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A Phase II Study of Dovitinib (TKI258) Combined with Abiraterone Acetate in Patients with Metastatic Castrate-Resistant Prostate Cancer Evaluating Markers of FGF and AR Signaling in Bone Marrow and Plasma

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1 Background

1.1 Overview of Metastatic Castrate-Resistant Prostate Cancer (mCRPC) and Current Treatment Options

Standard front-line androgen deprivation therapy (ADT) with medical castration (e.g. with LHRH agonists) initially induces a remission in 80% to 90% of patients with advanced prostate cancer. After progression on medical castration, patients can typically be "re-induced" into remission with conventional second-line hormonal ablative therapies including non-steroidal anti-androgens (e.g. bicalutamide), ketoconazole, and DES. The successful application of serial androgen-ablative therapies results in a median progression-free survival of 12 to 33 months, at which time a castrate-resistant phenotype dominates. Prostate cancer preferentially metastasizes to the skeleton, where it elicits an osteoblastic reaction that can produce significant pain, constitutional symptoms, anemia, and death. Until recently, after exhaustion of standard androgen-ablative therapies, patients with metastatic castrate-resistant prostate cancer (mCRPC) had few options besides cytotoxic chemotherapy. Unfortunately, however, chemotherapy results in only a modest survival benefit and is associated with significant toxicities.

Efforts to advance therapy options beyond chemotherapy have been met with little success until recently, when insights about basic prostate cancer biology encouraged rational integration of novel "targeted" agents that inhibit critical growth-promoting pathways involved in the development of castrate-resistant disease. Three principal insights have emerged from translational research:

1) During the evolution of castrate-resistant disease, there is a shift in androgen biosynthesis from endocrine (testes and adrenal glands) to paracrine/autocrine sources within the tumor-bone microenvironment. Intratumoral production of androgens (in addition to endocrine) is potently inhibited by novel CYP17 inhibitors such as abiraterone acetate.
2) Androgen receptor (AR)-independent, "stromal-epithelial" growth signaling pathways involved in normal prostate gland development frequently become dysregulated during the evolution of castrate-resistant disease. Examples of such pathways include c-Met, NOTCH, and Fibroblast Growth Factor (FGF) signaling. These pathways have presented novel targets for small molecule therapeutics.
3) The relatively modest effectiveness of agents that block stromal-epithelial interacting pathways suggests that persistent intratumoral androgen signaling is the dominant survival pathway driving castrate-resistant growth in bone. This line of reasoning has led to the hypothesis that efficient inhibition of intratumoral androgen signaling will be a critical aspect of rational combinatorial strategies with small molecule therapeutics that target stromal-epithelial interacting pathways.

Abiraterone acetate was recently FDA-approved for the treatment of patients with mCRPC who have previously received docetaxel after it was shown to prolong overall survival in a randomized phase III study. After a median follow-up of 12.8 months, overall survival was longer in the abiraterone acetate –prednisone group than in the placebo–prednisone group

(14.8 months vs. 10.9 months; hazard ratio, 0.65; 95% confidence interval, 0.54 to 0.77; P<0.001). Despite these encouraging results, up to one third of patients do not appear to respond to abiraterone acetate and the remaining 70% who do will eventually progress. Molecular-pathologic analysis of tumor-infiltrated bone marrow biopsies revealed that homogeneous, intense nuclear expression of AR, combined with CYP17 expression in ≥10% of tumor epithelial cells , was correlated with longer time to treatment discontinuation (≥4 months). Taken together, these findings suggest that androgen receptor (AR)-independent growth pathways promote castrate-resistant growth.

We, and others, have postulated that FGF/FGFR signaling is a critical AR-independent pathway that contributes to castrate-resistant growth. In support of this, preliminary data from a phase II study conducted at our institution show that dovitinib demonstrates significant clinical activity in ~25% of patients with mCRPC. The purpose of the present study is to explore the hypothesis that combining abiraterone acetate and dovitinib represents a rationale "co-targeting" strategy to inhibit AR-dependent and AR-independent pathways concurrently as therapy.

1.2 Overview of Dovitinib

Dovitinib is an inhibitor of RTKs: FGFR, VEGFR, PDGFRβ, CSF 1R, c-Kit, RET, TrkA, and FLT3 that mediate tumor cell proliferation and survival.

RTKs are involved in the growth of different types of tumors as well as in the initiation, growth, and maintenance of blood vessels supplying the tumor with blood, oxygen, and nutrients (Schlessinger 2000, Arteaga 2001, and Cohen 2002). Several RTKs are expressed on solid tumors and are involved in cancer cell growth and survival (Collett and Erikson 1978, Takahashi, et al 1995). In some cases, mutations of these RTKs and their subsequent aberrant signaling are directly linked to the abnormal growth of tumor cells (Mizuki, et al 2000, Deininger, et al 2000). In many other cases, expression and/or overexpression of these RTKs has been demonstrated; however, the exact role of these kinases in tumorigenesis is still unknown. It has been found that some tumors are dependent on a single mutation in a growth factor receptor kinase. These include FLT3 mutations in 20% to 30% of patients with Acute Myeloid Leukemia (AML) (Gilliland and Griffin 2002); c-Kit in gastrointestinal stromal tumors (GIST), a rare form of stomach cancer (DeMatteo 2002), and the Philadelphia chromosome fused gene translocation mutation (Bcr-Abl) in nearly all patients with Chronic Myeloid Leukemia (CML) (Druker, et al 2001).

RTKs such as VEGF receptors, FGF receptors, and PDGF receptors have been shown to play an important role in tumor angiogenesis (Dvorak 2003). VEGF is produced by both the host and the cancer cells and has a direct effect on endothelial cells, causing their proliferation, migration, invasion, and growth (Nagy, et al 2002). FGFs are potent stimulators of angiogenesis in both normal and pathological tissues, having a direct effect on both vessel assembly and sprouting (Auguste, et al 2003). Blockade of the FGF pathway can overcome resistance to VEGFR inhibitors, emphasizing the importance of FGFR and specifically the need for multi-targeted inhibitors (Casanovas, et al 2005). PDGF receptors are expressed on

pericytes - smooth muscle cells that surround the vasculature and provide maintenance and support to the tumor neovasculature (Bergers, et al 2003). Inhibition of these three growth factor receptor kinases should provide a powerful and broad inhibition of the angiogenesis process and provide potent anti-tumor effects.

Dovitinib is a broad-targeted-profiled RTK inhibitor active against these three RTKs (VEGF, FGF and PDGF) involved in tumor cell growth. Based on its potency as an inhibitor of these RTKs both in vitro and in vivo, and the compound's oral availability, dovitinib has been investigated as a single agent in metastatic renal cell carcinoma (RCC), metastatic breast cancer (mBC), hepatocellular carcinoma (HCC), endometrial cancer, advanced urothelial cancer (mainly bladder cancer), advanced melanoma, multiple myeloma (MM), acute myeloid leukemia (AML), and other solid tumor studies. The maximum tolerated dose (MTD) of dovitinib was 400 mg/day for the continuous once daily dosing regimen and 500 mg/day for the 5 days on/2 days off dosing regimen.

