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Protocol Title	**Maximal Androgen Depletion with Abiraterone Acetate Followed by Randomization of Maximal Androgen Ablation with Molecular Targeted Therapies Dasatinib or Sunitinib Malate. (CA180-320, Pfizer IIR WS520211)**
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LIST OF ABBREVIATIONS

AE	Adverse event
ANC	Absolute Neutrophil Count
BID	Twice a Day
BMS	Bristol-Myers Squibb Company
CAT (or CT scan)	Computed Axial Tomography
CBC	Complete Blood Count
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EKG	Electrocardiogram
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormone Replacement Therapy
IB	Investigators' Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IST	Investigator-Sponsored Trial
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NSAE	Non-Serious Adverse Event
PD	Progressive Disease
PFS	Progression Free Survival
PO	By Mouth
PR	Partial Response

QD	Once Daily
QoL	Quality Of Life
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNM Staging	Tumor, Node and Metastasis Staging
ULN	Upper Limit of Normal
WBC	White Blood Count
WOCBP	Women of Child-Bearing Potential

1.0 Objectives

1.1 Primary Objectives:

- To compare two two-stage treatment strategies for patients with castrate resistant prostate cancer that has progressed after treatment with Abiraterone Acetate.

1.2 Secondary objectives:

- Assess the time to treatment failure (TTF) prospectively in pretreated patients with abiraterone acetate and low-dose prednisone.
    - Assess the association between TTF with bone marrow testosterone concentrations.
    - Assess hypotheses generating associations between candidate pathway expression with response and progression free survival time.
- Determine the toxicity of the Src inhibitor, dasatinib, in combination with abiraterone acetate and low-dose prednisone in patients following progression on abiraterone acetate/prednisone.
    - Assess the progression free survival time of dasatinib + abiraterone acetate in abiraterone pretreated patients.
    - Assess hypotheses generating associations between candidate pathway expression with response and progression free survival time.
- Determine the toxicity of sunitinib in combination with abiraterone acetate and low-dose prednisone in patients following progression on abiraterone/prednisone.
    - Assess the progression free survival time of sunitinib + abiraterone acetate in abiraterone pretreated patients.
    - Assess hypotheses generating associations between candidate pathway expression with response and progression free survival time.
- Assess response, toxicity and progression free survival of patients following crossover.
- Identify associations with molecular markers implicated in prostate cancer with response and progression of each of the therapies investigated.
- Create a deeply annotated tissue resource for hypothesis generating discovery.

2.0 Introduction and Rationale

Prostate cancer is the most common cancer in males. The cancer is a major health care problem in the US and worldwide. It is anticipated that the challenge of prostate cancer, an age dependent neoplasm, will only increase with progressive aging of the population worldwide. Unlike other cancer types only modest advances have been made in therapy. The mainstay of therapy for patients with advanced cancer remains androgen ablation, and chemotherapy achieves responses and clearly palliates patients with advanced disease. The effects are modest and the earlier use of therapy has yet to increase its effectiveness. These observations stress the need to develop new therapy strategies based on the improved understanding of the biology driving prostate cancer progression [1].

Clinically, prostate cancer is characterized by a predictable pattern of progression in the majority of patients. The disease progresses from the primary site to lymph nodes and then bone. Osseous metastases are the preferred area of castrate progression that inevitably follows the initial response to androgen ablation in patients with metastases.

The mainstay of therapy for patients with prostate cancer metastases is androgen ablation. The vast majority of patients will initially benefit from a "response" and gratifying relief of symptoms. However, total disappearance of disease among patients presenting with metastases rarely occurs. Incurable castrate resistant progression occurs within three years in the vast majority of these patients. This stark reality prompted the study of chemotherapy upon castrate resistant progression. Prospective and properly powered randomized studies demonstrated meaningful palliation and subsequently a modest survival benefit.

Thus, chemotherapy has been the only new approved treatment that prolongs the survival of patients with castrate resistant prostate cancer.

2.1 Role of microenvironment

Bone is the dominant site of prostate cancer metastasis. Although the pattern of progression is predictable, the response to therapy has been unpredictable. This manifests clinically as variable results of therapy in otherwise similar patients. These observations suggest that prostate cancer bone metastasis is a biologic heterogeneous disease and understanding the various mechanisms that drive the progression in bone may improve the response to therapy. The inability to overcome the clinical heterogeneity of prostate cancer may account for the limited success of molecularly targeted therapies. In addition, the heterogeneity may account for our inability to apply our understanding of the biology of prostate cancer bone metastases to improving therapies for patients with prostate cancer. For example, two recent attempts to inhibit the osteoblast–epithelial interaction—blocking endothelin α receptor–mediated progression and blocking platelet-derived growth factor (PDGF)–mediated progression—resulted in modulation of bone-turnover markers without corresponding changes in the tumor. We interpret this experience as suggesting that the available experimental models of prostate cancer bone metastases do not reflect the complexity of the human disease and the multiple pathways that are implicated in its progression [1].

An additional observation that may contribute to the failure to translate experimental observations into improvement in therapy may be emerging appreciation of the role of persistent androgen signaling in the progression of castrate resistant prostate cancer. The finding challenges the prevailing endocrine dogma of androgen signaling and suggests that androgen signaling is a stromal-epithelial interacting pathway implicated in prostate cancer progression. Thus it may be important to maximally deplete microenvironment androgens to avoid the potential resistance attributed to sustained androgen signaling as resulting from paracrine production or androgens. These observations led us to conclude that elucidating the clinical heterogeneity of prostate cancer bone metastases will lead to effective and personalized care for the patients with prostate cancer bone metastases [1].

2.2 Paracrine androgen signaling

There is increasing evidence that "intracrine" (autocrine /paracrine) androgen signaling is implicated in the castrate resistant progression of prostate cancer. Furthermore persistent androgen signaling may account for the limited effectiveness of blocking androgen independent stromal- epithelial interacting pathways despite the compelling experimental data generated principally in androgen independent model systems. This reasoning leads us to speculate that there is a hierarchy of stromal – epithelial / interacting pathways with androgen signaling as dominant. The line of reasoning leads to the hypothesis that *efficient inhibition of "paracrine androgen signaling" will be a critical aspect of rational combinatorial strategies targeting the tumor microenvironment.*

2.3 Rationale for lead-in Abiraterone acetate

Abiraterone acetate has demonstrated antitumor activity in well-characterized patients with progressive castrate resistant prostate cancer. The response rates range from 40% to 60% by traditional criteria (Attard JCO 2008, JCO 2009, Danila ASCO 2008). These data provide confidence that further suppression of androgens can be achieved in patients with advanced castrate resistant prostate cancer. The expression of CYP 17 androgen receptor and increased bone marrow concentration of androgens were preliminarily predictive of response to abiraterone (Efstathiou GU Cancers Symposium 2009). These data support the hypotheses that resistance to castration results from increased expression of CYP 17, with "intracrine" production of androgens and increased androgen receptor expression. The initial suppression followed by continued suppression of the androgen signaling planned in this trial will test the hypotheses that the *continued androgen signaling accounts for some of the resistance observed to targeted therapies in patients with castrate resistant prostate cancer.*

2.4 Rationale for Sunitinib

Sunitinib has been studied and found to be safe in patients with advanced prostate cancer. Sunitinib was initially given alone then combined with chemotherapy. The findings suggest that sunitinib has a favorable tolerance and efficacy profile. We have observed pathologic complete remissions which we have not observed in similar patients over the last seven years, which is very encouraging. Of particular relevance is the

observation that sunitinib in combination with LHRH agonist results in ***pathologic complete remission*** in patients with locally advanced prostate cancer. This was not achieved with preoperative imatinib or chemotherapy combined with LHRH agonist. [2, 3] We interpret this finding to suggest that blocking of PDGF alone is inadequate where as inhibition of VEGF and PDGF signaling is efficacious by pathologic criteria in some patients with prostate cancer. Furthermore, the data suggest sunitinib may be superior to chemotherapy. The lack of a high rate of "response" by traditional cytoreduction analogous to that observed with vaccines. The addition of sunitinib to abiraterone will test the hypothesis that *the combination of sunitinib and abiraterone acetate is safe and more effective than sunitinib alone in patients with castrate resistant prostate cancer.*

2.5 Rationale for Dasatinib

Src is experimentally and clinically by association implicated in the progression of prostate cancer. The role of Src in prostate carcinogenesis is complex, through its partitioned role in host cells (osteoclast, endothelial cell, and osteoblast) and the epithelial compartment of prostate tumors. The partitioned role of Src is central to the theoretical therapeutic advantage of Src inhibitors such as dasatinib when compared to agents that exclusively target the host compartment (bisphosphonates) or the epithelial component (chemotherapy). This rationale forms the basis for the use of dasatinib in patients with castrate resistant prostate cancer and demonstrates further modulation of bone turnover marker in the setting of maximal pretreatment with zoledronic acid. Dasatinib, a multi-kinase inhibitor that is a potent Src inhibitor, is safe and has promising antitumor effects when combined with docetaxel. Based on the experimental and clinical observation we conclude that Src is a "credentialed" target for advanced prostate cancer. *These data lead us to the hypothesis that inhibition of Src signaling with dasatinib in patients with treated with maximal androgen ablation will be effective in prostate cancer* [4-10].

2.6 Rationale for Study

The overall goal of this study is to efficiently establish a clinical foundation for the development of combinatorial microenvironment targeting therapies following maximal androgen depletion with abiraterone. The assumptions are that the pathways targeted in the context of this study are implicated in the paracrine and autocrine progression of the cancer and paracrine androgen signaling, which is the most important pathway implicated in CRPC. *This study will efficiently validate candidate predictors of response to abiraterone acetate and assess the safety and efficacy of abiraterone acetate with the addition of two microenvironment targeting therapies with efficacy in prostate cancer. The result of the study will form the foundation for the development of a personalized treatment targeting the microenvironment for patient with advanced prostate cancer.*

3.0 Background Drug Information

3.1 Sunitinib

Sunitinib is an orally administered small molecule that inhibits the tyrosine kinase enzymatic activities of VEGFR and PDGFR and also blocks signaling through KIT. Vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) have been implicated in prostate cancer progression to hormone-refractory state and metastatic involvement [11-13]. Bone metastasis can occur in more than 95% of mHRPC patients and contributes to morbidity and mortality in this disease. Overexpression of PDGFR occurs in bone metastases as well as in the primary prostate adenocarcinoma.

Sunitinib has been approved multinationally for the treatment of gastrointestinal stromal tumor (GIST) after disease progression for intolerance to imatinib and for the treatment of advanced renal cell carcinoma (RCC). In clinical studies, sunitinib has been shown to have good oral bioavailability, linear pharmacokinetics, and a prolonged half-life for the parent compound, sunitinib (~40 hrs), and its active N-desethyl metabolite SU012662 (~80 hrs). Steady state levels of sunitinib and its metabolite are reached 7 to 10 days after repeat daily dosing. Drug accumulation with repeated 3-, 4-, 6-week cycles, or continuous daily dosing has not been observed. The most common adverse events attributed to sunitinib have been constitutional symptoms (eg, fatigue/asthenia), gastrointestinal effects (eg, nausea, diarrhea, stomatitis, dyspepsia), myelosuppression (eg, neutropenia, thrombocytopenia), and dermatological effects (eg, dermatitis, skin discoloration, hair depigmentation).

3.1.1 Mechanism of Action

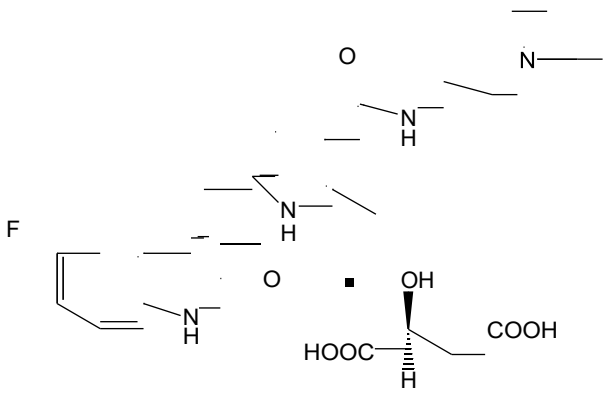
Sunitinib is a small molecule with antitumor properties that are pharmacologically mediated through inhibition of multiple receptor tyrosine kinases (RTKs) that are important in regulation of tumor cell growth, angiogenesis, and metastatic progression [14]. Specifically, sunitinib is a potent ATP-competitive inhibitor of the catalytic activity of a group of closely related RTKs consisting of PDGFR-α and -β, KIT, CSF-1R, FLT-3, VEGFR-1, -2, and -3, and RET. Due to its multi-targeted profile, the pharmacological activity of sunitinib is likely mediated by inhibition of multiple RTK targets and its antitumor mechanism is putatively mediated through inhibition of VEGF- and PDGF-dependent angiogenesis.

