in other androgen synthesis genes with clinical outcomes, or potentially gene expression array analyses. Pathways to be explored could include the androgen synthesis pathway as well as the PTEN/PI3 Kinase/mTOR pathways. See section 7.5.4 for CTC isolation rationale and methods

5.5 Metastatic Biopsies

Optional metastatic biopsies will be collected during study. While optional, these should be strongly encouraged for all study participants. Tumor biopsies will be conducted at the following times:

- prior to the first dose of Abiraterone Acetate AND
- at PD#1 prior to Abiraterone Acetate dose increase AND
- at PD# 2 after Abiraterone Acetate dose increase

Biopsy at UCSF will take place in the Department of Radiology using a CT guided or ultrasound guided approach. One biopsy will be processed for decalcification, fixation, and paraffin embedding for immunohistochemical analysis and identification of tumor sample. The other biopsies will be frozen immediately at the time of biopsy for microarray analysis which will take place in the Paris and Febbo labs at UCSF. Any leftover biopsy samples will be banked at the UCSF HDFCCC Tissue Core for up to 10 years for potential future genetic studies as outlined above.

Table 3: Treatment Calendar

All on-study visit procedures are allowed a window of ± 3 days unless otherwise noted.

	Screening	Day 1 of every cycle [a]	Day 15 of cycles 1-3	Every 2 cycles (C1,3,5,7…)	Every 3 cycles (C1,4,7,10…)	Time of initial clinical progression (PD#1) [b]	2 weeks after dose-increase	4 weeks after dose-increase	Second progression (PD#2) and end of study [c]
Procedures									
Informed Consent [d]	X								
Medical History, including demographics	X								
Physical exam, including height (only at screening) and weight	X	X				X	X [r]	X	X
Vital signs [e]	X	X				X		X	X
ECOG performance status	X	X				X		X	X
ECG	X				X	X [f]	X	X	X
Concomitant medications	X	X				X		X	X
Concurrent Anti Cancer Therapies [g]	X	X				X		X	X
Adverse Events	X	X				X		X	X
Laboratory Assessments [a]									
CBC, serum chemistries [h]	X	X [i]	X			X [j]	X	X [i]	X
Abiraterone Acetate Level [k]		X				X	X		X
PSA	X	X [i]				X [j]	X	X [i]	X
Adrenal Androgen Levels [l]	X			X		X	X [s]	X	X
HPA Axis hormone [m]	X			X		X [j]		X	X
LDH	X	X [i]				X		X [i]	X
Urinalysis (dipstick)	X								
Tumor Assessments [n]									
Bone scan	X [o]				X [p]	X [p]			X [p]
CT or MRI of the abdomen/pelvis	X [o]				X [p]	X [p]			X [p]
Correlative Studies [q]									
Circulating tumor cells	X					X			X
Metastatic Biopsy	X					X			X
Genotyping	X								

[a] Unless otherwise noted, may be performed up to 72 hours prior to visit.
[b] Required that drug and hormone levels be obtained from patients at the time of progression but *prior* to dose increase of Abiraterone Acetate. If progression occurs during a period between visits (e.g. due to imaging done to evaluate pain) every effort should be made to continue therapy until such time as the following tests (adrenal androgens, testosterone, HPA axis hormones, Abiraterone Acetate levels, circulating tumor cells, metastatic biopsy) can be obtained.
[c] End of study visit – within 2 weeks of the last Abiraterone Acetate dose.
[d] Written informed consent must be obtained before any screening assessments are performed (it can be no more than 28 days prior to starting the trial).
[e] Includes blood pressure, pulse, respiratory rate, and body temperature.
[f] ECG should be performed at the time of PD#1 and again 2 and 4 weeks later after dose-increase.
[g] Other than LHRH agonists that are required to maintain castrate levels of testosterone, anti-cancer therapies are excluded during this study. These include chemotherapy, radiotherapy, immunotherapy, ketoconazole, diethylstilbesterol, PC-SPES, and other experimental anticancer medications, such as herbal preparations. Bisphosphonates and bone anti-resorptive therapies may be started at any point during the course of treatment. See sections 3.5 and 5.6.
[h] CBC includes platelets and differential. Serum chemistry includes BUN, creatinine, ALT, AST, glucose, alkaline phosphatase, total bilirubin, electrolytes (K+, Cl-, Na+,CO_2, Mg, Ca+, Phos). These will be checked every 2 weeks for the first 3 cycles for a total of 6 evaluations, and then once each cycle thereafter. See section 5.1.2. These will be also be checked 2 weeks after the Abiraterone Acetate dose increase as described in section 5.1.4
[i] No need to repeat if performed within the previous 7 days.
[j] PSA, ACTH, and serum electrolytes and liver function to be drawn 2 weeks after initiating increased dose Abiraterone Acetate, then again 2 weeks later at the beginning of the next cycle.
[k] Abiraterone Acetate levels performed on first scheduled office visit (Cycle 2 day 1) after patient begins taking Abiraterone Acetate, then again at time of initial clinical progression, then again on first visit after patient begins taking higher dose Abiraterone Acetate, then at time of second clinical progression. Total = 4 Abiraterone Acetate levels. Patients should hold Abiraterone Acetate on these days until after the blood draw. Level should be obtained at similar times for each patient, ideally between 8AM and noon.
[l] Within 14 days up to and including on cycle 1 day 1 prior to the first dose of therapy, and then evaluated every 2 cycles - Testosterone, Dihydrotestosterone, Androstenedione, DHEAS, DHEA
[m] Within 14 days and then evaluated every 2 cycles - FSH and LH, ACTH.
[n] Can be either technetium-99 or sodium-fluoride PET. Choice of scan must be maintained for all subsequent evaluations. If no soft-tissue disease present at baseline then CT/MRI only needed at PD#1. If no soft-tissue disease present at PD#1 then next CT/MRI is at PD#2. Similarly if no bony disease present at baseline then bone imaging only needed at PD#1. If no bony disease present at PD#1 then next bone imaging is at PD#2.
[o] May be performed within 45 days of starting therapy
[p] Within +/- 8 days. Does not need to be repeated if performed within the previous 8 weeks. To be completed at the end of every 3 cycles.
[q] May occur any time during the screening period up to and including on cycle 1 day 1 prior to the first dose of therapy. Subsequent evaluations may occur within +/- 14 days provided no change in therapy (ie: commencement of therapy, dose escalation, dose discontinuation) has occurred yet.
[r] Blood pressure check only
[s] ACTH only

5.6 Concomitant medications

Concurrent Anti Cancer Therapies - Other than LHRH agonists that are required to maintain castrate levels of testosterone, anti-cancer therapies are excluded during this study. These include chemotherapy, radiotherapy, immunotherapy, ketoconazole, diethylstilbestrol, PC-SPES, and other experimental anticancer medications, such as herbal preparations. See Appendix E for comprehensive listing of medications that should be avoided. Bisphosphonates and bone anti-resorptive therapies may be started at any point during the course of treatment. Calcium and Vitamin D are allowed at any point on study.