A comprehensive review of dovitinib is contained in the Investigator's Brochure (IB) supplied by the study supporter. This document should be reviewed prior to initiating the study.

1.2.1 Mechanism of Action

Dovitinib exhibits a dual mechanism of action: anti-tumor effects via its anti-proliferative activity as well as anti-angiogenic activity. Dovitinib is a potent inhibitor in cells of the VEGFR 1, 2, and 3, FGFR1 (inhibitory concentration 50% (IC50) of 8nM), FGFR2 (IC50 of 40nM) and FGFR3 (IC50 of 9nM), PDGFRβ, c-Kit, RET, TrkA, CSF 1R, and FLT3 with IC50s of less than 40nM. Stem cell factor (SCF) also termed KIT ligand, or steel factor has been shown to modulate tumor angiogenesis (Zhang, et al 2000). In cultured human endothelial cells and c-Kit expressing cancer cells, dovitinib inhibited VEGF- and SCF-stimulated mitogenesis; in a second model of angiogenesis driven by FGF-2, dovitinib potently inhibited neovascularization of Matrigel plugs *in vivo* with an average effective dose (50% inhibition) (ED50) of 3 mg/kg. The effects on endothelial cells suggest that dovitinib may have potent anti-angiogenic activity. PDGFR and FGFR are also believed to play a role in the proliferation of certain tumor cells and supporting stromal cells. As a result of inhibition of target RTKs by dovitinib, other ligand-stimulated cellular functions are blocked, including activation of downstream signaling molecules, cellular proliferation, and survival. Anti-tumor effects for this agent may therefore be secondary to anti-angiogenesis, anti-proliferative activity against tumor cells, and anti-stromal activity.

1.2.2 Clinical Experience

As of 10 September 2011, a total of 628 patients have been enrolled into the dovitinib studies including approximately 578 patients treated with dovitinib and 50 patients with sorafenib in 15 phase I to phase III clinical trials (see Table 1-1).

Table 1-1 Dosing schedules and enrollment per study

Study[a]	Phase	Dosing[b]	Enrollment
CTKI258A2101 (advanced solid tumors)	I	25 – 175 mg once daily	35
CTKI258A2102 (AML)	I	50 – 600 mg once daily	32
CTKI258A2103 (MM)	I	50 – 500 mg once daily	21
CTKI258A2104 (MM)	I	50 – 100 mg twice daily 325 mg once daily	7
CTKI258A2105 (locally advanced or metastatic melanoma)	I	200 – 500 mg once daily	47
CTKI258A2106 (ADME trial) (advanced solid tumors)	I	500 mg single radio-labeled dose 400 mg once daily	4 9
CTKI258A2107 (locally advanced / metastatic RCC)	I/II	500 mg or 600 mg 5 days on/2 days off	84
CTKI258A2112 (advanced solid tumors)	I	500 mg 5 days on/2 days off	58
CTKI258A2116 (advanced solid tumors)	I	500 mg 5 days on/2 days off	40
CTKI258A2201 (advanced urothelial carcinoma)	II	500 mg 5 days on/2 days off	44
CTKI258A2202 (mBC)	II	500 mg 5 days on/2 days off	81
CTKI258A2204 (MM)	II	500 mg 5 days on/2 days off	38
CTKI258A2208 (HCC)	II	Dovitinib: 500 mg 5 days on/2 days off Or Sorafenib: 400 mg twice daily	11
CTKI258A2302 (RCC)	III	Dovitinib: 500 mg 5 days on/2 days off Or Sorafenib: 400 mg twice daily	89
CTKI258A1101 (Japan trial) (advance solid tumors)	I	100 – 500 mg 5 days on/2 days off	28
Total			628

Adverse events (AEs) and/or laboratory data (hematology and chemistry) were available from 594 patients as of 10 September 2011. The five most commonly reported non-laboratory AEs were nausea, fatigue/asthenia, diarrhea, vomiting and decreased appetite for both continuous daily dosing and 5 days on/2 days off dosing regimens. Commonly reported AEs were reversible and manageable; most were mild or moderate in severity (CTCAE grade 1 or 2).

The majority of the hematology laboratory abnormalities were grade 1 or 2 events across all dosing regimens. In the 5 days on/2 days off dosing regimen, there were 9 patients with grade 3 and 2 patients with grade 4 absolute neutrophil count (ANC) decreases out of 183 patients and 9 patients with grade 3 and 2 patients with grade 4 platelet count decreases out of 260 patients from the global phase I to phase II solid tumor studies; there were 3 patients with grade 3 and 1 patient with grade 4 ANC and 1 patient with grade 4 platelet count decreases out of 28 patients from the Japan solid tumor study. There were no grade 3 or grade 4 ANC or platelet count decrease out of 80 and 79 patients, respectively, from the phase III RCC study.

The most frequent lab test abnormalities observed for biochemistry were liver function test (LFT) elevations (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, and total bilirubin). In most cases these changes were CTC grade 1 or 2. Below

is a brief summary of the grade 3/4 LFT elevations for the 5 days on /2 days off dosing regimen as of 10 September 2011:

- AST: 17 grade 3 and 1 grade 4 were reported out of 295 patients from the global phase I to II studies; 1 grade 3 was reported out of 81 patients from the phase III RCC study; 4 grade 3 out of 28 patients from the Japan study
- ALT: 15 grade 3 and 2 grade 4 were reported out of 292 patients from the global phase I to II studies; 1 grade 3 was reported out of 81 patients from the phase III RCC study; 3 grade 3 out of 28 patients from the Japan study
- Total bilirubin: 14 grade 2, 6 grade 3 and 1 grade 4 were reported out of 294 patients (including 1 patient whose total bilirubin remained unchanged at grade 2 from baseline to post-baseline) from the global phase I to II studies; 1 grade 2 was reported out of 81 patients from the phase III RCC study; 1 grade 4 out of 28 patients from the Japan study

As of the 18 November 2011, there were 18 patients with hepatic dysfunction (defined as total bilirubin > 2 x ULN and AST or ALT > 3 x ULN). None of the 18 patients qualifies as a "Hy's Law" case (Rueben 2004). There was one fatal case of hepatotoxicity (cholestatic liver injury) and both the death and the hepatotoxicity were deemed related to dovitinib treatment by the investigator.

As of the 10 September 2011 cutoff date, data from a total of 6809 ECGs (of which 4237 were post-treatment) were obtained from 515 patients across 12 studies (CTKI258A2101, 2102, 2103, 2104, 2105, 2107, 2112, 2116, 2201, 2202, 2204 and 1101). Left ventricular ejection fraction (LVEF) data were available from 255 patients who had both pre- and post-treatment data from studies CTKI258A2101, 2102, 2103, 2104, 2105, 2107, 2112, 2116, 2201, 2202 and 2204. In summary, based on the available data, no consistent pattern of cardiac events related to dovitinib administration has been observed to date. More data will be collected to further assess the cardiac safety in relationship to dovitinib treatment.