In addition, sunitinib has demonstrated a higher response rate than that reported for anti-VEGF antibody treatment in patients with RCC [15]. Early evidence indicates that inhibition of multiple tumor targets may add to the efficacy of anticancer agents. This is consistent with results from preclinical experiments suggesting dual inhibition of VEGFRs and PDGFRs produces greater antiangiogenic and antitumor effects than inhibition of VEGF signaling alone [16].

3.1.2 Molecular Formula and Chemical Class

Sunitinib has the molecular formula $C_{22}H_{27}FN_4O_2$. The free base has a molecular weight of 398.48 and the L-malate salt, the form used in clinical trials (Figure 1), has a molecular weight of 532.57. The chemical name of the L-malate salt is: (Z)-*N*-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide (S)-2-hydroxysuccinate.

Figure 1. The Structural Formula of SU011248 L-Malat Salt



Sunitinib has been shown to inhibit tumor growth of PC3 tumor cells in xenograft mouse models [17], as well as in subcutaneous, orthotopic and bone metastasis models by 75% to 88% compared to control animcals [Pfizer data on file]. It has also been shown to have direct growth inhibitory effect on LNCAP cells in vitro at concentrations as low as 0.05 μM. Preliminary data from a Phase ½ study (Protocol A6181043) study in mHRPC suggest that sunitinib antitumor activity with acceptable safety profile.

Protocol A6181043 is an ongoing open-label, dose finding study of sunitinib given once daily on a 2 weeks on, 1 week off treatment dosing regimen (Schedule 2/1) in combination with docetaxel and prednisone in patients with mHRPC in the first-line treatment setting.

A 6-week sunitinib-only lead-in period (50mg/day administered on a 4 weeks on, 2 weeks off treatment dosing regimen) was incorporated into the study design in order to provide data on PSA modulation by sunitinib alone.

The Phase I portion of the study was recently completed:4 successive cohorts patients received escalating doses of sunitinib (12.5, 37.5, and 50 mg/day) given on Schedule 2/1 in combination with 60 or 75 mg/m^2 of docetaxel every 3 weeks and 5 mg BID of prednisone continuously. Dose-limiting toxicities (DLTs) were evaluated in the first 9

weeks on study (lead-in and one combination cycle) and the recommended combination dose was defined as the dose level at which ≤ 2 out of 6 patients experienced a DLT, with the most acceptable pharmacokinetic profile.

Two DLTs were observed among 25 patients which were manageable and reversible: one grade 3 hyponatremia in the 50mg sunitinib + 60 mg/m^2 docetaxel cohort and one grade 4 neutropenia in the 37.5 mg sunitinib + 75 mg/m^2 docetaxel cohort. Preliminary pharmacokinetic assessments in all patients indicated an increase in total sunitinib concentration when combined with docetaxel and prednisone, primarily related to an increase in the active metabolite SU012662 concentrations. There was also a small decrease in docetaxel concentrations, possibly related to prednisone induction. Based on these results, the combination dose was chosen as sunitinib 37.5 mg/day in combination with docetaxel 75 mg/m^2 and prednisone 5 mg BID.

As of the last data cutoff, a total of 14 patients had discontinued the study (6 due to disease progression and 8 due to adverse events, including 1 on-study death due to complications of the disease). Preliminary efficacy results showed a confirmed PSA response in 10 (40%) patients and an objective response rate of 20% (4 of 20 patients with measurable disease) [18]. The study has now proceeded to the Phase 2 portion to further assess the safety and efficacy of this regimen in the first-line treatment of mHRPC.

During the lead-in period, elevations in PSA levels without correlation with clinical signs and symptoms of disease progression were commonly seen. PSA results showed three distinct patterns of sunitinib-induced PSA modulation during the lead-in period:

1. PSA reduction: 7 patients (28%) exhibited a mean PSA decline of 40% (including 3 patients with a confirmed PSA response [>50% decline confirmed by a second value]).

2. Initial PSA increase: 12 patients had an initial PSA increase, followed by a drop during the sunitinib off-treatment period of 2 weeks (mean increase during the lead-in of 273%, followed by a decrease of 28%).

3. PSA increase: 6 patients experience PSA progression (mean increase of 73%) and eventually discontinued the study due to disease progression.

As seen with these results, further understanding of PSA kinetics during treatment with novel antiangiogenic agents is critical for the proper definition of efficacy, especially when the comparator arm is chemotherapy. Therefore, PSA alone is not likely to be a reliable marker for assessment of disease status in studies of sunitinib in patients with prostate cancer. Similar lack of correlation between PSA levels during treatment with clinical signs and symptoms of progressive disease has also been reported with sorafenib [19].

Formulation and Packaging
Sunitinib will be supplied to the clinical pharmacy by the sponsor as hard gelatin capsules containing 12.5-mg, 25-mg, 37.5-mg, or 50-mg equivalents of sunitinib free base, in light-resistant bottles containing 30 capsules each.

Preparation and Dispensing
Patients will receive one bottle containing 30 capsules of sunitinib every 4 weeks. Only one capsule strength will be dispensed to the patient at each dose level. In case of dose modifications, patients will be requested to return all of their previously dispensed medication to the clinic, and they will be dispensed new strength capsules.

Drug Storage and Drug Accountability
The investigator, or an approved representative, e.g., pharmacist, will ensure that all sunitinib is stored in a secure area, under recommended storage conditions (controlled room temperature 15-30°C) and in accordance with applicable regulatory requirements. All study drug supplies must be kept in a locked, limited access room. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from the sponsor.

3.2 Abiraterone Acetate

Pharmacology

Abiraterone acetate (CB7630) is the prodrug of abiraterone (CB7598). Once ingested, it is rapidly converted into abiraterone. Abiraterone is a selective steroidal inhibitor of 17α-hydroxylase/C17, 20-lyase (cytochrome P450c17 [CYP17]).

CYP17 is an important enzyme in the synthetic pathway for the production of androgens in the testes and adrenal glands. It catalyzes the conversion of pregnenolone or progesterone into dihydroepiandrosterone (DHEA) or androstenedione, respectively, 2 precursors of testosterone.

Thus, abiraterone inhibits the production of testosterone in adrenal glands and testes. Testosterone, a C19 androgen, is further converted to the more potent androgen, dihydrotestosterone (DHT), by testosterone 5α-reductase in the prostate; both testosterone and DHT are principal promoters of prostate cancer growth.

Inhibitory effects of abiraterone on CYP17 activity have been demonstrated in vitro in rat and human testicular microsome preparations, and in vivo, in mouse, rat, and monkey animal models [20-21]. As expected, inhibition of CYP17 resulted in a reduction in circulating testosterone levels and, accordingly, the weight of androgen-sensitive organs. Reversible microscopic changes were observed in the tissues of

reproductive organs and in the adrenal gland. These effects were clearly demonstrated in established animal models after administration of abiraterone acetate.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA

For the most current DDI information for abiraterone acetate, please refer to the full prescribing information.

Toxicology

Nonclinical safety studies (See Investigator's Brochure) included the following: both in vitro and in vivo genotoxicity studies of abiraterone acetate and abiraterone; a single oral dose study of abiraterone acetate in mice; a single oral dose study in rats, two 28-day repeated oral dose toxicology studies of abiraterone acetate in rats (with 28-day recovery periods), a 13-week oral toxicity and toxicokinetic study in rats (with a 4-week recovery period), a 28-day repeated oral dose toxicity and toxicokinetic (TK) study (with a 28-day recovery period) in monkeys, and a 13-week oral toxicity and toxicokinetic study in monkeys (with a 4-week recovery period) in monkeys.

In vitro and in vivo genotoxicity studies conducted with abiraterone acetate or abiraterone did not show any mutagenic or clastogenic activity. No carcinogenicity or developmental and reproductive toxicology studies have been conducted with abiraterone acetate at this stage of development.

In both single oral dose and 28-day repeated oral dose studies, administration of abiraterone acetate to rats resulted in marked effects on the reproductive systems at all dose levels tested (40, 126, 400 mg/kg/d [240, 756, 2,400 mg/m^2/d]). These effects were largely predictable from the pharmacological effects of the agent. The significance of changes seen in liver histology and liver function tests was further evaluated in 13-week toxicity studies in rats and monkeys.

Higher doses administered for extended periods in both male and female rats (13 weeks treatment with dose levels up to 2000 mg/kg/d) resulted in severe morbidity in some animals, necessitating euthanasia. The study was continued at reduced doses: 50 mg/kg/d (low dose), 250 mg/kg/d (mid) and 750 mg/kg/d (high). At the reduced low and mid dose levels, there were no test article-related clinical signs of toxicity during dosing or during the 4-week recovery period.

At the new maximum dose of 750 mg/kg/d, the male rats lost weight in a manner consistent with inhibition of testosterone synthesis by abiraterone acetate, as reflected by very low plasma testosterone levels on Day 2 of treatment. At the high dose level (750

mg/kg/d), weight loss was also associated with reduced food consumption in male animals. Clinical chemistry findings, such as increased bilirubin and alkaline phosphatase, were suggestive of changes in liver function. Liver weights in both male and female rats were increased at the mid and high dose levels. Liver and gall bladder weights correlated with the minimal or slight bile duct hyperplasia observed microscopically in some animals. Bile duct hyperplasia correlated with increases in total bilirubin in female rats only.

In male and female monkeys, 28-day repeated, once-daily, oral administration of abiraterone acetate induced effects in the adrenals, mammary gland, and reproductive organs at all doses tested (2, 10, 50, 250, and 1,000 mg/kg [24, 120, 600, 3,000, and 12,000 mg/m^2]). Treatment with abiraterone acetate was associated with hormonal, microscopic, and macroscopic changes that were considered to be consistent with the antiandrogenic activity of abiraterone acetate (ie, inhibition of CYP17). These changes were reversible during the 28-day recovery period following death of treatment. Clinical chemistry changes were fully reversible with the exception of plasma bilirubin levels in male monkeys in the 250 and 1000-mg/kg/d treatment groups, which remained elevated at the end of the recovery period.

In a 13-week, repeated oral dose study in male and female monkeys with a 4 week recovery period, preliminary, unaudited results indicated no mortality or treatment-related adverse clinical signs other than white colored vomit and feces. The white color was presumed to be due to the presence of unabsorbed test article. There were no test-article effects on body weight or food consumption. Hormonal changes and organ weights, especially in reproductive organs and the adrenals, were again consistent with the antiandrogen properties of the agent. Abiraterone acetate administration was associated with higher triglyceride and total bilirubin concentrations suggesting some liver function changes. Dose-dependent increases in liver weights were observed in male and female animals. Clinical pathology changes showed reversibility following the 4-week recovery phase. Minimal, slight or moderate bile duct hyperplasia was seen microscopically in some animals which correlated with increases in total bilirubin. The hyperplasia was partially reversed during the recovery period while the bilirubin levels returned to normal.

Pharmacokinetics and metabolism

The pharmacokinetic (PK) and toxicokinetic (TK) profiles of abiraterone, administered as abiraterone acetate has been characterized in mice (oral, intraperitoneal, and intravenous), rats (oral), and monkeys (oral). Abiraterone acetate administered orally was systemically absorbed by animals and rapidly converted to abiraterone. Bioavailability of abiraterone, administered as abiraterone acetate, was 37% in the mouse in one study. Toxicokinetic analyses revealed that animals were exposed mainly to the metabolite, abiraterone and TK values were not linear and did not increase proportionally to dose from 126 to 400 mg/kg/d in rats or from 2 to 1,000 mg/kg/d in monkeys. The exact mechanism(s) involved that would explain this observation

remain(s) to be determined. Lower Cmax and AUC at the end of the dosing period in the 28-day toxicology studies in rats and monkeys suggest a possible induction of hepatic catabolic metabolism of abiraterone.

Preliminary data from in vitro studies with human hepatocytes indicate that human hepatocytes can convert abiraterone acetate to abiraterone and to other metabolites by hydroxylation and demethylation and conjugation reactions.