5.7 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

5.7.1 Adverse Event (AE) Description and Grade**:** The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site. (See Appendix A)

5.7.2 Dose Modification Guidelines for Strong CYP3A4 Inducers
Avoid concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during ZYTIGA treatment. Although there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers, because of the potential for an interaction, if a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency to twice a day only during the co-administration period (e.g., from 1,000 mg once daily to 1,000 mg twice a day). Reduce the dose back to the previous dose and frequency, if the concomitant strong CYP3A4 inducer is discontinued. See appendix E

5.7.3 Management of Non-Mineralocorticoid Based Side Effects:

Management of specific toxicities attributed to Abiraterone Acetate and prednisone are discussed in Section 4.2, 4.3.

If Grade 1-2 toxicities, and for grade 3 toxicities that are not considered clinically relevant in the opinion of the treating investigator give supportive care per institutional guidelines. No study treatment dose reduction.

For Grade 3-4 toxicity related to study treatment that is considered clinically relevant in the opinion of the treating investigator, hold study treatment and adjust or add medications to mitigate the toxicity. When resolved to Grade 1 or less resume as follows:

- If subject was taking 1000 mg at the time of a Grade 3/4 toxicity then study drug may be restarted at full dose.

- If subject was taking 1000 mg BID at the time of a Grade 3/4 toxicity, when study drug is resumed it will be at 750 mg BID (a 25% dose reduction). There will be no dose reescalation for these patients.

If the same Grade 3-4 toxicity recurs that is considered clinically relevant in the opinion of the treating investigator and is due to study treatment, hold study treatment, and adjust or

add medications to mitigate the toxicity. When resolved to Grade 1 or less proceed as follows:

- If subject was taking 1000 mg at the time of a *recurrent* Grade 3/4 toxicity that is considered clinically relevant then permanently discontinue study treatment. No dose reduction below 1000mg will be permitted as patients intolerant of a 1000 mg dose will be intolerant of a 1000 mg BID dose as well.

- If subject was taking 750 mg BID at the time of *recurrent* Grade 3/4 toxicity that is considered clinically relevant, then permanently discontinue study treatment. No dose reduction below 750 mg BID will be permitted for these patients.

If Abiraterone Acetate is held for toxicity, missed days of therapy are not made up. When Abiraterone Acetate is held temporarily prednisone should be continued.

When Abiraterone Acetate is permanently discontinued prednisone can be continued or tapered off at the treating physician"s discretion.

Patients who require >4 weeks to recover from grade 3/4 toxicity (initial or recurrent) will not be allowed to restart study drug at any dose.

5.7.4 Hypokalemia

At the initial observation of Grade 1 or 2 hypokalemia (serum potassium <3.5 mM but >3.0 mM), oral potassium supplement will be initiated. Abiraterone Acetate may be continued at current dose. The dose of potassium supplement for patients with Grade 1 or 2 hypokalemia must be carefully titrated to maintain serum potassium at >3.5 mM but <5.0 mM. Any patient with low potassium while on study or a history of hypokalemia from a pre-existing or concurrent medical condition will undergo weekly or more frequent laboratory electrolyte evaluation. The investigator should consider maintaining the patient"s potassium level at ≥ 4.0 mM in these patients.

If any patient experiences Grade 3 hypokalemia (serum potassium levels <3.0 mM –but >2.5 mM) or Grade 4 hypokalemia (life-threatening hypokalemia with potassium levels <2.5 mM) study treatment will be withheld, and the patient hospitalized for intravenous potassium replacement and cardiac monitoring. Reinitiating study treatment after normalization of potassium levels must be discussed with and approved by the Sponsor-Investigator. Potassium levels should be monitored weekly or more frequently if clinically indicated until the end of treatment.

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Hypokalemia	
Grade 1 (< 3.5 mM – 3.0 mM)	Maintain dose level. Initiate oral potassium supplement. The dose of potassium must be carefully titrated to maintain serum K+ at ≥ 3.5 mM but ≤ 5.0 mM. Conduct weekly (or more) laboratory electrolyte evaluations. Consider maintaining K+ at ≥ 4.0 mM.

Grade 3 (< 3.0 mM – 2.5 mM)	Withhold Abiraterone and then: • Initiate IV K+ and cardiac monitoring • If resolved, contact Study PI prior to re-initiation of study treatment. Continue to monitor K+ every week or more frequently if clinically indicated until the end of treatment.
Grade 4 (< 2.5 mM)	Withhold Abiraterone and then: • Initiate IV K+ and cardiac monitoring • If resolved, contact Study PI prior to re-initiation of study treatment. Continue to monitor K+ every week or more frequently if clinically indicated until the end of treatment.

5.7.5 Hypertension

Grade 1-2 or Grade 3 not considered clinically relevant : Management per treating physician. No study treatment dose reduction.

Grade 3-4: If clinically relevant hold study treatment. Adjust or add medications to mitigate the hypertension and/or consider the specific mineralocorticoid receptor blocker, Eplerenone (Inspra). When hypertension resolves to Grade 1 or less, resume study treatment at full dose. Continue to monitor blood pressure at least monthly.

If Grade 3-4 toxicity recurs and is considered clinically relevant in the opinion of the treating investigator, hold study treatment, and adjust or add medications to mitigate the toxicity. When resolved to Grade 1 or less, proceed as follows resume study treatment as follows:

- If subject was taking 1000 mg at the time then permanently discontinue study treatment. No dose reduction below 1000mg will be permitted as patients intolerant of a 1000 mg dose will be intolerant of a 1000 mg BID dose as well.

- If subject was taking 1000 mg BID at the time then when study drug is resumed it will be at 750 mg BID (a 25% dose reduction). There will be no dose reescalation for these patients.

If Grade 3-4 hypertension recurs and is considered clinically relevant in the opinion of the treating investigator in patients taking 750 mg BID then permanently discontinue study treatment, and adjust or add medications to mitigate the toxicity.

5.7.6 Pedal edema

Supportive management per Investigator. No study treatment dose reduction. Monitor for symptoms of fluid retention at least monthly.

5.7.7 Anasarca or pulmonary edema requiring supplemental oxygen

Hold study treatment. Adjust or add medications to mitigate the edema and/or consider the specific mineralocorticoid receptor blocker, Eplerenone (Inspra). When edema resolves to Grade 1 or less, resume study treatment at full dose. Potassium levels should be followed closely

If Grade 3-4 toxicity recurs, hold study treatment, and adjust or add medications to mitigate the toxicity. When resolved to Grade 1 or less, resume study treatment with a dose reduction as specified above. Potassium levels should be followed closely.