As of the 28 April 2011 cut-off date, the median progression-free survival (95% CI) was 5.45 months (0.03 to 10.68 months) and the median overall survival (95% CI) was 11.79 months (0.95 to 15.57 months) for the 59 advanced RCC patients enrolled into the phase II portion of study CTKI258A2107. In phase I clinical pharmacology solid tumor studies (CTKI258A2112 and 2116), the following tumor types have demonstrated clinical benefit (i.e., prolonged disease stabilization for at least 4 months or tumor regression): thyroid cancer, RCC, pancreatic neuroendocrine tumors, colon cancer, adnexal tumor, melanoma, gastrointestinal stromal tumor, prostate cancer, thymoma, and adenoid cystic carcinoma with FGFR1 amplification. In addition, a confirmed partial response has been observed in one patient with advanced ovarian carcinoma (study 2112).

As of September 2011, pharmacokinetic data was available from about 505 patients in studies CTKI258A2101, 2102, 2103, 2104, 2105, 2106, 2107, 2112, 2116, 2201, 2202, 2204 and 1101.

Noncompartmental analysis was conducted on full plasma PK profiles of dovitinib. Coefficients of variation in the PK parameters (C_{max} and AUC_{24}) ranged from 16 to 111C_{max} was observed at approximately 4-8 hours after dosing, and the concentration of V declined monoexponentially thereafter. Within the tested dose levels ranging from 25 to 600 mg/day, linear absorption of dovitinib was observed. Dovitinib was extensively distributed to tissues.

Time-dependent PK of dovitinib was observed across all tested dose levels ranging from 25 to 600 mg/day. Following daily administration at doses below 400 mg, the auto-induction of CYP1A1/A2 resulted in lower plasma exposure of dovitinib on day 7 (steady state) than that observed on day 1. However, after increasing the daily dose to 400 - 600 mg, dovitinib plasma concentration on day 7 was found to be similar to or greater than that on day 1, suggesting a more pronounced accumulation of dovitinib at higher doses. In addition, an over-proportional increase in dovitinib plasma exposure was observed with doses from 400 to 600 mg/day. The maximum tolerated dose of dovitinib for the continuous daily dosing schedule was 400 mg (study 2105).

The time-dependent PK and the nonlinear PK resulted in dose-dependent time to reach steady state, as well as dose-dependent accumulation at steady state. To prevent the prolonged and over-proportional accumulation in dovitinib exposure with dose escalation, an intermittent dosing schedule of 5 days on/2 days off was proposed for study 2107. At tested dose levels of 500 mg and 600 mg, no accumulation was observed on day 15 (steady state). The MTD for the 5 days on/2 days off dosing schedule was 500 mg (studies 2107 and 1101).

A human ADME (absorption, distribution, metabolism and excretion) study identified the major metabolites of dovitinib as C-hydroxyl metabolites (in feces) and an N-oxide (in plasma). These metabolites are more than 5-fold less pharmacologically active than the parent drug. The ADME study demonstrated that the majority of the dose administered was recovered from feces, and less than 21% of the dose was recovered in urine. In addition, the oral absorption of dovitinib was ~75% of the dose (2106).

No formal drug-drug interaction studies with dovitinib have been conducted. Available data from human, as well as *in vitro* studies, demonstrate that dovitinib has low or no inhibition potential for CYP450s. Therefore, dovitinib is not expected to cause inhibitory metabolic drug-drug interactions when co-administered with drugs metabolized by CYP450s. Dovitinib, however, does induce CYP1A2, CYP2C9 and CYP2C19; hence co-administration with substrates of CYP1A2/2C9/2C19 could reduce the exposure of these substrates.

A relative bioavailability (BA) study (2112) was conducted to compare the final market image (FMI) capsule of dovitinib (monohydrate salt) with the clinical service form (CSF) capsule of dovitinib (anhydrate salt). PK data from 16 evaluable patients demonstrated that the FMI capsule and the CSF capsule have comparable bioavailability. Therefore, FMI capsules have replaced CSF capsules to be used in the clinical studies. Similarly, another relative bioavailability study (2116) is being conducted to compare the FMI tablet of dovitinib (monohydrate salt) with the CSF capsule of dovitinib (anhydrate salt). PK data from the first 16 evaluable patients demonstrated that the FMI tablet and CSF capsule have comparable

bioavailability. Therefore, FMI tablets are being used in some new clinical studies moving forward.

Tests of food effect (FE) on absorption of dovitinib FMI capsules demonstrated that there was no clinically relevant effect in humans (study 2112). Based on the results of the food effect test, dovitinib FMI capsules can be taken without food or with a low-fat meal (≤500 calories and ≤20 grams of fat).

Plasma VEGF levels have been reported as a pharmacodynamic (PD) biomarker for drugs of anti-VEGF/VEGFR pathways such as bevacizumab (Avastin®), sunitinib (Sutent®) and PTK787/ZK222584. The preliminary PD data from study 2102 (AML) indicated that VEGF levels were increased in patients treated with dovitinib at the 400 mg dose but not at lower doses. In the melanoma trial (study 2105), plasma VEGF level were increased 2-5 fold at cycle 1 day 26 in 3 patients treated at 400 mg and 4 out of 5 patients at 500 mg. Patients at all dose levels had 20-30% reduction of soluble VEGFR2 in plasma, which is consistent with other VEGFR2 inhibitors such as sunitinib (Sutent®) and sorafenib (Nexavar®).

1.2.2.1 Results of food effect study

The effect of food on the bioavailability of dovitinib was studied in 19 patients with advanced solid tumors (CTKI258A2112 Arm 2; FMI capsule formulation). The PK of dovitinib following administration with no meal (i.e. at least 1 hour prior to a light meal or at least 2 hours following a light meal) (NM), with a low-fat meal (LF) or with a high-fat meal (HF) were compared to determine the relative bioavailability of drug administered with LF and HF compared to NM. The results demonstrated that there was no clinically relevant effect on the AUC or Cmax of dovitinib when administered with either LF or HF meal relative to NM (please refer to the current IB for additional information). However, the study design did not allow an assessment of the impact of consistently taking the daily dovitinib dose with HF in the multiple-dosing condition, compared to no effect expected when consistently taking the drug with LF and NM, or occasionally with HF. Based on the results of the food effect test, dovitinib may be taken, as previously, without food, or with an amount of food up to the level tested, i.e. low-fat meal of ≤ 500 calories with ≤ 20 grams fat.

Summary of potential toxicity in patients

Gastrointestinal system
Nausea, vomiting, anorexia/decreased appetite, and diarrhea were reported as DLTs in clinical studies with dovitinib. Additionally, they were among the top commonly reported AEs for both continuous once daily dosing regimen (N = 155) and 5 days on/2 days off dosing regimen (N = 205 for global, N = 22 for Japan study 1101). Most of these events were mild to moderate (grade 1/2), with the grade 3 events occurring in 23.2% of patients (n=36) in continuous once daily dosing regimen, 18.0% of patients (n=37) in global 5 days on/2 days off dosing regimen, and 31.8% of Japanese patients (n= 7) with 5 days on/2 days off dosing regimen. There were no grade 4 events for these AEs. In most cases, these AEs improved with symptomatic treatments such as anti-emetics or anti-diarrhea medications, or with the

interruption of dovitinib. There were no grade 4 gastrointestinal events reported as DLTs in clinical studies with dovitinib.