3.2.1 Clinical Experience

Three Phase 1 dose-escalation studies of abiraterone acetate were conducted in the United Kingdom by the Institute of Cancer Research (ICR) to investigate the safety and pharmacokinetics of oral abiraterone acetate in medically castrated or noncastrated men with prostate cancer [23]. In these 3 studies, 2 single-dose studies (Protocols PH1/054 and PH1/059) and one repeated daily dosing study (Protocol PH1/063) were carried out to determine the dose levels required to adequately suppress testosterone synthesis in these subjects. Other endocrine effects, particularly suppression of cortisol synthesis, were also examined.

A total of 26 patients were treated at dose levels ranging from 10 to 800 mg/d in these Phase 1 studies. Overall, these studies showed that abiraterone acetate was safe and well tolerated. At doses of 500 and 800 mg/d, significant decreases in circulating testosterone were achieved in all 3 studies.

In patients receiving 12-day repeated dosing at 500 and 800 mg/d (Protocol PHI/063), there were no apparent clinical signs of mineralocorticoid excess or glucocorticoid insufficiency. While basal levels of cortisol were within normal limits, use of the short Synacthen test (synthetic adrenocorticotropic hormone [ACTH1-24]) on Day 11 showed diminished cortisol response at 30 minutes when compared with pretreatment test responses. This observation suggests potential effects of abiraterone on the adrenal reserve which might be predicted from its known pharmacologic effects on steroid synthetic pathways.

Subsequently, two Phase 1/2 studies (COU-AA-001 [124, 27, 28] and COU-AA-002 [15, 29]) have been sponsored by Cougar, to evaluate the safety and tolerability of abiraterone acetate administered continuously on a daily basis in patients who had castrate levels of testosterone, have been receiving ongoing GnRH agonists, and had not been treated with chemotherapy. These studies investigated the pharmacokinetics of abiraterone acetate, its effects on pituitary-adrenal axis, in addition to identifying the dose for additional antitumor activity assessment. At the conclusion of Phase 1 investigation, 1000 mg daily dose was selected for further evaluation of the antitumor activity of abiraterone acetate in a Phase 2 setting. A plateau of biologic effect appears to have been reached at 1000 mg daily dose in that the AUC values at a dose of 2000 mg are no higher than that for the 1000 mg dose.

Furthermore, a Phase 2 study (COU-AA-003 [26, 30]) was also initiated to assess the antitumor activity of abiraterone acetate in patients who have failed docetaxel-based chemotherapy.

Study COU-AA-001

Abiraterone acetate was well-tolerated at doses up to 2000 mg/day with no dose limiting toxicity being observed [27, 28]. Antitumor activity was observed with 23 out of 38 patients having a greater than 50% decline in PSA lasting at least three months. 11 out of 20 patients with disease measurable by RESIST criteria had partial responses. There are 3 cases of regressing bone disease on imaging and reports of symptom improvement (stopping opiates). Furthermore, a reduction in levels of alkaline phosphatase and lactic dehydrogenase (LDH) and circulating tumour cells has been reported. Of particular interest, 4 patients have received abiraterone acetate treatment for more than 12 months as a result of sustained tumor response.

For the Phase 2 study, the dose of 1000 mg has been selected as recommended dose as a plateau in endocrine effect was reached at that dose

Study COU-AA-002

In study COU-AA-002, a significant proportion of patients had prior treatment with ketoconazole for their prostate cancer [29]. Treatment with abiraterone acetate was found to be well-tolerated up to 1000 mg/day with no dose-limiting toxicity. All but one patient (24/25) had an initial decline in PSA and 12/25 (48%) patients showed a greater than 50%.

Study COU-AA-003

Study COU-AA-003 is a Phase 2, open-label, multicenter study in patients who have androgen independent prostate cancer and failed docetaxel-based chemotherapy. Although patients had more advanced disease, abiraterone acetate was generally well tolerated [30]. Preliminary antitumor activity was also apparent. A >50% decline in PSA levels was seen in 7 (54%) of the first 13 patients treated with abiraterone acetate. There were anecdotal reports of pain relief and decreased use of analgesics.

In summary, continuous single daily dosing with abiraterone acetate was well-tolerated in patients with prostate cancer who have failed hormonal therapy with agents including GnRH agonists, antiandrogens, and ketoconazole, as well as chemotherapy. Dose-limiting toxicity was not observed in up to 2000 mg/day. Antitumor activities were apparent in these studies.

3.2.2 Packaging and Labeling

Abiraterone acetate tablets will be provided to each site packaged in individual bottles for patient assignment at the time of randomization. Patients will be provided with a 30-day supply to allow for visits to occur every 28 days with a ± 2 day window.

Information presented on the labels for investigational product will comply with applicable local regulations.

Site pharmacist or medically qualified staff will dispense the blinded study treatment to each patient in accordance with this protocol.

3.2.3 Pharmacy Storage Requirements

The study treatment must be stored in a secure area and administered only to patients entered into the clinical study in accordance with the conditions specified in this protocol. Bottles study treatment should be stored at room temperature [15º-30º C; 59º-86º F] in the original container/closure with the cap on tightly; it should never be refrigerated. Additional information is provided in the abiraterone acetate Investigator's Brochure.

3.2.4 Formulation of Study Drug

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).

3.3 Dasatinib

Dasatinib [SPRYCEL®] is a potent, broad spectrum ATP-competitive inhibitor of 5 critical oncogenic tyrosine kinase/kinase families: BCR-ABL, SRC, c-KIT, PDGF receptor β (PDGFRβ), and ephrin (EPH) receptor kinases, each of which has been linked to multiple forms of human malignancies.[31]

Drug discovery and nonclinical pharmacology studies showed that dasatinib:[32]

- Kills BCR-ABL dependent leukemic cell lines, including a number that are resistant to imatinib due to kinase domain mutations or overexpression of SRC family kinases and is effective against all imatinib-resistant kinase domain mutations tested to date, except T315I
- Inhibited proliferation of cancer cell lines that express activated SRC or c-KIT
- Potently inhibits VEGF-stimulated proliferation and migration in HUVECs
- Has potent bone anti-resorptive activity

3.3.1 Preclinical Anti-tumor Activity

3.3.1.1 In Vitro Molecular Studies

Dasatinib potently inhibits: SRC kinases, BCR-ABL, c-KIT, PDGFRβ and EPHA and was less potent against 16 other unrelated protein tyrosine kinases (PTKs) and serine/threonine kinases. Imatinib is less potent against several key enzymes: for example, Dasatinib was 260-, 8-, 60-, and >1000-fold more potent than imatinib versus BCR-ABL, c-KIT, PDGFRβ, and SRC kinases, respectively. [32]

In vitro, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate sensitive and resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, dasatinib was able to overcome imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene overexpression. [31]

Dasatinib inhibits the BCR-ABL kinase with an *in vitro* IC_{50} of 3 nM, a potency 260-fold greater than that of imatinib mesylate (IC_{50} = 790 nM). In cellular assays, dasatinib killed or inhibited the proliferation of all BCR-ABL dependent leukemic cell lines tested to date. Dasatinib also demonstrated undiminished anti-tumor activity against several preclinically- and clinically-derived models of imatinib mesylate resistance. Evidence that SRC family kinase over expression may play a role in clinical resistance to imatinib mesylate was demonstrated in three CML cell lines established from patients who failed imatinib mesylate therapy. These cells remained highly sensitive to the cell-killing effects of dasatinib. [32]

These results demonstrate that dasatinib is effective in reducing the proliferation or survival of both imatinib mesylate-sensitive and resistant cells, and its inhibitory activity is not solely dependent on BCR-ABL.

3.3.1.2 In Vivo Studies

The activity of dasatinib against CML cells *in vitro* was reproduced *in vivo* against several human CML xenograft models grown subcutaneously in SCID mice. Against the K562/imatinib mesylate/R CML model, dasatinib was curative in 100% of the treated animals. In contrast, at its optimal dose and schedule, imatinib mesylate was inactive.

3.3.2 Preclinical Toxicology

Single or repeated oral administration of dasatinib principally affected the gastro-intestinal (GI) tract, including the liver, the hematopoietic and lymphoid

systems in rats and monkeys. Other prominent effects after single oral administration of dasatinib included renal and cardiac toxicity in rats at lethal doses, and cutaneous hemorrhage in monkeys. Dasatinib can also affect the immune system and bone turnover.

Dasatinib *in vitro* activity in the HERG/IKr and Purkinje-fiber assays indicated a moderate liability for prolongation of cardiac ventricular repolarization (QT interval) in the clinic. However, there were no dasatinib -related changes observed in electrocardiograms, nervous system function, respirations and heart rate, blood pressure, or arterial oxygen saturation in single-dose, 10-day, or 1-month oral toxicity studies in monkeys.

Dasatinib was found to exhibit a profile of broad-spectrum platelet inhibition best typified by anti-platelet agents such as the GPIIb/IIIa antagonists, integrelin and abciximab.

Finally, modulation of SRC kinase activity could also affect osteoclast morphology and function and bone remodeling. This effect could potentially result in an increase in bone mineral density and a phenotype analogous to osteopetrosis. [32]

3.3.3 Clinical Pharmacokinetics

The pharmacokinetics of dasatinib have been evaluated in 229 healthy subjects and in 137 patients with leukemia (CML or Ph+ALL) from a Phase I clinical study (CA180002).

3.3.3.1 Absorption

Maximum plasma concentrations (C_{max}) of dasatinib are observed between 0.5 and 6 hours (T_{max}) following oral administration. Dasatinib exhibits dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 mg to 240 mg/day. The overall mean terminal half-life of dasatinib is 3–5 hours. [31]

Data from a study of 54 healthy subjects administered a single, 100-mg dose of dasatinib 30 minutes following consumption of a high-fat meal resulted in a 14% increase in the mean AUC of dasatinib. The observed food effects were not clinically relevant.

3.3.3.2 Distribution

In patients, dasatinib has an apparent volume of distribution of 2505 L, suggesting that the drug is extensively distributed in the extravascular space. Binding of dasatinib and its active metabolite to human plasma proteins *in vitro* was approximately 96% and 93%, respectively, with no concentration dependence over the range of 100–500 ng/mL. [31]

3.3.3.3 Metabolism

Dasatinib is extensively metabolized in humans, primarily by the cytochrome P450 enzyme 3A4. CYP3A4 was the primary enzyme responsible for the formation of the active metabolite. Flavin-containing monooxygenase 3 (FMO-3) and uridine diphosphate-glucuronosyltransferase (UGT) enzymes are also involved in the formation of dasatinib metabolites. In human liver microsomes, dasatinib was a weak time-dependent inhibitor of CYP3A4.

The exposure of the active metabolite, which is equipotent to dasatinib, represents approximately 5% of the dasatinib AUC. This indicates that the active metabolite of dasatinib is unlikely to play a major role in the observed pharmacology of the drug. Dasatinib also had several other inactive oxidative metabolites.

Dasatinib is a time-dependent inhibitor of CYP3A3. At clinically relevant concentrations, dasatinib does not inhibit CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, or 2E1. Dasatinib is not an inducer of human CYP enzymes. [31]

3.3.3.4 Elimination

Elimination is primarily via the feces. Following a single oral dose of [^{14}C]-labeled dasatinib, approximately 4% and 85% of the administered radioactivity was recovered in the urine and feces, respectively, within 10 days. Unchanged dasatinib accounted for 0.1% and 19% of the administered dose in urine and feces, respectively, with the remainder of the dose being metabolites. [31]

3.3.4 Anticipated Adverse Events

Myelosuppression

Treatment with dasatinib is associated with severe (NCI CTC Grade 3 or 4) thrombocytopenia, neutropenia, and anemia. Their occurrence is more frequent in patients with advanced CML or Ph+ ALL than in chronic phase CML. Complete blood counts should be performed weekly for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding dasatinib temporarily or dose reduction. In a Phase 3 dose-optimization study in patients with chronic phase CML, Grade 3 or 4 myelosuppression was reported less frequently in patients treated with 100 mg once daily than in patients treated with 70 mg twice daily. [31]

Bleeding Related Events

In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction *in vitro*. In all clinical studies, severe central nervous system (CNS) hemorrhages, including fatalities, occurred in <1% of patients receiving dasatinib. Severe gastrointestinal hemorrhage occurred in 4% of patients and generally required treatment interruptions and transfusions. Other cases of severe hemorrhage occurred in 2% of patients. Most bleeding events were associated with severe thrombocytopenia.