If toxicity recurs despite optimal medical management and a dose reduction, discontinue study treatment.

5.7.8 Management of Abnormal Liver Function Tests

If Grade 1 increases in AST, ALT or bilirubin occur (e.g. increase in AST or ALT from ULN to 2.5X ULN; increase in total bilirubin from ULN to 1.5X ULN): The frequency of liver function test monitoring should be increased, if the Investigator judges that the laboratory abnormalities are potentially related to study medication. No study treatment dose reduction is required.

If Grade 2 increases in AST, ALT or bilirubin occur (e.g. increase in AST or ALT to >2.5-5X ULN; increase in total bilirubin from >1.5-3X ULN): The frequency of liver function test monitoring should be increased to at least once a week, if the Investigator judges that the laboratory abnormalities are potentially related to study medication. No study treatment dose reduction is required.

If Grade 3 or higher increases in AST, ALT, or bilirubin occur:

For patients who develop hepatotoxicity during treatment with Abiraterone acetate with the following parameters: ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN, interrupt treatment with Abiraterone acetate. All other medicines that are potentially hepatotoxic should be interrupted as well. The Sponsor Investigator should be contacted and frequent laboratory evaluations (at least once weekly) should be conducted until the liver function tests return to baseline value or Grade 1. Liver enzyme measurements should be made immediately, regardless of when the next study visit or monitoring interval is scheduled.

For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three cycles and every cycle thereafter.

If study treatment resumption is considered for subjects who have experienced Grade 3 increases in AST, ALT, or bilirubin, and the Sponsor Investigator agrees, patients will be treated as follows:

- If subject was taking 1000 mg at the time then permanently discontinue study treatment. No dose reduction below 1000mg will be permitted as patients intolerant of a 1000 mg dose will be intolerant of a 1000 mg BID dose as well.

- If subject was taking 1000 mg BID at the time then when study drug is resumed it will be at 750 mg BID (a 25% dose reduction). There will be no dose reescalation for these patients.

If Grade 3 increases in AST, ALT, or bilirubin recurs in patients taking 750 mg BID then permanently discontinue study treatment and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations (at least once weekly) should be

conducted until the liver function tests return to baseline value or Grade 1. Liver enzyme measurements should be made immediately, regardless of when the next study visit or monitoring interval is scheduled.

If Grade 4 increases in AST, ALT, or bilirubin occur:

The safety of Abiraterone Acetate re-treatment of patients who develop Grade 4 increases in AST or ALT (greater than or equal to 20X ULN) or bilirubin (greater than or equal to 10X ULN) is unknown. Patients must therefore discontinue study treatment and any potentially hepatotoxic medications immediately and will not be re-challenged with Abiraterone Acetate. The Sponsor Investigator should be contacted and frequent laboratory evaluations (at least once weekly) should be conducted until the liver function tests return to baseline value or Grade 1.

5.7.9 Management of Symptoms Related to Adrenocortical Insufficiency

Adrenocortical insufficiency has been reported in clinical trials in patients receiving Abiraterone Acetate in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Patients should be monitored for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with Abiraterone Acetate. Increased dosage of corticosteroids may be indicated before, during and after stressful situations. A requirement of >10mg of prednisone (or corticosteroid equivalent) per day to treat adrenal insufficiency lasting longer than 2 weeks will result in discontinuation of study treatment.

5.7.10 Management of Vasomotor Symptoms Related to Castration

Treatment with androgens, estrogens and progestin to control hot flushes is not allowed. Selective serotonin re-uptake inhibitors (SSRIs) are permitted for the management of hot flashes

5.8 Early stopping rule for safety

If clinically relevant Grade 3/4 events attributable to study therapy occur in >1 of the first 6 patients to take the 1000 mg BID dose, accrual will be stopped based on the observed frequency of toxicity and the Abiraterone Acetate dose to be administered will be reevaluated. If accrual continues after 6 patients then continuous monitoring will take place to ensure that Grade 3/4 events attributable to study therapy occur with a frequency of <20%. If at any time Gr3-4 events attributable to study therapy are observed at >20% frequency at the 2,000mg dose among all treated patients, then accrual will be stopped and the dose of Abiraterone Acetate reevaluated. See section 14 for data safety monitoring and adverse event reporting.

5.9 ANCILLARY TREATMENT/SUPPORTIVE CARE GUIDELINES

Concurrent supportive care is not restricted, including the use of narcotics for pain control and antiemetics for control of nausea, with the exception of the use of corticosteroids to treat nausea or acute adrenal insufficiency. Concurrent use of systemic corticosteroids for other reasons is prohibited.

No investigational or commercial agents or therapies other than those included in protocol treatment may be administered with the intent to treat the patient"s malignancy

Concurrent chemotherapy, immunotherapy and radiation therapy are not permitted while on study.

A requirement for radiation therapy will be considered as progression of disease even if PSA is not rising, and patients will be removed from study treatment.

6 CORRELATIVE STUDIES

6.1 Pharmacogenomics

All patients entering on study will have peripheral blood drawn for genotyping. Analysis of the association between genotype defined as homozygous wild type (A1A1), heterozygous (A1A2) and homozygous minor (A2A2) and PSA decline with standard-dose and with elevated-dose therapy will be considered exploratory.

6.2 Adrenal androgen levels

Adrenal androgen levels (Androstenedione, DHEAS, DHEA and Testosterone) will be collected at baseline, cycle 2 day 1 and every 2 cycles thereafter, as well as at the time of PD#1 (while patient is still on therapy with Abiraterone Acetate). Analysis of these levels in this patient population is considered exploratory.

6.3 Abiraterone Acetate Pharmacokinetics

Abiraterone Acetate levels will be measured at the following four (4) times: at first visit after beginning low dose therapy (cycle 2 day 1), at the time of initial clinical progression, at first office visit after beginning dose increased therapy, and at the time of second clinical progression. The relationship between these values with the decline in PSA and disease progression will be evaluated.

6.4 Circulating Tumor Cells and Metastatic Biopsies

All patients entering on study will have peripheral blood drawn for circulating tumor cell studies 3 times during study. Blood samples will be delivered freshly to the Paris Lab at UCSF or shipped directly to Veridex or Epic Biosciences. Biopsy will take place in the Department of Radiology at UCSF using a CT guided or ultrasound guided approach. One biopsy will be processed for decalcification, fixation, and paraffin embedding for immunohistochemical analysis and identification of tumor sample. The other biopsies will be frozen immediately at the time of biopsy for microarray analyses. Microarray analyses will take place in the Paris and Febbo labs at UCSF. A sample of CTCs isolated in the Paris lab may be sent to Xcell Biosciences for culture for the purposes of CTC expansion for biologic characteriztion and genomic analysis. All cultured CTCs and biomaterials will be returned to UCSF, Leftover biopsy tissue will be banked at the UCSF Helen Diller Family Comprehensive Cancer Center Tissue Core for future genetics research. Refer to section 7.5.3 and 7.5.4 for descriptions of the microarray analyses.