A case of small bowel obstruction and perforation with abscess with suspected relationship to the study drug has been reported. Dovitinib inhibits VEGF along with FGFR and PDGF; perforation is a known class effect for VEGF inhibitors.

Cardiovascular system
Sinus bradycardia and hypertensive crisis were reported as DLTs in clinical studies with dovitinib. Additionally, hypertension was the most commonly reported AE in the 15.1% of patients on 5 days on/2 days off dosing reschedule (N = 205, global studies). Hypertension is a well-known effect of VEGF inhibition. Patients should be monitored for blood pressure as per study protocol. In situation for which hypertension or worsening state is being reported, protocol toxicity management guideline should be followed. When needed adequate medical care (e.g. anti-hypertensive therapy) should be administered according to the standard practice.

As QT prolongation has been reported in other tyrosine kinase inhibitors, an extensive ECG monitoring schedule has been implemented in 10 clinical studies with dovitinib (N = 347). According to the central ECG analysis, available ECG data revealed no effect on cardiac repolarization of dovitinib across days and doses of therapy, nor is there any specific outlier signal observed consistent with the central tendency finding. This conclusion was also supported by a negative result in the exposure-ECG model. ECHO/MUGA evaluation was performed in 10 clinical studies with dovitinib (N = 200). The available data was reviewed by an independent cardiologist consultant, who concluded that, based on the available data, dovitinib had no effect on LVEF

Hematologic events
Neutropenia was reported as DLTs from dovitinib clinical studies (continuous once daily dosing regimen) in patients with acute myeloid leukemia or multiple myeloma.

Commonly reported hematologic adverse event (≥ 10% of patients) was anemia for the 5 days on/2 days off global studies (N = 205). For Japanese study (1101) using 5 days on/2 days off dosing regimen (N = 22), commonly reported hematologic AEs included lymphopenia, leukopenia, neutropenia/neutrophil count decreased, anemia/hemoglobin decrease, WBC decreased, and thrombocytopenia/platelet count decreased. Reported grade 3/4 hematologic AEs in 2 or more patients for the 5 days on/2 days off global studies (N = 205) were neutropenia (n = 9), thrombocytopenia (n = 7), anemia (n = 5), and leukopenia (n = 4). For Japanese study (N = 22), reported grade 3/4 hematologic AEs were lymphopenia (n = 6), neutropenia/neutrophil count decreased (n = 4), WBC decreased (n = 3), and anemia/hemoglobin decrease (n = 2). Because a small number of patients have been treated in the Japanese study, the available data is not sufficient to determine the difference in drug effect on the Japanese patients and the patients of other ethnicity at this time.

Hepatic effects
Delayed recovery from AST/ALT elevations was reported as a DLT from a patient on dovitinib once daily dosing schedule. In clinical trials conducted globally, except Japan, overall newly occurring or worsening grade 3/4 AST/ALT and total bilirubin were observed in no greater than 10% of patients. In the Japanese study (study 1101) using 5 days on/2 days off dosing regimen (N = 22), increased ALT/AST were among the commonly reported AEs (≥ 10% of patients) regardless of dovitinib relationship. Newly occurring or worsening grade 3/4 AST/ALT were three grade 3 AST (13.6%), and two grade 3 ALT (9.1%); there were no grade 4 AST/ALT. While no grade 3 increase in total bilirubin was observed, a grade 4 total bilirubin was reported in 1 patient (4.5%) during the study. As a small number of patients have been treated in the Japanese study, the available data is not sufficient to determine the difference in drug effect on the Japanese patients and the patients of other ethnicity at this time.

In addition, a fatal case of hepatoxicity (cholestatic liver injury) was observed in a patient with metastatic breast cancer after approximately one month of treatment with dovitinib; both the cholestatic liver injury and the death were deemed drug-related by the investigator. A review of the safety database for dovitinib showed that no other serious hepatotoxic event with a similar pattern and severity. Dovitinib inhibits VEGF, as well as, FGFR and PDGF. Hepatotoxicity is a known class effect for VEGF inhibitors. Investigators are reminded to evaluate the pattern of liver function test abnormalities and follow the management paradigm in the study protocols to interrupt or discontinue dovitinib treatment.

Renal system
No DLTs were reported in renal system. Newly occurring or worsening grade 3/4 increase in serum creatinine was reported in less than 1% of patients who received dovitinib treatment.

Other reported toxicities
Increased gamma glutamyltransferase and hypokalemia were the other laboratory DLTs, whereas fatigue/asthenia were the other non-laboratory DLTs reported. For both dosing schedules (once daily and 5 days on/2 days off), fatigue/asthenia were listed among the commonly reported AEs (≥10% of patients). In addition, fatigue/asthenia had high incidence among all grade 3/4 events.

Headache, rash, and dry mouth were listed as the commonly reported AEs (≥10% of patients) from both dosing schedules (once daily and 5 days on/2 days off). About 5.7% of patients (n = 13) reported for pelmar-plantar erythrodysesthesia syndrome (PPES) in the studies using 5 days on/2 days off dosing schedule (N = 205 global studies, and N = 22 Japan study 1101). Among them, 2 grade 3 events were reported and no grade 4 events were observed. PPES has also been reported with the use of other tyrosine kinase inhibitors.

Serum amylase and triglycerides are monitored in the clinical studies with dovitinib, because their abnormal levels were reported in the preclinical toxicology studies. Newly occurring or worsening grade 3/4 increase in triglycerides was reported in about 6.6% of patients who have received dovitinib treatment.

1.2.3 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biological processes, pathogenic processes and/or pharmacologic responses to a therapeutic intervention. Plasma VEGF levels have been reported as a pharmacodynamic (PD) biomarker for drugs of anti-VEGF/VEGFR pathways such as bevacizumab, sunitinib and PTK787/ZK222584. The preliminary PD data from CdovitinibA2102 study (AML) indicated that VEGF levels were increased in patients treated with dovitinib at 400 mg dose but not at lower doses. In the melanoma trial CdovitinibA2105, mean plasma VEGF and PLGF levels increased over baseline values by 100%, and 198%, respectively at the end of the first treatment cycle, while mean plasma sVEGFR2 levels decreased by 15% in patients treated with 400 mg/day dovitinib. The effect of dovitinib on tumor blood changes were assessed by DCE-MRI and dose dependent reduction of Ktrans was observed at doses ≥ 400 mg/day. These biomarker changes indicated VEGFR pathway inhibition by dovitinib at doses equal or higher than 400 mg/day.

FGF23 is a hormone that principally regulates phosphate, vitamin D homeostasis, and mineralization of bone. Plasma FGF23 induction has been suggested as a surrogate biomarker of FGFR1 inhibition and induction of FGF23 plasma concentrations by dovitinib has been observed in trials CdovitinibA2105 and CdovitinibA2107. In this study, plasma angiogenesis markers will be evaluated as core PD markers for FGFR and VEGFR pathway inhibition.

In addition, as a PD marker of anti-VEGF therapy, it has been reported that plasma VEGF levels are prognostic for PFS and OS in the sorafenib TARGET trial. The prognosis values of angiogenesis markers will also be evaluated in the current study.