Patients were excluded from participation in dasatinib clinical studies if they took medications that inhibit platelet function or anticoagulants. In some trials, the use of anticoagulants, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) was allowed concurrently with dasatinib if the platelet count was >50,000. Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants. [31]

Fluid Retention

Dasatinib is associated with fluid retention. In all clinical studies, severe fluid retention was reported in 8% of patients, including pleural and pericardial effusion reported in 5% and 1% of patients, respectively. Severe ascites and generalized edema were each reported in <1% of patients. Severe pulmonary edema was reported in 1% of patients. Patients who develop symptoms suggestive of pleural effusion such as dyspnea or dry cough should be evaluated by chest X-ray. Severe pleural effusion may require thoracentesis and oxygen therapy. Fluid retention events were typically managed by supportive care measures that include diuretics or short courses of steroids.

In the Phase 3 dose-optimization study in patients with chronic phase CML, fluid retention events were reported less frequently in patients treated with 100 mg once daily than in patients treated with 70 mg twice daily. [31]

QT Prolongation

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval). In single-arm clinical studies in patients with leukemia treated with dasatinib, the mean QTc interval changes from baseline using Fridericia's method (QTcF) were 3–6 msec; the upper 95% confidence intervals for all mean changes from baseline were <8 msec. Nine patients had QTc prolongation reported as an adverse event. Three patients (<1%) experienced a QTcF >500 msec.

Dasatinib should be administered with caution to patients who have or may develop prolongation of QTc. These include patients with hypokalemia or

hypomagnesemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to dasatinib administration. [31]

3.3.5 Phase I experience in Solid Tumors

In a Phase I study (CA180003) conducted by Bristol Myers Squibb (BMS), dasatinib was administered on a BID schedule to 42 subjects with refractory solid tumor. As of 10-Feb-2006, 33 subjects were treated for a full 4 weeks for evaluation of dose-limiting toxicities (DLTs). This study explored 8 dose levels with 2 different dosing schedules. The first schedule assessed 5 days of dasatinib followed by 2 days off-drug each week, and the second schedule assessed continuous daily dosing that was added in Amendment #3 (7-Mar-2005). In the 5 days on/2 days off schedule, the following dose levels were explored: 35 mg BID, 50 mg BID, 70 mg BID, 90 mg BID, 120 mg BID and 160 mg BID. Of the six subjects enrolled and evaluable for DLT determination at the dose level of 90 mg BID given on a continuous daily schedule, two episodes were considered possibly to represent DLT reported by 2 subjects. These were recurrent Grade 2 rash in 1 subject and removal from study for Grade 2 nausea and vomiting and lightheadedness in the other subject. Given the otherwise acceptable tolerability of this dose level with toxicities that are medically manageable with a maximum severity of Grade 2, further escalation to the next dose level of 120 mg BID continuous daily schedule is currently under investigation. No further escalation above 160 mg BID was explored on this schedule because, as per protocol, this represents the maximum tolerated dose (MTD). [32]

The preliminary safety results from CA180003 demonstrate that no severe clinical toxicity has been encountered. Dasatinib did not induce significant myelosuppression in this patient population Gastrointestinal symptoms including nausea and vomiting were reported in most subjects, fatigue was reported in 17 subjects (40%) and rash in 9 subjects (21%). Edema, lethargy and headache were uncommon, and appear to be dose-related. Additionally, the incidence and severity of fluid retention and of pleural effusion, in particular, appear to be less in subjects with solid tumors than in those with leukemia receiving comparable doses of dasatinib. There were 4 subjects with drug-related AEs leading to discontinuation of treatment; none of these events were related to myelosuppression or fluid retention. [32]

In another Phase I study (CA180021), dasatinib was administered on a QD schedule to 24 subjects with solid tumors in a drug-drug interaction and multi-ascending dose (MAD) study at doses up to 180 mg. This ongoing study investigated the effect of ketoconazole, a potent inhibitor of CYP3A4, on the PK of dasatinib (Segment 1) and the effect of dasatinib on pharmacodynamic

markers in subjects with advanced solid tumors that are refractory to standard therapies or for which no standard therapy exists (Segment 2).

Segment 1 includes 18 subjects, of which 16 subjects were treated with dasatinib as of 2-Jan-2006. Segment 2 includes approximately 30 additional subjects, of which 14 subjects were treated with dasatinib as of 2-Jan-2006. A total of 4 deaths, all related to disease progression, were reported. There were 4 subjects with drug-related AEs leading to discontinuation: 1 subject with Grade 1 amnesia, 1 with Grade 2 pleural effusion, 1 with Grade 3 dehydration, and 1 subject with Grade 3 dysphagia and Grade 3 dehydration. Hypocalcemia, GI symptoms and skin rash have been mild and infrequent. [32]

To date, the safety profile in solid tumor subjects has been similar to that in CP CML subjects with the exception of severe myelosuppression, which has not been observed in solid tumor subjects and is considered related to efficacy against the leukemia as noted above, and severe bleeding which is secondary to thrombocytopenia in most instances.[32]

3.3.6 Dasatinib Experience in Prostate Cancer

In a Phase I study (CA180085) conducted by Bristol Myers Squibb (BMS), dasatinib was administered to 95 subjects with metastatic prostate cancer and rising PSA who progressed during first-line androgen ablation or progressed despite multiple-androgen suppression after discontinuation of androgen ablation. Treatment was given in two study groups, one with a BID dosing schedule and one with QD dosing. Twenty-five of 95 treated subjects were responders. Confirmed prostate-specific antigen (PSA) response was observed in 2 subjects, 1 in each of the QD and BID groups. Stabilization of visceral/nodal disease as measured by RECIST was observed in 10 subjects in the QD group and 12 subjects in the BID group, and a partial response was observed in 1 (1.1%) subject (QD group). Stabilization of bone disease was also noted. The QD dosing schedule led to fewer and less severe side-effects [47].

In a Phase I/II study (CA180086) being conducted by Bristol Myers Squibb (BMS), dasatinib (QD schedule; dose escalation) is being administered in combination with docetaxel. Preliminary results indicate: Of the 46 treated subjects, confirmed partial response was observed in 16 subjects and stabilization of disease was observed in 9 subjects. Confirmed PSA response was observed in 28 subjects and confirmed bone scan improvement was observed in 10 subjects. Reduction of bone turnover markers (uNTX and BAP) was also observed. No drug-drug interactions (between dasatinib and docetaxel) were observed as demonstrated by extensive PK profiling, and neither compound interfered with the metabolism of the other [47].

3.3.7 Identification

Dasatinib is provided in 3 different strengths:

Table 5.1.1: Description of Dasatinib Dosage Forms

Strength	Description
5 mg	white, round, film coated tablet
20 mg	white to off-white, biconvex, round, film coated tablet with either "20" or "BMS" debossed on one side and "527" on the other side
50 mg	white to off-white, biconvex, oval, film coated tablet with either "50" or "BMS" debossed on one side and "528" on the other side

3.3.8 Packaging and Labeling

Dasatinib is supplied as 5 mg, 20 mg, and 50 mg film-coated tablets containing dasatinib with lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating contains hydroxypropyl methylcellulose, titanium dioxide, and polyethylene glycol (triacetin in the 5 mg film-coated tablet). Tablets for clinical studies are supplied in high-density polyethylene bottles containing a desiccant and cotton. The bottles are heat-induction sealed with child resistant caps.

Each bottle is labeled in an open label manner. Labels contain, at a minimum, the following information: product name, tablet strength, batch number, directions for use, storage conditions, and appropriate caution statements.

3.3.9 Storage, Handling, and Dispensing

3.3.9.1 Storage

Bottles containing dasatinib tablets should be stored at 15° - 25°C.
All investigational product should be stored in a secure area according to local regulations. The investigator is responsible for ensuring that it is dispensed only to study subjects and only from official study sites by authorized personnel, as dictated by local regulations.

The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity.

If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product, and contact BMS immediately.

3.3.9.2 Handling and Dispensing
Procedures for proper handling and disposal of anticancer drugs should be considered.

Dasatinib tablets consist of a core tablet (containing the active drug substance), surrounded by a film coating to prevent exposure of pharmacy and clinical personnel to the active drug substance. If tablets are crushed or broken, pharmacy and clinical personnel should wear disposable chemotherapy gloves. Personnel who are pregnant should avoid exposure to crushed and/or broken tablets.

The Investigator (or assigned designee, i.e., study pharmacist) will dispense the proper number of each strength tablet to the subject to satisfy dosing requirements for the study. The containers provided to the subject should be labeled with proper instructions for use. The lot numbers, dosing start dates and the number of tablets for each dosage strength must be recorded on the drug accountability pages of record for the site. The subject must be instructed to return all unused dasatinib in the provided packaging at each subsequent visit.

4.0 Patient Eligibility

4.1 Inclusion
Each patient must meet the following criteria to be enrolled in this study.

1. Willing and able to provide written informed consent
2. Male aged 18 years and above
3. Histologically or cytologically confirmed adenocarcinoma of the prostate
4. Metastatic disease documented by positive bone scan or metastatic lesions other than liver or visceral metastasis on CT or MRI.
5. Prostate cancer progression documented by PSA according to PCWG2 or radiographic progression according to modified RECIST criteria
6. Surgically or medically castrated, with testosterone levels of $\leq$ 50 ng/dL ($\leq$ 2.0 nM). If the patient is being treated with LHRH agonists (patients who have not undergone orchiectomy), this therapy must have been initiated at least 4 weeks prior to Cycle 1 Day 1 and must be continued throughout the study.

7. If the patient received previous anti-androgen therapy, then they have shown progression after withdrawal. Patients who received combined androgen blockade with an anti-androgen must have shown PSA progression after discontinuing the anti-androgen prior to enrollment (≥ 4 weeks since last flutamide, ≥ 6 weeks since last bicalutamide or nilutamide). If progression is documented prior to this time interval, patients are eligible. 8. Previous treatment with docetaxel is allowed. Patients must have recovered from any acute toxicity related to the treatment to be eligible.
9. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1.
10. Hemoglobin ≥ 9.0 g/dL
11. Platelet count ≥100,000/μL
12. Serum albumin ≥ 3.5 g/dL
13. Serum creatinine ≤ 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min
14. Serum potassium ≥ 3.5 mmol/L
15. Serum sodium, magnesium, potassium, phosphate, and calcium ≥ LLN (lower limit of normal)
16. ANC value ≥ 1,000/mm^3
17. Liver function:
    i. Serum bilirubin ≤ 1.5 x ULN (except for patients with documented Gilbert's disease)
    ii. AST or ALT ≤ 2.5 x ULN
18. Able to swallow the study drug whole as a tablet/capsule.
19. Patients who have partners of childbearing potential (e.g. female that has not been surgically sterilized or who are not amenorrheic for ⩾ 12 months) must be willing to use a method of birth control with adequate barrier protection as determined to be acceptable by the principal investigator during the study and for 13 weeks after last study drug administration.
20. Concomitant Medications
    (i) Patient agrees to discontinue St. Johns Wort while receiving dasatinib therapy (at least 5 days prior).
    (ii) Patient agrees that IV bisphosphonates will be withheld for the first 8 weeks of dasatinib therapy due to risk of hypocalcemia.
    (iii) Patient agrees to discontinue use of drugs primarily metabolized by CYP3A4 enzyme (see Section 5.6.1.1 for a list of these drugs).
    (iv) Patient agrees to discontinue use of H2 Inhibitors or proton inhibitors prior to dasatinib administration.