The change in methylation status of specific promoter and intragenic CpG sites in CYP17A1 and in a predefined set of 20 genes involved in androgen synthesis from prior to the first dose of Abiraterone Acetate 1000mg daily to the time of post-treatment disease progression (PD#1) will be explored in parallel using paired pre and post-treatment biopsy samples and in CTCs.

This analysis will take place in the Paris and Febbo labs at UCSF.CTCs isolated using Veridex CellSearch and Epic Biosciences will be assayed in an exploratory fashion for enumeration purposes, to provide a control for the Vitatex analyses, and to explore the relationship of disease progresson with the presence of nuclear and cytoplasmic AR, presence of PTEN deletion, and expression of mesenchymal markers.

7 STATISTICAL CONSIDERATIONS

7.1 Study Design

This is a single arm, non-randomized, open–label multicenter phase II study of standard-dose Abiraterone Acetate (1000 mg/d) followed by elevated-dose Abiraterone Acetate (1000 mg/BID) at the time of disease progression in patients with chemotherapy naïve, castration-resistant metastatic prostate cancer.

7.2 Sample Size

The hypothesis that patients who are refractory to standard dose Abiraterone Acetate will respond to dose increased Abiraterone Acetate will be tested. Using Simon"s 2 stage minimax design for accrual, a test of a 20% (null) vs. 40% (alternative) proportion of patients achieving a ≥ 30% PSA decline from baseline just prior to starting elevated-dose abiraterone after 12 weeks of treatment requires a total of 33 patients. This test assumes a directional level of significance of 0.05 and power of 0.80. Based on the finding that approximately 85% of patients will achieve some PSA decline to standard-dose abiraterone in this population in Phase II and Phase III studies, 41 patients will need to be accrued in order to have 33 patients evaluable for the primary endpoint. If at least 5 out of the first 18 patients taking elevated-dose abiraterone achieve a ≥ 30% PSA decline, accrual will continue to the second stage and additional patients will be entered in order to enroll a total of 33 patients at the 1000mg BID level. It is not necessary to stop accrual until stage 1 has been completed as these patients are Abiraterone Acetate naïve and are expected to respond to this therapy for a number of months prior to progression. If less than 5 out of the initial 18 patients achieve a ≥30% PSA decline then accrual will be stopped. If at least 11 of the total 33 patients at the 1000mg BID dose on study achieve a ≥ 30% PSA decline, then the null hypothesis will be rejected. The probability of stopping accrual at the first stage is 0.72 if the null hypothesis is true.

7.3 Primary Objective

The primary objective of this study is to determine the efficacy of increased-dose Abiraterone Acetate for patients who experienced disease progression following standard-dose abiraterone acetate therapy. The primary study outcome measure is the proportion of patients who have had a PSA decline after 12 weeks of therapy with standard-dose Abiraterone Acetate, then had disease progression (Appendix C) and then achieved a ≥30% PSA decline after 12 weeks from the start of elevated-dose therapy. The proportion achieving a ≥30% PSA decline among those treated with elevated dose therapy among all patients entered on study along with 95% confidence intervals will be calculated to summarize the treatment effect. In addition to observing a ≥30% PSA decline, the proportion of patients treated with elevated-dose therapy achieving any PSA decline, maximum decline in PSA, and duration of initial and second response will be determined. The analysis of the primary objective will follow the decision rules for accrual to test the primary study objective.

7.4 Secondary Objectives

7.4.1 Methods for analysis

The frequency of any toxicity with increased-dose Abiraterone Acetate by maximum observed grade will be tabulated for the study cohort. The Kaplan-Meier product limit method will be used to estimate the probability of PSA progression and PFS. Durations will be measured from the start of increased dose Abiraterone Acetate until PSA failure and progression or death due to any cause, respectively, as defined in Appendix C. Point estimates from these analyses with 95% confidence intervals will be presented to summarize the results.

7.4.2 Pharmacokinetics

Abiraterone Acetate levels will be measured at the following four (4) times: at first visit after beginning low dose therapy, at the time of initial clinical progression, at the first office visit after beginning dose increased therapy, and at the time of second clinical progression. For standard and increased dose Abiraterone Acetate the difference in means in baseline Abiraterone Acetate levels will be compared using a paired t test or to compare the distributions the nonparametric Wilcoxon matched pairs test will be performed for patients achieving any decline in PSA after 12 weeks of therapy with standard-dose abiraterone and are then treated with increased-dose Abiraterone Acetate. Similar methods for analysis will be used to investigate the change from baseline in Abiraterone Acetate levels at the time of PSA progression and overall disease progression. Additional exploratory analyses including correlations between the change in Abiraterone Acetate levels and change in PSA at progression will also be performed.

7.4.3 Hormone Levels

Testosterone, DHEA, DHEA-S and androstenedione will be measured prior to the start of initial Abiraterone Acetate 1000mg mg daily and then every 2 cycles during standard and elevated-dose study therapy. Measurements will be obtained at an earlier time point if the patient comes off study for disease progression before week 12. Pearson"s correlation coefficients will be calculated to summarize the relationships among the 4 hormones at baseline and for the change from baseline at 12 weeks as well as between the baseline value and change at 12 weeks for each hormone.

The distribution of the baseline testosterone, DHEA, DHEA-S and androstenedione levels and the change in hormone level at 12 weeks will be compared between patients experiencing a PSA decline $\geq$30% and patients without such a PSA decline using a two group t statistic. Similarly, exploratory analysis using the t statistic will compare baseline and change from baseline at 12 weeks in hormone levels between each of the individual genotypes (A1A1, A1A2, A2A2) on the CYP 17 gene being evaluated versus the other two genotypes pooled together. Cox"s proportional hazards model will be applied to explore the effect of the baseline level for each hormone on time to initial and second progression, as defined by PSAWG-2 criteria. The relationship will be summarized by the hazard ratios with 95% confidence intervals.

7.5 Exploratory Objectives

7.5.1 Genotype analysis

The association of the presence of variant genotypes of CYP17A1 and a PSA decline $\geq$30% to standard dose therapy will be determined as a secondary outcome measure of this analysis. PSA decline of >30% to elevated-dose therapy will also be explored here. It is estimated that approximately 40% of patients will respond to increased-dose Abiraterone Acetate therapy (based on the alternative hypothesis defined in this clinical trial) and there are three potential genotypes for CYP17 (A1A1, A1A2, A2A2). Additionally, the duration of initial response to therapy is of interest.