Signaling through TK receptors (RTK) is critical for cell proliferation and survival. This is obtained through positive regulation of cell cycle, transcription and translation, and repression of apoptotic machinery. Therefore, it is expected that dovitinib would inhibit cellular proliferation and/or induce apoptosis which would then reflect in anti-tumor effect of the therapy. Tumor expression of VEGF, bFGF and hypoxia factor CA9 has been reported as prognosis factors in mRCC. In the current study, archival tumor samples will be collected and ligands and receptors for FGF and VEGF pathways will be analyzed to assess their role as potential predictive and/or prognostic biomarkers.

When feasible, pre- and post-tumor biopsies will be collected to measure pharmacodynamic effect of dovitinib to understand how the target inhibition correlates with downstream molecular effects and cellular responses. Cellular proliferation biomarker Ki-67, apoptotic markers (like cleaved caspase-3), and pFGFR in tumor tissue will be evaluated when pre-treatment vs. post-treatment biopsies are available.

1.3 Overview of Abiraterone Acetate

The most common adverse reactions (≥ 5%) are joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension,

arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection. In addition abiraterone acetate has been associated with the following conditions:

Mineralocorticoid excess: abiraterone acetate should be used with caution in subjects with a history of cardiovascular disease. The safety of abiraterone acetate in subjects with LVEF < 50% or NYHA Class III or IV heart failure is not established. Hypertension should be controlled and hypokalemia should be corrected before treatment. Blood pressure, serum potassium and symptoms of fluid retention should be monitored at least monthly.

Adrenocortical insufficiency: symptoms and signs of adrenocortical insufficiency should be monitored. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Hepatotoxicity: Increases in liver enzymes have led to drug interruption, dose modification and/or discontinuation. Liver function should be monitored and modify, interrupt, or discontinue abiraterone acetate dosing as recommended. Study subjects will have liver function tests (including alkaline phosphatase, AST, ALT, direct and total bilirubin, and LDH) every 2 weeks for the first 12 weeks of treatment.

Abiraterone acetate must be taken on an empty stomach. Exposure of abiraterone acetate increases up to 10 fold when abiraterone acetate is taken with meals.

Abiraterone acetate may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle abiraterone acetate without protection (e.g., gloves). Subjects will also be informed that it is not known whether abiraterone acetate or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The subjects should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with abiraterone acetate.

Additional information is available in the Zytiga® Prescribing Information found at the following web address: http://www.zytigahcp.com/prescribing-information

1.4 Overview of Prednisone

Fluid and electrolyte disturbances: sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension.

Musculoskeletal: muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, tendon rupture, particularly of the Achilles tendon, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathological fracture of long bones.

Gastrointestinal: peptic ulcer with possible perforation and hemorrhage, pancreatitis, abdominal distention, ulcerative esophagitis, increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following

corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome are reversible upon discontinuation.

Dermatologic: impaired wound healing, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, may suppress reactions to skin tests.

Neurological: convulsions, increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment, vertigo, headache.

Endocrine: menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos.

Metabolic: negative nitrogen balance due to protein catabolism.

Additional reactions: Urticaria, and other allergic, anaphylactic or hypersensitivity reactions.

1.5 Risk-Benefit Assessment

Dovitinib and abiraterone acetate have not yet been given together. Dovitinib is metabolized mainly by CYP1A1/2 and FMO, while abiraterone acetate is metabolized mainly by CYP3A4 and SULT2A1. Thus, the potential for drug interaction when administering both drugs at the same time is relatively low. Based on the safety and tolerability profile of both drugs, no severe toxicity with the proposed combinations is expected. None the less, particular attention will be placed on monitoring liver tests as both drugs have the potential for hepatotoxicity. Patient safety will be monitored through clinical vigilance. Subject safety is assured through clinical monitoring during the study. 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 subjects will be treated at M.D. Anderson Cancer Center and will be provided with their treating physicians and research nurse contact information.

2 Study Purpose/Rationale

Pre-clinical studies from our group using human prostate cancer xenografts support the hypothesis that FGF signaling contributes to evolution of AR-independent, castrate-resistant disease. MDA PCa 118b is a prostate cancer xenograft derived from bone metastases in a man with advanced castrate-resistant disease. Molecular-pathologic analysis revealed that MDA PCa 118b cells do not express AR but do overexpress high FGF9 levels. MDA PCa 118 cells induce the proliferation of cocultured osteoblasts in vitro and induce a strong osteoblastic

reaction in the bone of immunodeficient mice in an FGF9-depependent manner. MRI analysis of MDA PCa 118b orthotopic bone tumors five weeks after cell injection demonstrated that mice treated with FGF9 neutralizing antibody developed significant smaller tumors than controls. These compelling pre-clinical data prompted us to test FGF inhibition in human patients with mCRPC.

We are presently conducting a study of dovitinib in patients with castrate-resistant prostate cancer and skeletal metastases (mCPRC) with the goal to evaluate markers of bFGF signaling in bone marrow biopsy specimens. Patients are receiving 500 mg PO q Day for 5 days, followed by a 2 day rest period. Each cycle is 28 days and response is assessed every 56 days (8 weeks). Patients are continued on dovitinib until disease progression, unacceptable toxicity, or withdrawal of consent. Twenty-two of 40 patients have been enrolled thus far. Median age is 68, all patients have skeletal metastases, 11/22 (50%) of patients also have lymph node and/or visceral metastases, and 18/22 (80%) of patients have previously received at least one regimen of cytotoxic chemotherapy. Median follow up is 50 days and median PFS has not yet been reached. Most common therapy-associated toxicities have been grade 1/2 including fatigue (37%), nausea (50%), and diarrhea (50%). Grade 3 toxicities have been rare including fatigue (10%) and dyspnea (10%). There have been no grade 4 toxicities thus far. Dose reductions reduce toxicities. Of the first 4 patients enrolled, three had rapidly progressive disease prior to initiation of dovitinib came off study within 14 days of starting drug for clinical deterioration. **Soft-tissue effects**: Of 5 evaluable patients ($\geq$2 cycles of therapy) with soft tissue disease, tumor shrinkage occurred in 2 patients, 1 had stable disease, and 2 had progressive disease. **Effects on Bone**: Of 11 evaluable patients with skeletal metastases, 2 exhibited partial responses and 9 demonstrated stable disease. Five of these patients have demonstrated responses $\geq$12 weeks. PSA changes were independent of clinical activity. Preliminary analysis of bone marrow biopsies obtained at baseline and at 8 weeks on therapy reveals dovitinib -mediated down-regulation in FGFR1 and phospho-MAPK, suggesting tumor-specific inhibition of FGF signaling.

Based on these promising preliminary results, we now want to explore the hypothesis that dovitinib will improve the anti-tumoral activity of abiraterone acetate by inhibiting FGF, an AR-independent signaling pathway that contributes to castrate-resistant growth. dovitinib and abiraterone acetate plus prednisone have individually demonstrated suppression of androgen signaling and efficacy in subjects with CRPC. However, no formal trials have been conducted to further explore additive or synergistic activity.