4.2 Exclusion

Patients who meet any of the following criteria will be excluded from the study:

1. Active infection (requiring oral or IV antibiotics) or other medical condition that would make prednisone/prednisolone (corticosteroid) use contraindicated
2. Any chronic medical condition requiring a higher dose of corticosteroid than 5mg prednisone/prednisolone BID.
3. Pathological finding consistent with small cell carcinoma of the prostate

4. Radiation therapy for treatment of the primary tumor within 6 weeks of Cycle 1, Day 1. Patients who have received palliative radiation to a single site and recovered are eligible.
5. No malignancy [other than the one treated in this study] which required radiotherapy or systemic treatment within the past 5 years.
6. Previously treated with ketoconazole (for prostate cancer) for greater than 7 consecutive days OR previously treated with any other -azole drug (e.g. fluconazole, itraconazole) within 4 weeks of Cycle 1, Day 1.
7. Prior flutamide (Eulexin) treatment within 4 weeks of Cycle 1, Day 1 (patients whose PSA did not decline for three or more months in response to antiandrogen given as a second line or later intervention will require only a two week washout prior to Cycle 1, Day 1)
8. Bicalutamide (Casodex), nilutamide (Nilandron) within 6 weeks of Cycle 1 Day 1(patients whose PSA did not decline for three or more months in response to antiandrogen given as a second line or later intervention will require only a two week washout prior to Cycle 1, Day 1).
9. Uncontrolled hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg). Patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment
10. Prolonged QTc interval on pre-entry electrocardiogram (≥ 450 msec)
11. Active or symptomatic viral hepatitis or chronic liver disease
12. History of pituitary or adrenal dysfunction
13. Known brain metastasis
14. Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes), Subjects with hypokalemia or hypomagnesemia if it cannot be corrected prior to dasatinib administration or New York Heart Association (NYHA) Class II-IV heart disease or cardiac ejection fraction measurement of < 50% at baseline
15. History of significant bleeding disorder unrelated to cancer, including:
    i) Diagnosed congenital bleeding disorders (e.g., von Willebrand's disease)
    ii) Diagnosed acquired bleeding disorder within one year (e.g., acquired anti-factor VIII antibodies)
    iii) Ongoing or recent (≤ 3 months) significant gastrointestinal bleeding
16. Atrial fibrillation or other cardiac arrhythmia requiring digitalis
17. Other malignancy, except non-melanoma skin cancer, with a ≥ 30% probability of recurrence within 24 months
18. Clinically significant pleural effusion as determined by the Principal Investigator.
19. Administration of an investigational therapy for prostate cancer within 30 days of Cycle 1, Day 1
20. Any condition which, in the opinion of the investigator, would preclude participation in this trial.

21. Patients taking category I drugs thatare generally accepted to have a risk of causing Torsades de Pointes including: (Patients must discontinue drug 7 days prior to starting dasatinib)
    i) quinidine, procainamide, disopyramide
    ii) amiodarone, sotalol, ibutilide, dofetilide
    iii) erythromycin, clarithromycin
    iv) chlorpromazine, haloperidol, mesoridazine, thioridazine,pimozide
    v) cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine.
22. Prisoners or subjects who are involuntarily incarcerated.
23. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

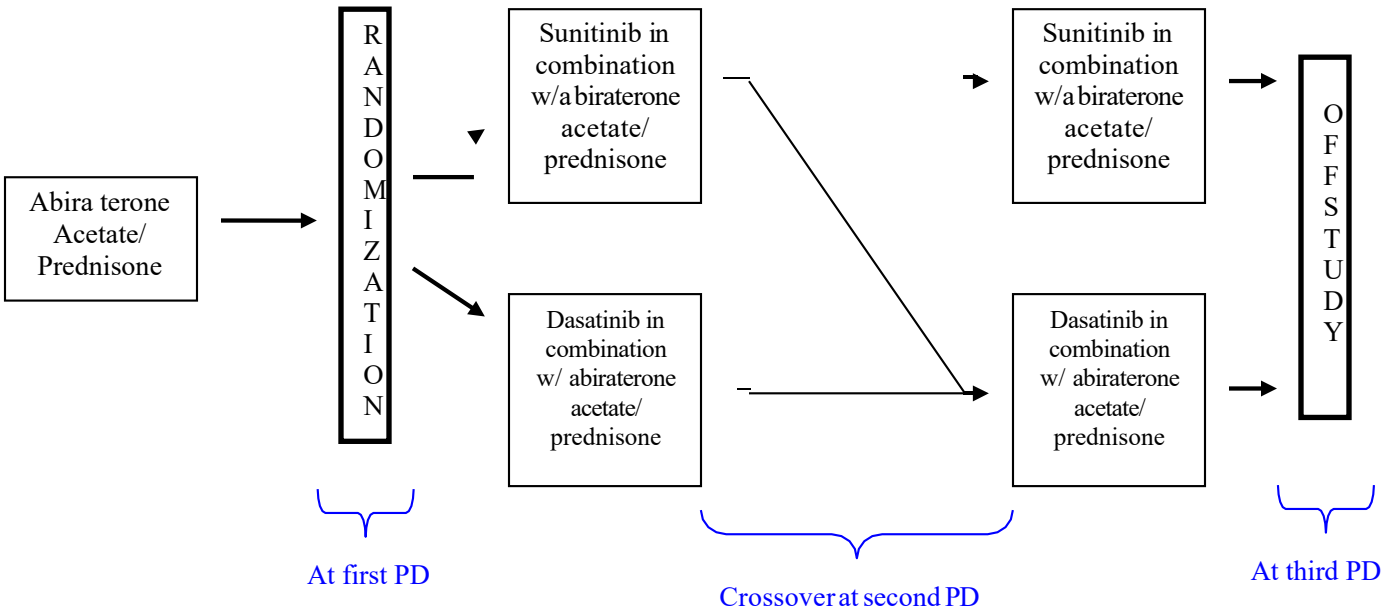
5.0 Treatment Plan

Patients found to be eligible based on the criteria above, will provide informed consent and begin treatment with abiraterone acetate at 1000 mg orally each day, given in combination with 5mg of prednisone orally twice daily.

If a patient demonstrates “progression” (as defined in Section 10.0) after treatment with abiraterone acetate in combination with prednisone, he will then be evaluated and randomized to receive either sunitinib at a dose of 37.5 mg orally daily for two weeks followed by a week of rest or dasatinib at a dose of 100 mg orally each day, both while continuing treatment with abiraterone acetate and prednisone. All patients will remain on treatment until “composite progression” is established or toxicity (see Section 10.1). After composite progression, patients will crossover to the alternate agent (a patient treated with sunitinib will cross over to treatment with dasatinib in combination with abiraterone and prednisone, while those randomized to dasatinib will crossover to treatment with sunitinib in combination with abiraterone and prednisone). A 4 week washout period is planned between targeted agents; and patients must have fully recovered from treatment related adverse events prior to starting the second targeted agent. Patients will be taken off study following the crossover based on the accepted criteria in the initial portion of study**.**

Abiraterone, dasatinib, and sunitinib will be provided free of charge by the manufacturer during trial participation.

Study Schema



5.1 Registration

All patients will be registered in the University of Texas M. D. Anderson Cancer Center Office of Research Administration database. Registration should occur following informed consent process and prior to initiation of investigational therapy. All eligibility criteria must be satisfied.

5.2 Study Drug Administration:

Abiraterone Acetate: Patients will be instructed to take 4 tablets (250 mg each) orally (PO) at least 1 hour before a meal or 2 hours after a meal. Treatment with abiraterone will continue throughout the duration of participation.

Prednisone: Patients will be instructed to take 5-mg oral prednisone, twice daily. Treatment with prednisone will continue throughout the duration of participation.

Patients will be randomized to receive either dasatinib or sunitinib after progression on single-agent abiraterone.

Dasatinib Starting Dose: Patients will be instructed to take 100 mg (2 tablets @ 50 mg each) of dasatinib orally once daily. Dasatinib is formulated in 20, 50 mg and 100mg tablets. Tablets should not be crushed or cut; they should be swallowed whole. Dasatinib can be taken with or without a meal. The dosing time may be adjusted as required. If doses are missed for toxicity, they should not be replaced. If a dose is not

taken due to an error, it may be taken up to 12 hours later. If vomiting occurs within 30 minutes of intake, that dose may be repeated.

Sunitinib Starting Dose: Patients will be instructed to take 37.5 mg (3 capsules at @ 12.5 mg each) of sunitinib orally once daily.

A total of 4 weeks (± 3 days) will constitute a course of therapy. A pill diary will be provided to each patient to document study drug compliance.

5.3 Laboratory Assessments and Imaging Studies:
Patients may have standard lab studies drawn by a local physician and results faxed to MDACC prior to their scheduled clinic visit. If a patient is unable to return for restaging scans due to symptoms of progressive disease, a patient may have scans done at a local physician. These scans should be sent to the PI for review.

5.4 Duration of therapy:

Patients will continue on each treatment arm until progression by PCWG2 criteria or persistent grade 3 toxicity after dose modification or patient withdraws consent**.**

5.5 Response to Therapy:

Clinical patient assessments will occur at four week intervals. Response to therapy will be determined by PCWG2 criteria with tumor evaluations taken as clinically indicated. Detailed information regarding response criteria is located in section 9.0.

5.6 Concomitant therapy:

5.6.1 Prohibited and/or Restricted Treatments
At each visit, all concomitant treatments, including blood and blood products, must be reported on the source documentation and on the Concomitant Medications page of the case report form. Concomitant medications must also be documented at the time of discontinuation and at the 30 day follow-up visit.

No other systemic therapy for treatment of prostate cancer is permitted while subject is on study. Concomitant palliative radiotherapy is not permitted for disease progression on treatment, but is allowed for pre-existing non-target lesions with approval from the Principal Investigator. Bisphosphonate treatment may not be initiated during study; if already begun, it may be continued at Investigator discretion.

Subjects requiring any prohibited therapy should not be enrolled. If enrolled, the prohibited agent(s) will be withdrawn prior to first dose of study drug.

5.6.1.1 Potent CYP3A4 Inhibitors

Dasatinib is primarily metabolized by the CYP3A4 enzyme. In drug-drug interaction studies, concomitant use of ketoconazole (a potent CYP3A4 inhibitor) produced an increase of > 5-fold in dasatinib exposure. Therefore, potent inhibitors of CYP3A4 are prohibited during study; for such medications, a wash-out period of ≥ 7 days is required prior to starting dasatinib. Subjects should be advised not to consume substantial quantities of grapefruit or pomegranate juice. (Less-potent inhibitors, inducers and substrates of CYP3A4 are restricted, see Section 5.6.2.1.) Most commonly-used potent CYP3A4 inhibitors are:

- itraconazole, ketoconazole, miconazole, voriconazole;
- amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir;
- ciprofloxacin, clarithromycin, diclofenac, doxycycline, enoxacin, imatinib, isoniazid, ketamine, nefazodone, nicardipine, propofol, quinidine, telithromycin.

5.6.1.2 Medications that prolong QT Interval

Subjects enrolled in this study may not take concomitant medications known to prolong the QT interval (Class I; see http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm). For such medications, a wash-out period of ≥ 7 days is required prior to starting dasatinib. Agents which possibly prolong the QT interval are restricted; see Section 5.6.2.3. Medications known to prolong the QT interval are:

- quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dofetilide;
- erythromycins, clarithromycin;
- chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide;
- cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine.

5.6.2 Other Restrictions and Precautions

The following restricted therapies are not recommended, but are permitted with caution when clearly medically indicated.

5.6.2.1 CYP3A4 Inducers, Inhibitors, Substrates

Drugs that induce CYP3A4 activity may decrease both dasatinib and exemestane plasma concentrations. In subjects in whom enzyme-inducing anticonvulsants (eg, phenytoin, carbamazepine, phenobarbital) are used, alternative agents with lesser enzyme-induction potential should be considered.

Dasatinib is predominantly metabolized by the CYP3A4 isoenzyme. Potent inhibitors are prohibited, but less-potent inhibitors may also increase exposure to dasatinib. If administration of a CYP3A4 inhibitor cannot be avoided in subjects receiving dasatinib, close monitoring for toxicity and dasatinib dose reduction should be considered. Subjects should be advised not to consume substantial quantities of grapefruit or pomegranate juice.

Other CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in subjects receiving dasatinib. Note: subjects treated with a fentanyl patch are eligible for this trial.

As warfarin is metabolized through the CYP450 system, therapeutic anticoagulation with warfarin (eg, Coumadin® or Cournadine®) is not recommended. As an alternative, therapeutic anticoagulation may be accomplished using low-molecular weight heparin (eg, Lovenox®) or heparin. Mini Dose Coumadin® (eg, 1 mg QD) is permitted for prophylaxis of central venous catheter thrombosis.

Please see a comprehensive list of CYP drugs at the following web address. http://www.medicine.iupui.edu/Flockhart/table.htm)

5.6.2.2 CYP2D6 and CYP1A2 inhibitor Inducers, Inhibitors, Substrates
Drugs metabolized through the CYP2D6 and CYP1A2 pathways should be used with caution while participating in this study. A list of these drugs can be found at the link provide above.

5.6.2.3 Medications that may Prolong QT Interval
Concomitant medications known to prolong the QT interval are prohibited (Section 5.6.1.2); medications which may possibly prolong the QT interval (non-Class I; see http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm) are restricted. Should the Investigator believe that beginning therapy with a potentially QT-prolonging medication (other than those prohibited) is vital to an individual subject's care, the Investigator must check that the prior on-therapy ECG does not show QTcF ≥ 450 msec or an increase in QTc ≥ 60 msec over the baseline value.