The proportion of patients for each of the 3 genotypes of CYP 17 achieving a PSA decline ≥30% to initial and to dose escalated Abiraterone Acetate therapy will be measured in this analysis. For each patient the genetic profile will be defined according to the combinations of reference type and variant genotypes. Proportions will summarize the distribution of the individual 3 genotypes. Estimates of prevalence of genotypes in a prostate cancer population, as in the general population, are shown below.

a) Common homozygote (Reference) - A1A1 (estimate 43%)
b) Variant homozygote - A2A2 (estimate 14%)
c) Heterozygote- A1A2 (estimate 43%)

To evaluate the association between declines in PSA (<30% vs ≥30%) and the genotypes, the association between each of the 3 individual genotypes vs. the others combined (e.g. presence of A1 allele vs none: A2A2 vs. A1A1+ A1A2) and PSA decline to Abiraterone Acetate therapy will each be tested using Fisher"s exact test with a conservative level of significance of 0.05/3 = 0.0167 using the Bonferroni correction for 3 comparisons. If there is no difference in achieving a PSA decline of at least 30% in a genotype subset, then a similar percent of the patients with an individual genotype and of the remaining pooled patients would be expected to respond to therapy.

Exploratory multivariate models, logistic regression for PSA decline coded as a binary variable and Cox"s proportional hazards model for time to progression, will be developed to analyze the combined effects of baseline hormone levels, change in hormone levels after 12 weeks of Abiraterone Acetate 1000mg daily and the presence of a genetic variant in the 3 genotypes on the CYP 17 gene. Each hormone will be evaluated separately due to the total planned sample size of 33. It is recognized that the sample size is small which will limit the number of variables that can be included in a model. The convention is to include 1 variable for every 10 evaluable patients. This will allow for evaluating up to 3 predictors in each model (baseline hormone level, change in hormone level at week 12 and 1 genotype). A forward stepwise approach will be used (probability to enter set at 0.05 and the probability to remove set at 0.10) and univariate results will determine which variables will be included as potential independent predictors of outcome. Additional terms indicating an interaction between variables will be analyzed based upon the results. Because these are exploratory analyses the results will be used to develop future research. Cross-validation methods will be incorporated applied into to the multivariate analysis to control evaluate for overfitting of the model for overfitting.

7.5.2 AR Expression Signature

AR expression signatures will be derived in this study to determine whether the AR is transcriptionally active at the outset of therapy and at the time of treatment resistance. To determine the AR activation state at each time point, the level of expression of a defined set of 300 AR-induced gene transcripts which have previously been shown to reliably predict AR activation[24] will be examined in metastatic biopsies of men with ABI-naïve CRPC both prior to Abiraterone Acetate therapy and then again at the time of disease progression on Abiraterone Acetate 1000mg daily. This 300 gene AR transcriptional signature was derived by examining the set of genes with the strongest levels of differential expression between an androgen-sensitive prostate cancer cell line prior to and following exposure to ligand, correcting for false discovery, and then subsequently validated on human prostate samples with known levels of androgen. To perform this analysis frozen biopsies will be processed for microarray analysis in the Febbo lab using laser capture microdissection and RNA amplification using adaptations of methods previously published. Briefly, prostate cancer cells will be microdissected from frozen

sections using an Arcturus Veritas Microdissection system and RNA isolated per a standardized protocol using the Absolutely RNA Nanoprep Kit (Stratagene, Agilent, Santa Clara, CA). RNA will be quantified, assessed for quality, amplified, labeled, hybridized to U133 Plus 2.0 arrays for analysis (Affymetrix, Santa Clara, CA) and then analyzed using Affymetrix software. Standardized metrics will be used to assess RNA quality and only samples meeting quality standards will be used. Tumors will be assigned a probability of AR activity ranging from 0 (absent) to 1 (present). Tumors will then be assigned an outcome variable of AR-active or AR-inactive using a conservative cutoff of >0.5 as previously published[24] to define AR-active tumors. Because expression analysis of CTCs is not well established this transcriptional analysis will be performed only in metastatic biopsy tissue taken before treatment with Abiraterone Acetate 1000mg daily and at the time of initial treatment resistance.

The probability of AR activity determined from the pretreatment biopsy and at the time of first progression with standard dose Abiraterone Acetate will be compared using a t statistic for paired data. The distributions of the probability values will be compared using the nonparametric Wilcoxon test for paired data. In addition, when the probability outcome is coded as a binary outcome and is dichotomized at the median at each time point, the agreement or change in AR activity will be analyzed using McNemar"s chi square test of agreement for paired binary data.

7.5.3 Metastatic Biopsy and CTC analysis

Circulating tumor cells will be isolated for genetic analysis using the Vitatex VitaCap assay. Cells will be isolated from peripheral whole blood according to a published protocol for isolation of prostate cancer CTCs using this platform.[25] Based on experience with this methodology it is expected that >90% of patients will have detectable CTCs, that yields will range from 150-750 CTCs/ml, and that using a 40ml draw, adequate DNA suitable for downstream genomic analyses will be isolated from >70% of patients. Optional CTCs isolated using Veridex CellSearch and Epic Biosciences will be assayed in an exploratory fashion as well for enumeration purposes, to provide a control for the Vitatex analyses, and to explore the relationship of disease progresson with the presence of nuclear and cytoplasmic AR, presence of PTEN deletion, and expression of mesenchymal markers . Because Veridex CTCs are fixed using a preservative, no downstream genomic analyses will be performed on the Veridex CTCs. CTCs may also be sent to Xcell Biosciences for CTC culture in order to expand the population of cells available for genomic analysis and biologic characterization. All cultured CTCs and biomaterials will be returned to UCSF.

The methylation status of specific promoter and intragenic CpG sites in CYP17A1 and in a predefined set of 20 genes involved in androgen synthesis from prior to the first dose of Abiraterone Acetate 1000mg daily to the time of post-treatment disease progression will be explored using paired pre and post-treatment biopsy samples and in CTCs. This analysis will take place in the Paris and Febbo labs at UCSF. Methylation will be assessed using an Illumina platform and will be expressed as a continuous variable as the β ratio of signal from a methylated probe relative to the sum of methylated and unmethylated probes at an individual site and as a binary categorical variable with presence defined using a conservative β ratio of >0.8. Descriptive statistics for continuous and binary variables will be calculated to summarize the methylation state as well as the change from baseline post Abiraterone Acetate 1000mg daily therapy for each gene from biopsy and CTC specimens. For binary outcomes this will include the proportion of patients with methylation pre and/or post treatment for the 4 combinations and the proportion of patients with an increase in the number of methylation sites in the gene body following treatment, each with 95% confidence intervals. For each gene

considered as a continuous variable the mean baseline methylation β value and the mean difference from baseline post-treatment change will be reported with standard deviations and 95% confidence intervals. A paired t statistic or the Wilcoxon matched pairs test will be used to test for a difference from pre to post-treatment in mean values or distributions, respectively. No adjustment for multiple comparisons will be made for these initial analyses of the relationship between methylation with ABI resistance. To summarize the results multivariable clustering analyses will be performed including genes identified to reflect change after ABI therapy in the univariate methods just described with at least a probability value $\leq$0.10. Hierarchical clustering may be used to explore relationships among the genes.