3 Objectives and Endpoints

Primary Objective

In this study, we will evaluate the safety and tolerability of dovitinib combined with abiraterone acetate in men with metastatic castration-resistant prostate cancer.

Secondary Objective
To assess clinical efficacy of dovitinib combined with abiraterone acetate in men with metastatic castration-resistant prostate cancer.

Exploratory Objective
To assess the changes of biomarkers.

Primary Endpoint
1) Safety and tolerability of dovitinib in combination with abiraterone acetate in this patient group.

Secondary Endpoints
1) To assess Progression Free Survival (PFS)
2) To assess overall survival (OS)

Exploratory Endpoints
1) To collect and bank blood and tissue specimens in order to create a deeply annotated tissue resource for hypothesis generating discovery.
2) Biomarker modulation (for example PSA, CTCs, serum cytokine and angiogenic factor (CAF) profiles, bone specific alkaline phosphatase, urine n-telopeptides).
3) Tumor pharmacodynamic measures (molecular-pathologic analysis of FGF and Androgen-Receptor (AR) signaling pathways using metastatic tissue samples).

4 Investigational Plan

4.1 Study Design

This is an open label phase II study to determine the safety and efficacy of dovitinib in combination with abiraterone acetate plus prednisone in patients with mCRPC by clinical evaluations at protocol specified intervals. Tumor tissue will be collected via trans-iliac bone marrow biopsies to determine AR and FGF signaling and candidate pathways that may be part of a signaling network implicated in therapy resistance. The baseline determination and subsequent assessment of AR and FGF signaling will be correlated with progression free survival.

The starting dose for dovitinib will be 400 mg PO q Day 5 days on, 2 days off and the dose for abiraterone acetate will be 1,000 mg PO q Day. Prednisone will be administered at 5mg PO BID.

Up to sixty (60) patients will receive treatment on study until any of the following criteria are met:

1) Unacceptable toxicity
2) Disease progression:
    - Progression of measurable disease by RECIST criteria. To be considered measurable, baseline lymph nodes, visceral metastases, and soft tissue

metastases must be ≥2 cm in longest dimension. Equivocal RECIST progression must be confirmed by a follow up scan > 6 weeks later.

- Two or more new areas by bone scan attributable to prostate cancer (rather than flare) OR new/increasing size of lytic lesions by CT scan or MRI. In the event of borderline progression or ambiguity on scans, a follow-up scan may be considered ≥ 4 weeks later.
- Need for palliative radiation involving more than one site
- Surgery or kyphoplasty to any neoplastic bone lesion
- Cancer-associated clinical deterioration as determined by the treating physician.

Note: PSA progression alone will not be used to define progression.

3) Patient decision to withdraw
4) In the judgment of the investigator, further treatment would not be in the best interest of the patient.

For the study duration, all subjects will maintain androgen deprivation with a GnRH agonist or antagonist or orchiectomy.

5 Population

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered enrollment in the study.

5.1 Inclusion Criteria

Patients eligible for inclusion in this study have to **meet all** of the following criteria:

1) Patient or his legally authorized representative must provide written informed consent.
2) Age ≥ 18
3) ECOG performance status ≤ 2
4) Histologic evidence of prostate adenocarcinoma
5) Diagnosis of metastatic castration-resistant prostate cancer, with measureable disease (lymph nodes and/or visceral metastases by RECIST) or bone metastases.
6) Patients must have surgical or ongoing chemical castration (with LHRH agonists or LHRH antagonists), with a baseline testosterone level < 50ng/dL.
7) Patients must have documented evidence of progressive disease as defined by any of the following:
   - PSA progression: minimum of 2 rising values (3 measurements) obtained a minimum of 7 days apart with the last result being at least ≥ 2.0 ng/mL
   - New or increasing non-bone disease (RECIST)
   - A positive bone scan with 2 or more new lesions (PCWG2). Patients must have evidence for metastatic prostate cancer by bone scan and/or CT/MRI (i.e., soft tissue, visceral, lymph node). If lymph node, visceral and/or soft-tissue metastases are the only evidence of metastasis, at least one lesion must be ≥ 1.5 cm in diameter.
8) Laboratory requirements:

- Absolute neutrophil count (ANC) ≥ 1,500/ml
- Platelets ≥ 100,000/ml
- Total bilirubin ≤ 1.5 x ULN;
- SGPT (ALT) AND/OR SGOT (AST) ≤ 3.0 × ULN
- Creatinine ≤ 1.5 x ULN
- WBC ≥ 3,000 μL
- Hb ≥ 8.0 g/dL independent of transfusion

9) Men whose partner is a woman of childbearing potential must be willing to consent to using effective contraception (e.g. male condom with spermicide, diaphragm with spermicide, intra-uterine device) while on treatment and for at least 3 months thereafter.

10) Patients may have received prior treatment with androgen ablative therapies (e.g. bicalutamide, DES, enzalutamide) and/or "targeted" therapies (such as tyrosine kinase inhibitors). Androgen ablative therapies must be discontinued ≥3 days prior to initiation of study treatment with the exception of enzalutamide which may be continued during protocol treatment per the practice preference of the treating physician. Patients who are predicted to benefit from an antiandrogen withdrawal response should be tested for this possibility before being considered for eligibility to this study. Targeted therapies must be discontinued ≥ 2 weeks before initiation of study treatment.

11) Patients may have received up to 2 prior cytotoxic chemotherapy regimens for the treatment of metastatic castration-resistant disease, but these therapies must be discontinued ≥ 3weeks before initiation of study treatment. At least one of the regimens must have contained docetaxel and patients must have recovered to < Grade 2 adverse events from prior chemotherapy or to pretreatment baseline.

5.2 Exclusion Criteria

Patients eligible for this study **must not meet any** of the following criteria:

1) Patients with histologic evidence of small cell carcinoma of the prostate
2) Prior therapy with dovitinib or abiraterone acetate or other FGF targeted therapy.
3) Radiation therapy (including palliative radiotherapy to a metastatic lesion) within 14 days
4) Major surgery (e.g., open abdominal, pelvic, thoracic, orthopedic or neurosurgery) within 28 days of the date of the first dose of study drugs.
5) Samarium-153 within 28 days of the date of the first dose of study drugs, or Strontium-89 within 12 weeks (84 days) of the date of the first dose of study drugs. Patients who have received 2 or more doses of bone-seeking radioisotopes are not eligible.
6) Current treatment on another therapeutic clinical trial
7) Impending complication from bone metastases (fracture and/or cord compression). Properly treated or stabilized fractures and/or cord compression is allowed.