5.6.2.4 Antacids
Nonclinical data demonstrate that the solubility of dasatinib is pH dependent and a clinical study has shown that dasatinib exposure is substantially and durably reduced after treatment with famotidine. Administration of dasatinib with H2 inhibitors or proton pump inhibitors should therefore be avoided. If antacid therapy is needed, a locally-acting antacid may be used, and should be administered at least 2 hours before or after the dose of dasatinib.

5.6.2.5 St. John's Wort (Hypericum perforatum)
Data suggests that St. John's Wort may decrease dasatinib and exemestane plasma concentrations unpredictably. Subjects receiving dasatinib should not take St. John's Wort. Subjects should discontinue St. John's Wort at least 5 days before starting dasatinib.

5.6.2.6 Medications that Inhibit Platelet Function and Anticoagulants
Src-family kinase inhibition potentially reduces platelet aggregation. Caution should thus be exercised if subjects are required to take medications that inhibit platelet function or anticoagulants. Such medications include:aspirin or aspirin-containing combinations, clopidogrel, dipyridamole, tirofiban, dipyridamole, epoprostenol, eptifibatide, cilostazol, abciximab, ticlopidine, cilostazol warfarin, heparin/low molecular weight heparin [eg, danaparoid, dalteparin, tinzaparin, enoxaparin] exceptions are low-dose warfarin for prophylaxis to prevent catheter thrombosis and heparin for flushes of intravenous lines.

5.6.2.7 Bisphosphonates
Subjects who had been receiving bisphosphonates prior to study entry may continue on therapy with caution. Although concomitant use of bisphosphonates is not recommended, clinically-significant hypocalcemia has been uncommon. Oral serum calcium (Ca^{+2}) supplementation, including Vitamin D if appropriate, is warranted.

5.6.3 Supportive Care Guidance
Supportive care, especially pain control, will be optimized in all subjects. Guidance is provided for management of common side effects of dasatinib in order to maximize opportunity for benefit. Investigators are strongly urged to discuss with Medical Monitor prior to discontinuing study treatment for reasons other than radiographic PD.

Non-hematologic side effects are typically CTCAE v4.0 Grade 1 - 2. Interruption and/or dose reduction may be necessary, especially if Grade ≥ 2. Usual supportive care measures should be used for nausea/emesis, diarrhea, pain, fever or headache. Neither clinically significant myelosuppression nor use of hematopoietic growth factors is expected.

Osteoclast inhibition is expected; therefore, calcium supplementation (eg, calcium carbonate 500 mg PO TID) is warranted to maintain serum Ca^{+2} above LLN during dasatinib treatment. Vitamin D supplementation (eg, ergocalciferol 400 IU PO QD) may be appropriate for persistent hypocalcemia. Bisphosphonate therapy should be deferred in the presence of hypocalcemia.

Fluid retention, including clinically-significant pleural effusion, has been observed during dasatinib treatment. Refer to Section 3.3.4 for treatment recommendations.

5.7 Treatment and evaluation outside M.D. Anderson Cancer Center (MDACC):

Patients enrolled at MDACC may have their interim evaluations performed with their local oncologist according to the protocol after 2 cycles of initial treatment or treatment change. The patient will return to MDACC at 8 week intervals. A two month drug supply will be dispensed to patients ensuring adequate supply before their return visit to MDACC. The patient will be given a follow-up phone call by the research team approximately at 4 weeks between MD Anderson visits for safety

assessment. The M. D. Anderson Study Chair will provide the local oncologist with the protocol treatment plan, evaluation schedule and data collection requirements.

5.7.1 MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record

5.7.2 A letter to the local physician outlining the patient'sparticipation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix M)

5.7.3 Protocol required evaluations performed outside MDACC will be provided by the local physician to the MDACC investigator and will include drug administration records, progress notes, laboratory reports, diagnostic studies, and documentation of any hospitalizations. The outside evaluations will be reviewed by the investigator and the review will be documented in the patient record.

5.7.4 Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

5.7.5 A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.

5.7.6 The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.

5.7.7 Patients will return to MDACC every 8 weeks for evaluation.

6.0 Pre-treatment evaluation

6.1 Within 21 days of study entry: History and physical to include ECOG performance status, weight, height, and documentation of concurrent non-malignant disease and medical therapy. Any residual toxicity from prior therapies that is unresolved by date of study registration must be recorded, using the grading schema in NCI Common Toxicity Criteria v4.0.

Laboratory studies shall include a CBC w/differential, platelet count, PT, PTT, urinalysis, serum chemistries including albumin, alkaline phosphatase, ALT, AST, calcium, LDH, total bilirubin, BUN, creatinine, magnesium, phosphate, electrolytes (sodium, potassium, chloride, CO_2), PSA, Testosterone, and Prostatic Acid Phosphatase.

6.2 Within six weeks of study entry: Tumor assessment shall include a chest X-ray, ECG, ECHO or MUGA scan, bone scan, bone marrow biopsy and aspirate, and CT scans of the abdomen and pelvis. Appropriate additional studies should be obtained to fully define the extent and severity of existing or suspected malignant disease. Location, type, and size of representative measurable lesions must be recorded prior to treatment. At least one lesion representative of all involved organ sites must be recorded prior to treatment.

6.3 Use of archival pathology material may be requested of the patient, e.g. paraffin embedded block, unstained slides, etc. (Appendix 1).

7.0 Evaluation During Study

On-study tests/visits that must occur within a defined time frame will have a standing window of allowance that is equal to +/- 3 days. If necessary, imaging scans and/or laboratory testing may be completed at a local physician's office. The results must be received via fax or other medium prior to the scheduled clinic visit.

	Screening	Every 2 Weeks	Every 4 weeks[h]	PD/Treatment Change	End of Treatment[e]	Safety FU[f]	Long-Term FU
Medical History	x[a]						
Physical Exam	x[a]		x		x	x	
Vital Signs	x[a]		x		x	x	
Weight	x[a]		x		x		
Height	x[a]						
ECOG PS	x[a]		x		x	x	
CBC/ diff. and plt.	x[a]		x		x	x	
Serum Chemistry[c]	x[a]	x[g]	x	x[g]	x	x	
PT/PTT	x[a]			x			
PSA	x[a]		x		x		
Testosterone	x[a]						
Prostatic Acid Phosphatase	x[a]		x		x		
Urinalysis	x[a]						
Bone Marrow Asp/Bx or Bx of metastatic site	x[b]			x	x		
CT Scan Abd/Pelvis	x[b]			x[d]			
Chest X-ray	x[b]			x[d]			
MUGA or ECHO	x[b]			x			
ECG	x[b]			x			
Bone Scan	x[b]			x[d]			
Monitor Adverse Events	<.....>						
Concomitant Medications	<.....>						
Blood for Correlative Studies	x		x	x	x		

Archived Tissue for Correlative Studies	x						
Survival Follow Up							x[i]

a. Within 21 days of registration
b. Within 6 weeks of registration
c. Serum chemistries including albumin, alkaline phosphatase, ALT, AST, calcium, LDH, total bilirubin, BUN, creatinine, magnesium, phosphate, electrolytes (sodium, potassium, chloride, CO2).
d. May be at other timepoints as clincally indicated. Will not have to be repeated if done within 8 weeks of treatment change
e. Off study visit will occur after final PD or early removal from the study.
f . To be completed 30 days after the last dose of study drug
g. Patients will have liver function tests (including alkaline phosphatase, AST, ALT, total bilirubin, and LDH every 2 weeks f or the first 3 cycles of abiraterone, and every 2 weeks for the first 3 cycles of each combination arm.
h. Follow up visits may be rescheduled for every 8 weeks at the discretion of the treating physician.
i. Every 6 months after Safety Follow Up (+/- 1 month)

8.0 Criteria for Toxicity and Dose Modification:

8.1 Intrapatient dose reduction will be permitted once a patient has experienced unexpected toxicity provided the criteria for patient withdrawal from study treatment have not been met. All intrapatient dose reductions are relative to the lowest dose of the current cycle. Dose modifications may involve sunitinib in a single decrement of 12.5 mg to a minimum of 25 mg. Table 1 describes the recommended dose modifications for study treatment-related toxicities.

Table 1. Dose Modifications for sunitinib associated toxicity

Toxicity	Gra de 1	Gra de 2	Gra de 3	Gra de 4
Non-hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤1 or has returned to baseline, then resume treatment at the same dose level, or reduce the dose by 1 level at the discretion of the investiga tor.*	discontinue thera py
Hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤2 or has returned to baseline, then resume treatment at the same dose level.**	Withhold dose until toxicity is grade ≤2, then reduce the dose by 1 level and resume treatment.**

* Patients who develop grade 3 hyperlipasemia or hyperamylasemia without clinical or other evidence of pancreatitis, grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting, or diarrhea must persist at grade 3 despite maximal medical therapy.
** Patients with recurrent gra de 3 neutropenia or thrombocytopenia for >7 days will dose reduce in the next cycle. Patients who develop grade 3 or grade 4 lymphopenia may continue study treatment without interruption.

Dose Re-Escalation

Doses reduced from the 37.5-mg/d level for drug-related toxicity should generally not be re-escalated. However, intrapatient re-escalation back to the previous dose level may be permitted provided the toxicity responsible for dose reduction has not recurred at a grade 2 for at least 30 days, and with the agreement of the principal investigator of the study.

Overdose Instructions

In the event of an overdose, the supporting drug company should be contacted to discuss the details of the overdose and formulate a clinical management plan. However, this contact will not delay patient care under any circumstance.

8.2 Dasatinib

8.2.1 If patients taking dasatinib present with recurring dyspnea and fatigue after an initial dose interruption, with no explanation or evident underlying cause, the diagnosis of pulmonary arterial hypertension (PAH) should be considered. If PAH is confirmed, dasatinib should be permanently discontinued and patients will be followed per standard practice guidelines.

Dose Levels:
Dose level 0 (100mg daily)
Dose level -1 (70mg daily)
Dose level -2 (50mg daily)

Dose Modification Schema for Hematological Toxicity

Grade 1	ANC < LLN - 1500/mm^3	None
	Platelets < LLN - 75,000/mm^3	
Grade 2	ANC < 1500 - 1000/mm^3	None
	Platelets < 75,000 - 50,000/mm^3	
Grade 3	ANC < 1000 - 500/mm^3	Hold therapy, resume at 100mg after recovery to ≤ Gr 1. If recurrence at

	Platelets < 50,000 - 25,000/mm^3	100 mg, hold therapy and resume at 70mg after recovery to ≤ Gr 1.If recurrence at 70mg reduce dasatinib dose to 50mg. If recurrence at 50mg discontinue treatment due to intolerance.
Grade 4	ANC < 500/mm^3	Withhold dasatinib until recovery to ≤ G1. Reduce dose to 70mg. If recurrence at 70mg , reduce dose to 50mg. If recurrence at 50mg, discontinue treatment due to intolerance.
	Platelets < 25,000/mm^3	

- Subjects who develop Grade 4 hematologic toxicity and are receiving dasatinib at 70 mg QD should have therapy withheld until recovery to Grade 0 – 1. Decrease dasatinib to 50mg Daily.

- Treatment should be withheld and counts rechecked in one week. If hematological toxicity persists for > 14 days, patient is to be removed from study.

Non-hematological Toxicity

Toxicity	Drug Modification
Grade 2	Withhold dasatinib until recovery to Grade ≤ 1 or baseline, with the exception of toxicities which are non life-threatening and for which resolution to Grade 1 may not occur and/or may require > 21 days, such as alopecia, nail changes, weight changes, and peripheral neuropathy (unless it is persistent and/or repeating) Resume dosing without dose reduction
Grade 3	Withhold dasatinib until recovery to Grade ≤ 1 or baseline If the identical toxicity recurs at Grade 3, withhold dasatinib until recovery to Grade ≤ 1 or baseline Decrease dasatinib to 70 mg QD starting with the next dose
Grade 4	Discontinue treatment with dasatinib

Discontinue Treatment with Dasatinib for any delay in scheduled therapy of 2 weeks or more secondary to any form of toxicity

8.3 Abiraterone Acetate

Dose-Reduction Procedure for Adverse Event Management
In the event where dose-reduction is used for AE management, 2 dose reductions are allowed. At each dose reduction, one tablet of abiraterone will be removed, e.g., 4→3 tablets, and 3→2 tablets. Any return to protocol dose level after dose reduction must follow documentation of AE resolution and a discussion with the Principal Investigator.