8 CRITERIA FOR PSA RESPONSE/PROGRESSION

8.1 PSA RESPONSE

All patients will be evaluated for PSA response. Because it is possible that short-term increases in PSA will be followed by a meaningful response, PSA increases to Abiraterone Acetate during the first 12 weeks will not result in automatic discontinuation of therapy. The required sample size for this study is based upon the number of patients with progressive disease after achieving a PSA response of any magnitude after 12 weeks of treatment with standard-dose Abiraterone Acetate. Response to Abiraterone Acetate will be closely monitored to avoid over accrual.

a) PSA Response: For patients receiving standard-dose therapy this is defined as a PSA decline of any magnitude from baseline confirmed by a second measurement at least 2 weeks later. The reference for these declines should be a PSA measured within 2 weeks prior to starting therapy. For patients receiving elevated-dose therapy PSA response is defined as a ≥30% PSA decline from baseline after 12 weeks of elevated-dose therapy

b) PSA Progression: If any PSA decline from baseline has been achieved, PSA progression occurs when the PSA has increased to at least 25% above the nadir and the increase in the absolute-value PSA level is at least 2 ng/mL, or back to baseline, whichever is lower, on at least 2 measurements at least 2 weeks apart. If no PSA decline has been achieved then PSA progression occurs when the PSA has increased by at least 25% and the increase in the absolute-value PSA level is at least 2 ng/mL after 12 weeks of therapy.

c) PSA Response Duration: For patients receiving standard-dose therapy the PSA response duration commences on the date of the decline of any magnitude in PSA from baseline. The response duration ends when the PSA value first increases by at least 25% above the nadir, provided that the increase in the absolute-value PSA level is at least 2 ng/mL or back to baseline, whichever is lower. For patients receiving elevated-dose therapy the PSA response duration commences on the date of a ≥30% PSA from baseline. The response duration ends when the PSA value first increases by at least 25% above the nadir, provided that the increase in the absolute-value PSA level is at least 2 ng/mL or back to baseline, whichever is lower.

d) Progressive Disease: Defined by PSA Progression **OR** RECIST defined criteria for progressive disease **OR** the appearance of 2 new bone lesions on bone scan (note that for the first assessment only a confirmatory scan performed 6 or more weeks later is required

that shows a minimum of 2 or more new lesions) **OR** a new requirement for radiation therapy thought to be due to prostate cancer.

e) Time to PSA Progression: The start of the time to PSA progression is the day treatment is initiated. The end date is the first of the measurements determining progressive disease.

f) Criteria for Definition of Progression #2. The criteria for defining progression #2 are the same as for the definition of progression #1 however the PSA value at the time of progression #1 will be the baseline for progression #2.

a. Example: Patient begins study with a PSA of 100, which declines to 40 ng/mL at week 12, PD #1 will occur when PSA reaches 50 ng/mL or higher. Following dose-increased Abiraterone Acetate therapy a "second PSA response" will be defined as a decline below 35ng/ml and PD #2 will be defined as per standard criteria using 50 ng/mL as the baseline.

RECIST Criteria (Please see Appendix B)

9 REPORTING AND DOCUMENTATION OF ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

9.1.2 Adverse Events of Special Interest

Events that Janssen Services is actively monitoring as a result of a previously identified signal, including mineralocorticoid excess, cardiac adverse reactions, and liver toxicities.

9.1.3 Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

9.1.4 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

9.1.5 Unexpected

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or package insert(s) or, is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.
Some adverse events are listed in the investigator brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

9.1.6 Serious

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalization or prolongation of existing hospitalization
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
5. A congenital anomaly/birth defect
6. A suspected transmission of infectious agent by the study drug

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.1.7 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of

death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

9.1.8 J&J Medicinal Product

The specific J&J drug under study and any other J&J medicinal product.

9.1.9 Product Quality Complaint (PQC)

Any discrete concern that questions the identity, quality, durability, reliability, safety, efficacy or intended performance of a drug product. A complaint may allege an injury or malfunction associated with the use of the drug product. It may also involve the design, literature, packaging, advertising, availability, physical appearance or promotion of the drug product.

9.1.10 Special Reporting Situations

When a report contains a J&J product, an identifiable patient, and identifiable reporter, the following events represent Special Reporting Situations:

- overdose of a J&J medicinal product
- pregnancy exposure (maternal and paternal)
- exposure to a medicinal product from breastfeeding
- suspected abuse/misuse of a medicinal J&J product
- inadvertent or accidental exposure to a medicinal J&J product
    - any failure of expected pharmacological action (i.e., lack of effect) of a J&J medicinal product
    - unexpected therapeutic or clinical benefit from use of a Janssen Services medicinal product
    - medication error involving a J&J product (with or without patient exposure to the medicinal J&J product, e.g., name confusion)
    - Suspected transmission of any infectious agent via a medicinal product.

9.2 Management of Adverse Events, Serious Adverse Events and Special Reporting Situations

For each subject, AEs SAEs, and Special Reporting Situations should be recorded after informed consent is obtained until the subject has completed participation in the study as follows:

A Serious Adverse event or Special Reporting Situations must be reported if it occurs during a subject"s participation in the Study (whether receiving Study Product or not) and within 30 days of receiving the last dose of Study Product.

Any serious adverse event or Special Reporting Situations that is ongoing when a subject completes his/her participation in the Study must be followed until any of the following occurs:

- the event resolves or stabilizes;
- the event returns to baseline condition or value (if a baseline value is available);
- the event can be attributed to agents(s) other than the Study Product, or to factors unrelated to Study conduct.

In general, the Principal Investigator must immediately report to JANSSEN SERVICES any serious adverse event and Special Reporting Situations, whether or not considered drug related. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death as a result of anaphylactic reaction or fatal hepatic necrosis).

In that case, the investigator must immediately report the event to JANSSEN SERVICES. The Principal Investigator must record non-serious adverse events and report them to JANSSEN SERVICES according to the timetable for reporting as specified either in the protocol or to fulfill regulatory reporting requirements.