8) Presence of ongoing urinary obstruction (e.g., urinary retention, hydronephrosis) requiring medical intervention. Urinary obstruction relieved with treatment is allowed.
9) Patient has an uncontrolled intercurrent illness (e.g., uncontrolled diabetes, uncontrolled hypertension).
10) Patient has another serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the patient's ability to provide informed consent or with the completion of treatment according to this protocol.
11) Patients with an active second malignancy that could, in the investigator's opinion, potentially interfere with the patient's ability to participate and/or complete this trial.
12) Patients with known brain metastases
13) Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
    a. History or presence of serious uncontrolled ventricular arrhythmias
    b. Clinically significant resting bradycardia
    c. LVEF assessed by 2-D echocardiogram (ECHO) < 50% or lower limit of normal (whichever is the higher), or 2-D multiple gated acquisition scan (MUGA) < 45% or lower limit of normal (whichever is the higher)
    d. Any of the following within 6 months prior to starting study drug: myocardial infarction (MI), severe/unstable angina, Coronary Artery Bypass Graft (CABG), Congestive Heart Failure (CHF), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA)
    e. Chronically uncontrolled hypertension, defined conventionally as consistent/repeated systolic pressures above 140 mmHg or diastolic pressures above 90 mmHg despite anti-hypertensive therapy. This may be established with home BP readings. There is no criterion related to a specific BP result required for eligibility, nor are acute BP elevations that are related to iatrogenic causes, acute pain, or other transient reversible causes considered an exclusion criterion. The intent is to exclude patients with chronically uncontrolled hypertension that might be further exacerbated by the study drugs.
14) Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of dovitinib (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or gastric or small bowel resection)
15) Cirrhosis, chronic active hepatitis or chronic persistent hepatitis
16) Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory) or HBV or HCV disease or antigen positivity
17) Initiation of bisphosphonate and/or RANKL inhibitors within 4 weeks prior to first dose of study drug. Patients already on stable doses of bisphosphonates and/or RANKL inhibitors may continue these drugs. However, patients are not allowed to initiate bisphosphonate and/or RANKL inhibitors during the study.
18) Any bleeding dyscrasia.

6 Treatment

6.1 Administration

Dovitinib: Patients will receive a single daily oral dose of dovitinib for 5 consecutive days, followed by a 2-days rest period. The starting dose will be 400mg daily. The dose of dovitinib is NOT individually adjusted by weight or body surface area. Dovitinib should be ingested with sufficient amount of water with or without food.

Abiraterone acetate: Patient will be instructed to take 4 tablets (250 mg each) orally (PO) daily, at least 1 hour before a meal or 2 hour after a meal. The tablets should be swallowed whole with water. Do not crush or chew tablets

Prednisone: Subjects will be instructed to take 5-mg oral prednisone, twice daily.

Patients should be instructed to swallow the required number of capsules/tablets at approximately the same time on each day.

6.3 Toxicity Management/Dose Modifications

While Dovitinib and abiraterone acetate have not yet been combined, the safety/tolerability profile of both drugs does not predict for severe toxicity. Dovitinib is metabolized mainly by CYP1A1/2 and FMO and abiraterone acetate is metabolized mainly by CYP3A4 and SULT2A1, suggesting the potential for drug interactions is relatively low. Nonetheless, particular attention will be placed on monitoring liver tests as both drugs have the potential for hepatotoxicity and undergo hepatic metabolism. Patient safety will be monitored through clinical vigilance. Subject safety is assured through clinical monitoring during the study. 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 subjects will be treated at M.D. Anderson Cancer Center and will be provided with their treating physicians and research nurse contact information.

6.3.1 Shared Toxicities (dovitinib and abiraterone acetate)

In subjects who experience toxicity that cannot be ameliorated by the use of adequate medical intervention, dose reductions can be performed. In these cases dose reductions of abiraterone acetate should be performed first, followed by reduction in dovitinib doses (if needed).

Toxicity intensity [a]	**Dose modification** [b, c]
Cardiovascular	
Hypertension	Treatment-emergent hypertension should be treated as per standard cardiology practice.
SBP < 160 mmHg AND DBP < 100 mm Hg, with or without anti-hypertensive medication	Maintain dose level
SBP ≥ 160 mmHg and/or DBP ≥ 100 mm Hg, with or without anti-hypertensive	Delay the study treatments and initiate/intensify antihypertensive therapy. Consider adding the specific mineralocorticoid receptor blocker,

medication, but not immediately life-threatening	eplerenone (Inspra), if hypertension may be related to mineralocorticoid excess. Dovitinib and abiraterone acetate may be restarted in conjunction with standard anti-hypertensive medication if BP is controlled (i.e. BP < 160/100 mmHg). Once BP is controlled after suspending dovitinib and abiraterone acetate, maintain dose level or ↓ 1 dose level at the discretion of the investigator.
Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Discontinue study treatments permanently
Hepatic	
≥ Grade 3 alkaline phosphatase or GGT	Isolated ≥ grade 3 alkaline phosphatase or GGT values will NOT require dose interruption.
ALT or AST	
> ULN to 3.0 x ULN	Maintain dose levels with LFTs[d] monitored as per protocol.
> 3.0 to ≤ 5.0 x ULN without bilirubin elevation to > 2.0 x ULN	Maintain dose levels with weekly monitoring of LFTs[d], or more frequently if clinically indicated, until resolved to ≤ grade 1 or baseline.
> 5.0 to ≤ 20 x ULN	Delay study treatments until resolved to ≤ grade 1 or baseline, then ↓ 1 dose level. Monitor LFTs[d] weekly, or more frequently if clinically indicated, for 8 weeks; then, every 2 weeks for 4 weeks; then, every 4 weeks as per protocol. Following re-introduction of dovitinib and abiraterone acetate, if ALT or AST elevations > 3 x ULN recur as assessed on 2 separate measurements no more than 1 week apart, then study treatments should be permanently discontinued. If study treatments are permanently discontinued, then patients should be monitored weekly (including LFTs[d]), or more frequently if clinically indicated, until AST or ALT have resolved to ≤ grade 1 or stabilization (i.e., no CTCAE grade change over 4 weeks).
> 20 X ULN	Discontinue study treatments permanently. Patients should be monitored weekly (including LFTs[d]), or more frequently if clinically indicated, until ALT and AST have resolved to ≤ grade 1 or stabilization (i.e., no CTCAE grade change over 4 weeks).
Total Bilirubin	
≤ 1.5 x ULN	Maintain dose levels with LFTs[d] monitored as per protocol.
> 1.5 to ≤ 3.0 x ULN with ALT AND AST ≤ 3.0 x ULN	Maintain dose levels with weekly monitoring of LFTs[d], or more frequently if clinically indicated, until resolved to ≤ grade 1 or baseline.
> 3.0 x ULN	Discontinue study treatments permanently. Patients should be monitored weekly (including LFTs[d]), or more frequently if clinically indicated, until total bilirubin has resolved to ≤ grade 1 or stabilization (i.e., no CTCAE grade change over 4 weeks). *Note: If grade 3 or grade 4 hyperbilirubinemia is due to the indirect component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at*

	the discretion of the investigator.
ALT or AST, and concurrent Bilirubin	
ALT or AST > 3.0 x ULN AND Total Bilirubin > 2.0 x ULN	Discontinue study treatments permanently. Patients should be monitored weekly (including LFTs[d]), or more frequently if clinically indicated, until ALT/AST and total bilirubin have resolved to ≤ grade 1 or stabilization (i.e., no CTCAE grade change over 4 weeks).
All dose modifications should be based on the worst preceding toxicity.	
[a] Common Terminology Criteria for Adverse Events (CTCAE)) v4.0	
[b] Patients are allowed two dose reductions for abiraterone and dovitinib. For abiraterone, a dose reduction from 1000mg to 750mg, and if necessary, a dose reduction from 750 mg to 500mg. For dovitinib, a dose reduction from 400 mg to 300 mg, and, if necessary, a dose reduction from 300 mg to 200 mg.	
[c] If a patient requires a dose interruption of > 21 days starting from the first day a dose was missed, then the patient must be discontinued from the study treatment. Patients who discontinue the study treatment for a study related adverse event including an abnormal laboratory value must be followed at least once a week for 28 days and subsequently at 28 days intervals until resolution or stabilization of the event, whichever comes first.	
[d] LFTs include albumin, GGT, ALT, AST, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated [quantification of isoenzymes], if alkaline phophatase ≥ Grade 2).	