Patients experiencing any Grade 4 non-hematological toxicity will be withdrawn from the study.

8.4 Clinical Vigilance During Combination Treatment

No formal phase I trial has been conducted for the proposed two-drug combinations to be used in this study. Although we do not expect severe toxicity with the proposed combinations, we will assure patient safety through clinical vigilance during the combination phase. The assigned research nurse and the Principal Investigator will review all study patients at weekly intervals during the combination treatment portion of the trial. Any

unusual clinical observations will be discussed immediately with the Principal Investigator or a sub-investigator if the PI is absent or not available. All patients will be treated at M.D. Anderson Cancer Center and will be provided with their treating physicians and research nurse contact information.

Any Grade 4 toxicity will be communicated directly with the sponsors (in the combination phase or in a single arm phase) by the study team.

Toxicities attributed to the treatment will be reported as described in Section 13.

9.0 Criteria For Response and Progression (RECIST v1.1)

9.1 Tumor Measurements:

9.1.1 A measurable lesion can be accurately measured in at least one dimension (longest diameter to be recorded). The minimum measurable lesion size on CT should be 1.5 cm (15 mm). All superficial disease (e.g. palpable lymph nodes) is considered measurable. All measurable lesions up to a maximum of 5 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 repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum LONGEST DIAMETER (LD). The baseline sum of the LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

9.1.2 Sites of disease detected by bone scan will be recorded. Note will be made of changes in number of lesions seen on subsequent studies.

9.1.3 Serum PSA will be also used as a basis for assessing response and will be reported alongwith measurable disease outcomes.

9.1.4 Measurable disease will be evaluated and recorded by the attending physician and the radiologist. The Principal Investigator will be the final arbiter for any discrepancies. The oncology research nurse may assist with the documentation under the supervision of the Principal Investigator.

9.1.5 An estimate of disease status will be made and recorded on clinic notes at each visit as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

9.2 Response Definitions (per PCWG2 guidelines [40]):

9.2.1 Complete Response (CR): Disappearance of target lesions.

9.2.2 Partial Response (PR): PSA: Decline of PSA by ≥ 50% without normalization maintained for 6 weeks will be reported as a PSA-response. Patients with measurable disease must demonstrate 30% decrease in the sum of the longest diameter (LD) of target lesions on the restaging study, taking as reference the baseline sum LD. No evaluable lesion may increase in size and no new lesion may appear.

9.2.3 Stable Disease (SD): Neither PR or CR and in the absence of progression as defined below.

9.2.4 Progressive Disease (PD): Any increase of 20% in the sum LD of target lesions taking as reference the smallest sum LD recorded since treatment began; or the appearance of an unequivocally new lesion on pre-operative restaging studies or on post-operative surveillance studies. Worsening symptoms clearly attributable to disease progression qualifies as progression e.g. worsening malignant bony pain. There are no biochemical definitions of progressive disease for this study.

9.2.5 PSA criteria for failure to further respond: A failure to further decline or a rise in serum PSA concentration measured at four week intervals: A change in either will be considered a 5 ng/ml or 25% change nadir measurement.

9.2.6 Progression-free survival (PFS) and overall survival (OS): The time from randomization to disease progression or death (if earlier than progression) will be referred to as progression-free survival. The time from randomization to death from any cause will be annotated as well. Patients will be followed for PFS and OS, and will consist of phone call, an e-mail, or a review of medical and/or other records every 6 months (+/- 1 month).

10.0 Criteria for Initial Randomization/Crossover/Discontinuation/Removal

10.1 Criteria for Initial Randomization: Patients will be randomized after treatment on abiraterone acetate in combination with prednisone until composite progression is established as defined by one of the following criteria:

1) PCWG2 criteria for progression(see Appendix L)

OR

2) Failure to achieve PCWG2 response by 8 weeks

OR

Plateau of PSA as only manifestation of "progression"(Failure to further suppress PSA measured at 4 week intervals) - For PSA, less than 25% decrease from previous PSA for 2 consecutive measurements. For PSA less than 5ng/ml, a single measurement above 1ng/ml following nadir is sufficient.

If patients require dose reduction on two consecutive times or suffer from grade 3 or greater toxicity despite maximal dose reduction, the patient will be taken off the study and will be counted as exhibiting progression.

10.2 Criteria for Crossover: The criteria for crossover are progression by PCWG2 criteria or excess toxicity as defined in criteria for initial randomization

10.3 Criteria for Discontinuation of Therapy: Discontinuation of therapy will either occur for progression or excessive toxicity. Progression criteria will include composite criteria which includes PSA working group to criteria, patients withdrawal from the study due to failure.

10.4 Criteria for removal from study: (a) Patient withdrawal of consent, progressive disease, or investigator/PI discretion for safety concerns; (b) Non-compliance by patient with protocol requirements; (c) The development of unacceptable toxicity as defined in Section 8.0 or serious inter-current events.

11.0 Statistical Considerations

11.1 Preliminaries and Background: This is a randomized clinical trial to evaluate and compare two two-stage treatment strategies for patients with castrate resistant prostate cancer that has progressed despite treatment with Abiraterone. The design is motivated by the presence of multiple pathways that facilitate survival of the tumor cells. The factors motivating the design include (1) the redundancy of these pathways for paracrine tumor survival, (2) the substantial variability between patients with regard to the likelihood and duration of response to any particular agent (3) the desire to obtain unbiased comparisons of clinical effects among three qualitatively different agents, (4) the desire to account for the common and appropriate clinical practice, when treating an individual patient, of switching away from an agent at the time of its clinical treatment failure and replacing it with a different agent and (5) the desire to account for effects of baseline patient covariates characterizing pathway activity levels.

11.2 Treatment Regimes: Each patient's treatment regime will consist of up to three stages, indexed by s = 1, 2, 3. In stage s=1, all patients will receive the CYP17 blocker Abiraterone acetate (A) alone. At the time of disease progression (defined below, in 11.3) with A alone, the patient will be randomized between A + Dasatinib (D) or A + Sunitinib (S) for their stage s=2 treatment. The randomization will be dynamically balanced on three binary patient covariates using the method of Pocock and Simon [41]. The covariates are (i) quality if response to Abiraterone, defined as time to progression

being either > 3 months or ≤ 3 months, (ii) alkaline phosphatase either > 120 or ≤ 120, and (iii) performance status either 0, 1 or > 1. At the time of disease progression with the assigned treatment in stage s=2, the patient will be crossed over to the other stage 2 treatment combination for treatment in stage s=3. Consequently, two three-stage treatment regimes are possible, either (A, A+D, A+S) or (A, A+S, A+D). For brevity, since A is given in all three stages, below these two two-stage regimes will be denoted by (D, S) and (S, D).

This randomization will be carried out using the Pocock-Simon software on the MDACC Biostatistics website ***https://biostatistics.mdanderson.org/ClinicalTrialConduct***.

11.3 Outcomes: For the purpose of treatment evaluation, in each of the three stages of treatment, the following events are defined: Composite disease progression is defined in Section 10.1. In any stage, treatment failure is defined as disease progression or death, whichever occurs first. The time to treatment failure in each stage is denoted by TTF. From the start of therapy, overall survival (OS) time is defined as the time to death

.

11.4 Primary Outcome: Comparison of the two strategies (D, S) and (S, D) will be done in terms of the subgroup of patients for whom the first failure with A is disease progression. For this purpose, the time to the final treatment failure will be recorded from the time of randomization, which is carried out at the start of stage 2. The primary outcome will be U = the time to final treatment failure starting from the time that treatment is initiated in stage 2 (randomization) after the patient's disease has progressed on Abiraterone alone in stage 1. Consequently, aside from censoring, since only patients who progress but do not die in stage 2 proceed to stage 3, U equals either (i) the time to death in stage 2, or (ii) the time to progression in stage 2 plus the time to death or progression in stage 3.

11.5 Group Sequential Design: Based on historical experience, the null values of the mean time to failure in each of stages 2 and 3 are both 4 months and the probability that the failure in stage 2 is a progression and not a death is .90. These give null value 7.6 months for the mean of U = time to final failure, as defined. The primary goal will be to test the null hypothesis that there is no difference between the two strategies in terms of these two means. A two-sided group-sequential log rank testing procedure will be used [41], with one interim test and possibly a second, final test, having overall size .05 and power .90 to detect a 75% increase in the mean from 7.6 to 13.3 months. O'Brien-Fleming boundaries will be used, with the null hypothesis of no treatment difference rejected if the absolute value of the observed Z-score computed from the log rank statistic, $|Z_{obs}|$, is larger than the Z-score test cut-off in the following table.

	Number of Failure Events when the tests are conducted	Z-score cut-offs for concluding there is a difference
Test 1	68	+/- 2.9626
Test 2	136	+/- 1.9686

Based on an assumed accrual rate of 7 patients per month, and assuming that approximately 90% of all patients progress with A and thus 6 patients per month are randomized between A+D and A+S in stage 2, the expected trial duration will be 35 months with total expected accrual (1.1)x153 = 168 patients under the alternative and (1.1)x 164 = 180 patients under the null. All computations were carried out using East version 5 (Cytel Corporation), [42].

11.6 Safety Monitoring: For the purpose of safety monitoring, toxicity will be defined as grade 2 or higher cardiac toxicity or grade 3 or higher hepatotoxicity, that is possibly attributed to the agents, occurring at any time within the first 3 months from the start of treatment. Denote the probability of this event by p_{TOX}. Based on clinical experience and judgment, a toxicity rate of 0.05 will be considered acceptably low while a toxicity rate of 0.16 or higher will be considered unacceptably high. Assuming that p_{TOX} follows a non-informative beta(.05, .95) prior, the trial will be terminated early if the following Bayesian criterion for excessive toxicity is met, with the criterion applied starting when 20 patients have been accrued and their toxicity evaluated at 3 months, and at every 20th patient thereafter, up to a maximum of 180 patients. The trial will be stopped early if $Prob(p_{TOX} > 0.05 \mid data) > 0.98$. This translates to stopping the trial if [number of patients with toxicity]/ [number of patients evaluated for toxicity] is greater than or equal to 4/20, 6/40, 8/60, 10/80, 11/100, 13/120, 14/140, or 15/160. If the true value of p_{TOX} is 0.16 then the probability that this rule will stop the trial early is > .99 and the sample size quartiles are all 180. If the true value of p_{TOX} is 0.05 then the probability that this rule stops the trial early is .04 and the sample size quartiles are 20, 40, 60. Consequently, if the true value of p_{TOX} is .05 the nominal power figure .90 of the group sequential test will be reduced to .90 x (1- .04) = .86 due to the possibility of a false negative stop by the toxicity monitoring rule.

As an additional precaution, in the first three patients of the combination study (post initial randomization), if grade III or higher toxicity is observed, that is possibly attributed to the agents, the combination will be held. If two or more grade III toxicities possibly attributed to the drugs are observed in the first six patients, the arm will be held until further assessment. The overall trial will continue with patients on the alternative arm.

11.7 Detailed Notation for Patient Outcomes:

11.7.1 Death

A patient's treatment is continued from stage 1 to stage 2, or from stage 2 to stage 3, if progression occurs. Denote the TTF in stage 1 by T_1, the time from progression at T_1 to second treatment failure by T_2, and the time from progression at T_2 to third treatment failure by T_3. Thus, the total time to first, second and third treatment failure are T_1, $T_1 + T_2$, and $T_1 + T_2 + T_3$, respectively. Since a patient's therapy may end at any time due to Death, denote the indicator that T_s is the time of disease progression rather than a death time by Y_s, for s=1, 2, 3. In particular, (Y_2 , T_2 , Y_3, T_3) are defined only if $Y_1 = 1$ and (Y_3, T_3) are defined only if $Y_2 = Y_1 = 1$. Denote the time in stage s=1 to treatment failure or death by T_1^o, so that $T_1^o = T_1$ if $Y_1 = 1$ or T_1^o is the time of death if $Y_1 = 0$ at stage s=1. Similarly, the time from T_1 to second treatment failure is T_2^o, with $T_2^o = T_2$ if $Y_2 = 1$ or T_2^o the time of death if $Y_2 = 0$ at stage s=2. Finally, the time from T_2 to treatment failure is T_3^o, with $T_3^o = T_3$ if $Y_3 = 1$ or T_3^o the time of death if $Y_3 = 0$ at stage s=3.