9.3 Recording of Adverse Events, Serious Adverse Events and Special Reporting Situations

All adverse events will be entered into OnCore®, UCSF"s Clinical Trial Management System, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (V4.0), when applicable, on the appropriate case report forms (CRFs). The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention[1]	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention[1]	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they are to be graded by the Investigator as none, mild, moderate or severe according to the following grades and definitions:

Grade 0: No AE (or within normal limits).
Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL).
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.

9.4 Follow-up of Adverse Events

All adverse events must be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a rechallenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

9.5 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the Data and Safety Monitoring Committee (DSMC), UCSF"s Committee on Human Research (CHR), and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration.

All adverse events entered into OnCore® will be reviewed by the Site Committee on a monthly basis. The Site Committee will review and discuss at each monthly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all adverse events and suspected adverse reactions considered "serious," entered into OnCore® will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings which take place every six (6) weeks.

9.6 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee (DSMC)

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 24 business hours of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF's Committee on Human Research (CHR)

The Investigator must report events meeting the CHR definition of "Unanticipated Problem" (UP) within 10 working days of his/her awareness of the event. Guidance on Adverse Event Reporting to the CHR is available online at the UCSF Human Research Protection Program website.

Expedited Reporting to the Food and Drug Administration (FDA)

The Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32). The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in 9.1.4)
- Unexpected (as defined in 9.1.5)
- Serious (as defined in 9.1.6)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeframe for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction must be reported to FDA no later than **7 calendar days** after the Investigator"s initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report must be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

The investigator (or designee) should prepare Form FDA 3500A (MedWatch) detailing the event, and contact the Institutional Trials Unit for assistance in the preparation of the IND Safety Report.

For additional information and guidance on IND Safety Reports, please refer to FDA"s Guidance document Safety Reporting Requirements for INDs. It is the Sponsor-Investigator"s responsibility to meet regulatory requirements for expedited reporting.

Reporting to Janssen Services

All safety information (SAEs, Adverse Events of Special Interest, Special Reporting Situations, and Product Quality Complaints) should be reported within **24 hours** of becoming aware of the event(s).

All non-serious AEs should be reported according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.
The following methods are acceptable for transmission of safety information to JANSSEN SERVICES:

- Facsimile (fax), receipt of which is evidences in a successful fax transmission report,
- Electronically subject to strict compliance with the following condition: Reporting may be done electronically only upon written approval by JANSSEN SERVICES, which approval must acknowledge that the electronic transmission is in an acceptable encrypted email format. Without such acknowledgement, the approval to use an electronic transmission shall not be valid. The Parties hereby acknowledge the importance of strict precautions with the use of electronic transmission for the security, protection and maintenance of confidentiality of patient health information contained in the reports, or
- Telephone (for business continuity purposes, if fax or authorized electronic system is non functional).

10 DATA AND SAFETY MONITORING PLAN

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all HDF CCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of subject data
- Review of suspected adverse reactions considered “serious”
- Monitoring every six months (depending on study accrual)
- Minimum of a yearly regulatory audit

10.1 Monitoring and Reporting Guidelines

All institutional Phase 2 therapeutic studies are designated with a moderate risk assessment. The data is monitored every six months, with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate quarterly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety and discuss each subject"s treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, quarterly conference calls with the participating sites or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Adverse Events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol Violations
- Other issues affecting the conduct of the study

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring and query data entered in OnCore for the 20% of subjects it reviews at the UCSF Coordinating Center and the participating sites. The data (i.e. copies of source documents) from the participating sites will be faxed over to the UCSF Coordinating Center prior to the monitoring visits in order for the DSMC to monitor the participating site"s compliance with the protocol, patient safety, and to verify data entry.

Adverse Event Review and Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF"s Clinical Trial Management System.

All adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled quarterly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

In addition, all suspected adverse reactions considered “serious” must be entered in OnCore® and reported to the UCSF Coordinating Center within 1 business day. The suspected adverse reactions considered “serious” will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meeting, which take place every six (6) weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within **1 business day** from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The contact may be by phone or e-mail.

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, a report should be submitted to the DSMC at the time the increased rate is identified. The report will indicate if the incidence of AEs observed in the study is within the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues the DSMC Chair and administrator must be notified within **1 business day** via e-mail. The DSMC must receive a formal letter within **10 business days** and the CHR must be notified.

Data and Safety Monitoring Committee Contacts:

DSMC Chair: [redacted]

[redacted]

11 STUDY MANAGEMENT

11.1 Prestudy Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory

requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

11.2 Institutional Review Board

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Committee on Human Research (CHR) (UCSF"s IRB). Prior to obtaining CHR approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

11.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

11.4 Changes in the Protocol

Once the protocol has been approved by the UCSF Committee on Human Research (CHR), any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the CHR prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation.

11.5 Handling and Documentation of Clinical Supplies

The Investigator shall maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

11.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. All study data will be entered into OnCore®, UCSF"s Clinical Trial Management System (CTMS) via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The

Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

Each participating site will complete study specific CRFs for safety monitoring and data analysis. Each site will enter the study data into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The participating site"s Clinical Research Coordinator (CRC) will complete the CRFs; the Investigator will review and approve the completed CRFs – this process must be completed within 3 business days of the visit. Study data from the participating site will be reported and reviewed in aggregate with data from patients enrolled at the coordinating center, UCSF. All source documentation and CTMS data will be available for review/monitoring as needed.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient"s medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. Each CRF must be reviewed for accuracy by the Investigator, corrected as necessary, and then approved. Alternatively, the Investigator may sign individual, printed CRFs. These signatures attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the Data and Safety Monitoring Committee (DSMC) and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement among the Principal Investigator, the Trial Statistician, and the Protocol Project Manager.

11.7 Oversight and Monitoring Plan

The Helen Diller Family Comprehensive Cancer Center Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will regularly review all adverse events and suspected adverse reactions considered “serious” and protocol deviations associated with the research to ensure the protection of human subjects. The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable.

11.8 Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, biweekly conference calls with the participating sites for Phase I dose escalation studies prior to each cohort escalation and at the completion of each cohort or

more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Cohort updates (i.e. DLTs)
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

11.9 Record Keeping and Record Retention

The investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

11.10 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

11.11 Regulatory Documentation

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF Committee on Human Research (CHR). Prior to implementing this protocol at the participating sites, approval for the UCSF CHR approved protocol must be obtained from the participating site"s IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB"s Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

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13 APPENDICES

Appendix A NCI CTC Common Toxicity Criteria

V4.0 (CTCAE): publish date May 28, 2009:
http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

Appendix B RESPONSE EVALUATION CRITERIA in SOLID TUMORS (RECIST)

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

  Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

  Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

  Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized

centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Appendix C PROSTATE CANCER WORKING GROUP 2 CRITERIA

Variable	PCWG2
PSA	Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drug
	Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression
	Ignore early rises (prior to 12 weeks) in determining PSA response
	For control/relieve/eliminate end points:
	Record the percent change from baseline (rise or fall) at 12 weeks, and separately, the maximal change (rise or fall) at any time using a waterfall plot
	Progression:
	Decline from baseline: record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend)
	The requirement of an increase of 5 ng/mL is decreased to 2 ng/mL, and the requirement for a 50% increase is reduced to 25%
	Recording the duration of PSA decline of little value
	No decline from baseline:
	PSA progression ≥ 25% and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	**For control/relieve/eliminate end points:**
	Use RECIST with caveats
	Only report changes in lymph nodes that were ≥ 2 cm in diameter at baseline
	Record changes in nodal and visceral soft tissue sites separately
	Record complete elimination of disease at any site separately
	Confirm favorable change with second scan
	Record changes using waterfall plot
	For delay/prevent end points:
	Use RECIST criteria for progression, with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later
	Note that for some treatments, a lesion may increase in size before it decreases
Bone	**For control/relieve eliminate end points:**
	Record outcome as new lesions or no new lesions
	First scheduled reassessment:
	No new lesions: continue therapy
	New lesions: perform a confirmatory scan 6 or more weeks later
	Confirmatory scan:
	No new lesions: continue therapy
	Additional new lesions: progression
	Subsequent scheduled reassessments:
	No new lesions: continue

Variable	PCWG2
	New lesions: progression
	For prevent/delay end points (progression):
	The appearance of ≥ 2 new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions
	The date of progression is the date of the first scan that shows the change
Symptoms	Consider independently of other outcome measures
	Document pain and analgesia at entry with a lead in period and measure repeatedly at 3- to 4-week intervals
	Perform serial assessments of global changes in health related quality of life (HRQOL), urinary or bowel compromise, pain management, additional anticancer therapy
	Ignore early changes (≤ 12 weeks) in pain or HRQOL in absence of compelling evidence of disease progression
	Confirm response or progression of pain or HRQOL end points ≥ 3 weeks later

Appendix D Drug Diaries

Standard Dose (1,000 mg daily)

First Last Name MRN: CYCLE Month

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
6/3/12	6/4/12	6/5/12	6/6/12	6/7/12	6/8/12	6/9/12
Reminder: *Abiraterone should be taken 1 hour before or 2 hours after each meal.*		**CYCLE X Day 1** Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____
6/10/12	6/11/12	6/12/12	6/13/12	6/14/12	6/15/12	6/16/12
Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____
6/17/12	6/18/12	6/19/12	6/20/12	6/21/12	6/22/12	6/23/12
Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____
6/24/12	6/25/12	6/26/12	6/27/12	6/28/12	6/29/12	6/30/12
Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____
7/1/12	7/2/12	7/3/12				
Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	**HOLD DRUG!** **CYCLE X Day 1** **BLD DRAW** **APPT TIME:**				

If you have been instructed by your provider not to take your study medication, your UCSF oncology nurse, Nurse Practitioner or doctor will let you know when you can restart the medicine and at what dosage. You should not restart drug without his or her prior approval.

*Drug Accountability: Please sign the calendar to indicate you have taken the above medication as instructed and return the signed calendar at the next study visit. Please note any missed doses and the reason missed on the specific date.

Dose Increased (1,000 mg twice a day)

First Last Name MRN: CYCLE Month

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
6/3/12	6/4/12	6/5/12	6/6/12	6/7/12	6/8/12	6/9/12
Reminder: *Abiraterone should be taken 1 hour before or 2 hours after each meal.*		**CYCLE X Day 1** Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____
6/10/12	6/11/12	6/12/12	6/13/12	6/14/12	6/15/12	6/16/12
Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____
6/17/12	6/18/12	6/19/12	6/20/12	6/21/12	6/22/12	6/23/12
Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____
6/24/12	6/25/12	6/26/12	6/27/12	6/28/12	6/29/12	6/30/12
Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____
7/1/12	7/2/12	7/3/12				
Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	Abiraterone: 1000mg _____ Pred AM 5mg _____ Pred PM 5mg _____	**HOLD DRUG!** **CYCLE X Day 1** **BLD DRAW** **APPT TIME:**				

If you have been instructed by your provider not to take your study medication, your UCSF oncology nurse, Nurse Practitioner or doctor will let you know when you can restart the medicine and at what dosage. You should not restart drug without his or her prior approval.

*Drug Accountability: Please sign the calendar to indicate you have taken the above medication as instructed and return the signed calendar at the next study visit. Please note any missed doses and the reason missed on the specific date.

Appendix E Prohibited Concomitant Medications

Drug Type	Generic Drug Name	Brand Name
Hormonal Therapy	Bicalutamide	Casodex, Cosudex, Calutide, Kalumid
	Nilutamide	Nilandron or Anandron
	Flutamide	Eulexin or Flutamin
	Cyproterone acetate	Androcur, Cyprostat,Cyproteron, Procur, Cyprone, Cyprohexal, Ciproterona, Cyproteronum,Neoproxil, Siterone
	Enzalutamide	Xtandi
	ARN-509	
	Finasteride	Proscar, Propecia
	Dutasteride	Avodart
	Spironolactone	Aldactone, Novo-Spiroton, Aldactazide, Spiractin, Spirotone, Verospiron or Berlactone
	Megestrol acetate	Megace
	Diethylstilbestrol (DES)	Stilbestrol, Stilboestrol, Honvol
	Herbal Mixture	PC-SPES
	Herbal Mixture	PC-Hope
	Herb	Saw Palmetto
	Ketoconazole	Nizoral
	TAK-700	Orteronel
	TOK-001	
Immune therapy	Provenge, Ipilumumab, ProstVac	Sipuleucel-T, Yervoy, ProstVac
	GM-CSF	Sargramostim, Leukine
Chemotherapy	Docetaxel	Taxotere
	Mitoxantrone	Novantrone
	Vinorelbine	Navelbine
	Estramustine	Emcyt

	Ixabepilone	Ixempra
	Cabazitaxel	Jevtana
Radiotherapy	Strontium	Metastron
	Samarium	Quadramet
	Radium-223	Alpharadin
Drug-drug interactions	Phenytoin	Dilantin
	Carbamazepime	Tegretol
	Rifampin	Rifadin, Rimactane
	Rifabutin	Mycobutin
	Rifapentine	Priftin
	Phenobarbital	Luminal
	Itraconazole	Sporanox
	Clarithromycin	Biaxin
	Atazanivir	Reyataz
	Nefazodone	Serzone
	Saquinavir	Invirase
	Telithromycin	Ketek
	Ritonavir	Norvir
	Indinavir	Crixivan
	Nelfinavir	Viracept
	Voriconazole	Vfend
	Thioridazine	Mellaril
	Dextromethorphan	Robitussin, NyQuil