11.7.2 **Overall final failure time:** The time to final failure from the start of therapy with A is $T = T_1 + Y_1(T_2 + Y_2T_3) = T_1 + Y_1T_2 + Y_1Y_2T_3$. Thus, the overall final failure time from the start of therapy equals:

- T_1 if $Y_1=0$, which is death on A in stage 1 before randomization between A+S and A+D in stage s=2,
- $T_1 + T_2$ if $Y_1=1$ and $Y_2 = 0$, which is progression with A followed by randomization between A+S and A+D followed by death before crossover or
- $T_1 + T_2 + T_3$ if $Y_1= Y_2=1$, which is progression with A followed by randomization between A+S and A+D followed by progression with the stage 2 treatment combination followed by crossover followed by a failure of any type in stage 3. The 4 weeks washout period between stage 2 and 3 (see section 5.0) will be included in TTF.

11.7.3 **Response:** For evaluating the effects of A in stage 1, response will be defined as non-increasing PSA as measured at 8 weeks compared to baseline.

11. 8 **Failure times following randomization between A+S and A+D:** For comparing the two strategies (D, S) and (S, D), we will consider the subgroup of patients for whom the first failure with A is disease progression ($Y_1=1$) and start at the time of randomization, which is the start of stage 2. In this subgroup, we will use as primary outcome variable the time from randomization to final failure defined as $U = T_2 + Y_2T_3$. Thus, $U = T_2$ if $Y_2 = 0$, which is Death before crossover, and $U = T_2 + T_3$ if $Y_2=1$, which is progression with the stage 2 treatment combination followed by crossover followed by a failure (P or Death) in stage 3. An essential point regarding evaluation of U is that U may be censored by the non-failure events C in either stage 2 or stage 3

11.81 **Parameters**. Denote $\mu s = E(Ts)$ for s=1,2,3 and $\pi s = Pr(Ys=1)$ for s = 1,2. The mean overall final failure time is $\mu T = E\{T\} = E\{T_1 + Y_1(T_2 + Y_2 T_3)\} = E\{T_1\} + Pr(Y_1 = 1)E\{T_2 + Pr(Y_2=1) E(T_3)\} = \mu_1 + \pi_1 \mu_2 + \pi_1 \pi_2 \mu_3$. The mean final failure time from randomization is $E(U) = \mu_U = E(T_2 + Y_2 T_3) = \mu_2 + \pi_2 \mu_3$.

11.8.2 **Parameter of Primary Interest.** The parameter of primary interest for evaluation and comparison of the two strategies (D,S) and (S,D) is $E(U) = \mu_U = \mu_2 + \pi_2 \mu_3$., the mean time from randomization to final failure in either stage 2 or stage 3.

11.8.3 **Parameter of Secondary Interest.** The parameter of secondary interest for evaluation and comparison of the two strategies (D,S) and (S,D) is $E(T_2) = \mu_2$, the mean time from randomization to first failure in stage 2.

11.9 **Data Analyses:** The distributions of Y_1, Y_2 and Y_3 will be estimated using logistic regression. The unadjusted distributions of T_1, T_2 and T_3 and of the composite times $T = T_1 + Y_1(T_2 + Y_2 T_3)$ and $U = T_2 + Y_2 T_3$ will be estimated using Kaplan-Meier (KM) plots [43]. For each time, an appropriate time-to-event regression model determined by goodness-of-fit analyses will be fit to account for treatment strategies and patient covariates [44]. Denote the stage 2 and stage 3 treatments by τ_2 and τ_3, each equal to either D = Dasatinib or S = Sunitinib. Thus, (τ_2, τ_3) = (D,S) or (S,D). To account for the effects of the stage 2 treatment, τ_2, on Y_2 and T_2, the linear terms of the logistic model for $Pr(Y_2 = 1)$ and of the event-time regression model for T_2 will be of the general form $\beta_2 Z_2 + \gamma_2 I(\tau_2 = D)$, where $\beta_2 Z_2$ denotes a linear combination of patient covariates and γ_2 is the D-versus-S effect on the stage 2 outcome. Similarly, to account for the effects of the treatment pair (τ_2, τ_3) given at stages 2 and 3 on the stage 3 outcome, the linear terms of the logistic model for $Pr(Y_3 = 1)$ and of the event-time regression model for T_3 will be of the general form $\beta_3 Z_3 + \gamma_3 I(\tau_2 = D, \tau_3 = S)$, where $\beta_3 Z_3$ is a linear combination of patient covariates and γ_3 is the (D,S)-versus-(S,D) effect on the stage 3 outcome. The covariate vectors Z_2 and Z_3 are indexed by stage to allow updated values, and this includes the possibility that T_2 or possibly $\log(T_2)$ will be used as a covariate in Z_3. Thus, there are two treatment effects, the D-versus-S between-treatment effect γ_2 on the stage 2 outcomes and the (D,S)-versus-(S,D) between-strategy effect γ_3 on the stage 3 outcomes. These estimates will be used, in turn, to estimate the mean of the primary outcome, the time to overall failure, specifically the mean of $U = T_2 + Y_2 T_3$, for each of the two strategies (D,S) and (S,D).

12.0 Data and Protocol Management

12.1 Protocol Compliance: All required interim and pretreatment data should be available and the physician must have made a designation as to toxicity grade and performance status as defined by structured clinical notes. If dose modifications or treatment interruptions are necessary, the reasons including grade and type of toxicity must be documented. When relevant, the reasons for removal from study must be documented. If treatment

related toxicity accompanies progression events then these must be documented (type and grade) by the specified criteria.

The Investigator will follow the MDACC policy for protocol deviations and violations. Documentation or a report of these events will be available for all monitoring visits. The Principal Investigator will be the final arbiter of these events and the continuation of a patient on study.

12.2 Data Entry: All data will be entered to the Department of Genitourinary Medical Oncology Oracle database (GURU). GURU is a password protected database with an audit trail. Data can be collated with a unique GURU identification in order to de-link information. The minimum required fields will be entered to the MDACC required data collection systems (CORe/PDMS). Data will be derived from the patient chart and the Principal Investigator will be the final arbiter of any conflicting entries. The Principal Investigator will be the final arbiter of response, toxicity, or progression should a difference of opinion exist.

Patient Confidentiality: In order to maintain patient privacy, all database generated case report forms, study drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations (21CFR312.63, 21CFR312.68).

12.3 Study Drug Management

Returned or expired study drug will be destroyed on site per MDACC Investigational Pharmacy policies.

12.4 Data Safety Monitoring

An independent data safety monitoring committee, comprised of Richard Theriault, DO (medical oncologist) and Xuemei Wang, MS (biostatistician) will be utilized to monitor safety. Toxicity will be monitored after 20 patients have been enrolled and every 20 patients thereafter in order to apply the above listed stopping rules. Enrollment will continue during these safety analyses.

13.0 Reporting Requirements

13.1 Adverse Drug Reaction Reporting

Toxicity will be scored using CTC Version 4.0 for toxicity and adverse event reporting. A copy of the CTC Version 4.0 can be downloaded from the CTEP homepage (**http://ctep.info.nih.gov**). All appropriate treatment areas have access to a copy of the CTC Version 4.0.

Adverse events will for this protocol will be documented and entered into the case report form according the Recommended Adverse event Recording Guidelines for Phase II protocol.

Recommended Adverse Event Recording Guidelines					
Attribution	Gra de 1	Gra de 2	Gra de 3	Gra de 4	Gra de 5
Unrelated	Pha se I	Pha se I	Pha se I Phase II	Pha se I Phase II Phase III	Pha se I Phase II Phase III
Unlikely	Pha se I	Pha se I	Pha se I Phase II	Pha se I Phase II Phase III	Pha se I Phase II Phase III
Possible	Pha se I Pha se II	Pha se I Phase II Phase III	Pha se I Phase II Phase III	Pha se I Phase II Phase III	Pha se I Phase II Phase III
Probable	Pha se I Pha se II	Pha se I Phase II Phase III	Pha se I Phase II Phase III	Pha se I Phase II Phase III	Pha se I Phase II Phase III
Definitive	Pha se I Pha se II	Pha se I Phase II Phase III	Pha se I Phase II Phase III	Pha se I Phase II Phase III	Pha se I Phase II Phase III

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

13.2 Serious Adverse Event Reporting (SAE)

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

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience 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 drugabuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

13.3 Investigator Communication with Supporting Companies:

Toxicities are to be assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), Version 4.0.

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. Collection of all SAEs must continue for 30 days after the last administration of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should notify the supporting companies of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

All SAEs, whether considered related or unrelated to dasatinib, must be reported to BMS (by the investigator or designee) within 24 hours of study personnel becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

All non-serious adverse events must be reported to Janssen Scientific Affairs, LLC on a quarterly basis. The summary of non-serious AEs should include a listing of: Patient ID, AE term (uncoded), severity, relationship to abiraterone acetate, and action taken with abiraterone acetate.

Additionally, all SAEs, whether considered related or unrelated to abiraterone acetate, must be reported to Janssen Scientific Affairs, LLC (by the investigator or designee) within 24 hours of study personnel becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

All SAEs should be faxed or emailed to the following supporting companies:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

Janssen Scientific Affairs, LLC
Fax #: 1-866-451-0371

Pfizer, Inc
Fax #: 1-866-997-8322

If the investigator believes that an SAE is not related to the investigational product but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the potential relationship should be specified in the narrative section of the SAE report.

If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent within 24 hours to the supporting companies. As follow-up information becomes available it should be sent within 24 hours using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

13.4 Abnormal Laboratory Results

The criteria for determining whether an abnormal laboratory test result should be reported as an adverse event are as follows:

1. Test result is associated with accompanying symptoms, and/or
2. Test result requires additional diagnostic testing or medical/surgical intervention (merely repeating an abnormal test, in the absence of any of the above conditions, does not meet criteria for reporting and an AE), and/or
3. Test result leads to a change in study dosing or death from the study, significant additional concomitant drug treatment or other therapy, and/or
4. Test result leads to any of the outcomes included in the definition of a serious adverse event, and/or
5. Test result is considered to be an adverse event by the investigator or sponsor

Any abnormal test result that is determined to be an error does not require reporting as an adverse event, even if it did meet one of the above conditions except for condition #4. Clinically significant laboratory results must be recorded in the patient's CRF

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Appendix 1 – Tissue Collection for Correlative Studies

Assay / Matrix	**Medium**	**Frequency**	**Required Storage**
Serum Biomarkers (Bone markers, Cytokines and Caveolin-1)	Serum (~20ml) Total required volume 2 X 10ml SST Vacutainers	Screening/baseline, every 4 weeks on study, randomization, crossover and end of treatment	Samples are aliquoted into 500 ul fractions, frozen and stored at -80 °C until analysis.
Whole Blood	Whole blood (1 X 10ml) Heparin Vacutainer	Screening/baseline, every 4 weeks on study randomization, crossover and end of treatment	Samples are frozen and stored at -80 °C until analysis
Tumor Tissue	Bone marrow biopsy collected in formalin and sodium heparin. Aspirate (1 x4 ml) Sodium Heparin Vacutainer Biopsy Tissue	Pretreatment, Prior to randomization, Prior to crossover and at progression of disease (4 total)	Fresh frozen or Paraffin embedded (biopsy) Samples are aliquoted into 500 ul fractions, frozen and stored at -80 °C until analysis. (Aspiration) Fresh frozen or Paraffin
Archived Diagnostic Tissue	Bone marrow or tissue	At the time of any routine test or procedure (not related to this study)	Fresh frozen or Paraffin
Plasma and circulating cells	Sodium Citrate CPT (2 X 8 mL)Vacutainers	Screening/baseline, every 4 weeks on study randomization, crossover and end of treatment	Samples are aliquoted into 500 ul fractions, frozen and stored at -80 °C until analysis. PBMCs are stored at LN_2 until analysis.

Circulating Tumor Cells (see Appendix K)	Streck Cell-Free DNA BCT (1 x 10mL)	CTC at baseline, at 8 weeks, at time of first randomization, and at cross-over	Specimens to be shipped ambient, on the same day as collection to Kuhn Laboratory USC. (see Appendix K)

*Specimens will be sent to Kuhn Laboratory USC for analysis

All left over samples will be stored and banked for future use, including genetic testing, in the GU Biorepository (blood and bone marrow) and the Prostate Tissue Bank (tissue).