6.3.2 Abiraterone Acetate

The most common adverse drug reactions (≥5%) reported in clinical studies were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, fractures and upper respiratory tract infection.

The most common adverse drug reactions that resulted in drug discontinuation were aspartate aminotransferase increased, alanine aminotransferase increased, urosepsis and cardiac failure (each in <1% of patients taking abiraterone acetate).

Adverse reactions and laboratory abnormalities related to mineralocorticoid effects were reported more commonly in patients treated with abiraterone acetate than in patients treated with placebo: hypokalemia 28% versus 20%, hypertension 9% versus 7% and fluid retention (edema) 27% versus 18%, respectively. In patients treated with abiraterone acetate, grades 3 to 4 hypokalemia occurred in 5% of patients and grades 3 to 4 hypertension was reported in 1% of patients.

Dose Modifications

In the event where dose reduction is used for AE management, 2 dose reductions are allowed. At each dose reduction, one tablet of abiraterone acetate will be removed, e.g., 4→3 tablets, and 3→2 tablets. The minimum dose of abiraterone acetate will be 500 mg daily. Any return to protocol dose level after dose reduction must follow documentation of AE resolution and a discussion with the Principal Investigator. Other toxicities, although anticipated in this study, are primarily related to underlying advanced prostate cancer and its management; therefore, approaches other than dose reduction are recommended.

Abiraterone acetate may be held for toxicity for up to 4 weeks before a patient is removed from study.

If abiraterone acetate is held, prednisone should be continued if the patient is expected to resume abiraterone acetate after resolution of the precipitating cause of the interruption in therapy.

Toxicity management recommendations are described below:

Management of Hypokalemia

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

If any patient experiences Grade 3 hypokalemia (serum potassium levels < 3.0 mM – 2.5mM, NCI CTCAE v4.0) or life-threatening hypokalemia with potassium levels < 2.5 mM (NCI CTCAE v4.0 hypokalemia Grade 4), abiraterone acetate treatment will be withheld, and the patient hospitalized for intravenous potassium replacement and cardiac monitoring.

Other concurrent medical conditions that could contribute to hypokalemia, such as diarrhea, hypomagnesemia, and poor oral intake, must be managed. In the event that potassium supplementation fails to maintain serum potassium above 3.5mM and in the absence of other contributing factors, the mineralocorticoid specific antagonist, eplerenone may be initiated and titrated to keep serum potassium < Grade 3. When toxicity resolves to ≤ Grade 1, resume study medication at full dose.

If toxicity recurs to ≥ grade 3, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤ Grade 1, resume study medication with the first dose level reduction (3 tablets, 750 mg of study medication). If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤ Grade 1, resume study medication with the second dose level reduction (2 tablets, 500 mg of study medication).

If toxicity recurs despite aggressive medical management and two dose level reductions, discontinue study medication.

Management of Corticosteroid Side Effects

Patients receiving abiraterone acetate and prednisone may develop adverse effects as the result of elevated ACTH and corticosteroid levels. At time of observation, if corticosteroid side effect (e.g. hypertension, hyperglycemia, fluid retention, skin thinning, proximal muscle weakness, altered mood or osteoporosis) is Grade ≥ 2 (NCI CTCAE, version 4), prednisone should be discontinued and hydrocortisone 20mg PO qAM should be started, and appropriate additional medical management per standard of care for the steroid side effect should begin.

If Grade ≥ 2 toxicity persists for more than 14 days, despite conversion to hydrocortisone and medical intervention, glucocorticoid use should be discontinued.

In patients who do not show any evidence of corticosteroid excess, the prednisone dose may be reduced from 5 mg PO BID to 5mg PO q Day to minimize long-term sequelae from chronic corticosteroid use.

Management of Edema (Fluid Retention)

Pedal edema: Supportive management per Investigator. No study medication dose reduction.

Anasarca and/or pulmonary edema requiring supplemental oxygen: Hold study medication. Adjust or add medications to mitigate the toxicity and/or consider the specific mineralocorticoid receptor blocker, eplerenone (Inspra). When toxicity resolves to ≤ Grade 1, resume study medication at full dose.

If toxicity recurs to ≥ grade 3, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤ Grade 1, resume study medication with the first dose level reduction (3 tablets, 750 mg of study medication). If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤ Grade 1, resume study medication with the second dose level reduction (2 tablets, 500 mg of study medication).

If toxicity recurs despite optimal medical management and two dose level reductions, discontinue study medication.

Other Clinically Significant Adverse Events

If Grade 1-2 toxicities, give supportive care per institutional guidelines. No study medication dose reduction.

If Grade 3 toxicities (except for hyperlipidemia), delay study treatment until resolved to ≤ grade 1 or baseline, then maintain dose level or reduce 1 dose level at the discretion of the investigator

If Grade 4 toxicities, delay study treatment until resolved to ≤ grade 1 or baseline, then reduce 1 dose level or discontinue abiraterone acetate at the discretion of the investigator

If toxicity recurs to ≥ grade 3, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤ Grade 1, resume study medication at reduced dose. If toxicity recurs, hold study medication, and adjust or add medications to mitigate the

toxicity. When resolved to ≤ Grade 1, resume study medication at reduced dose. Only 2 reductions are allowed.

Patients Remaining on Enzalutamide During this Study (see Inclusion 10)

There is a drug interaction (p450 2C8), and abiraterone can increase enzalutamide levels. Providers may consider dose reduction of enzalutamide to 80 mg if continued on the medication during this protocol.

6.3.3 Dovitinib

For patients who are unable to tolerate the protocol-specified dosing schedule, dose reductions or interruptions are permitted to manage drug-related toxicities. When dose reduction is necessary, the dose of dovitinib may be reduced to a minimum dose of 200 mg daily for 5 days on/2 days off. Once the dovitinib dose is reduced due to an adverse event, the dose of dovitinib cannot be re-escalated. All dose reductions should be based on the worst preceding toxicity. Patients are allowed only 2 dose reductions (to 300 mg and 200 mg).

Patients whose treatment is interrupted or permanently discontinued due to an adverse event including abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. The maximum time allowed for treatment interruption due to toxicity is 21 days (3 weeks) from the intended dosing day. If interruption is > 3 weeks, the patient must be discontinued from the study treatment. However, the patient will continue to be followed for toxicity.

Treatment interruptions, missed doses, and dosing errors

The decision whether to continue with study treatment should be based on individual circumstances and the physician's judgment that continuation of treatment is in the patient's best interest. If dovitinib is interrupted, the guidelines described below should apply.

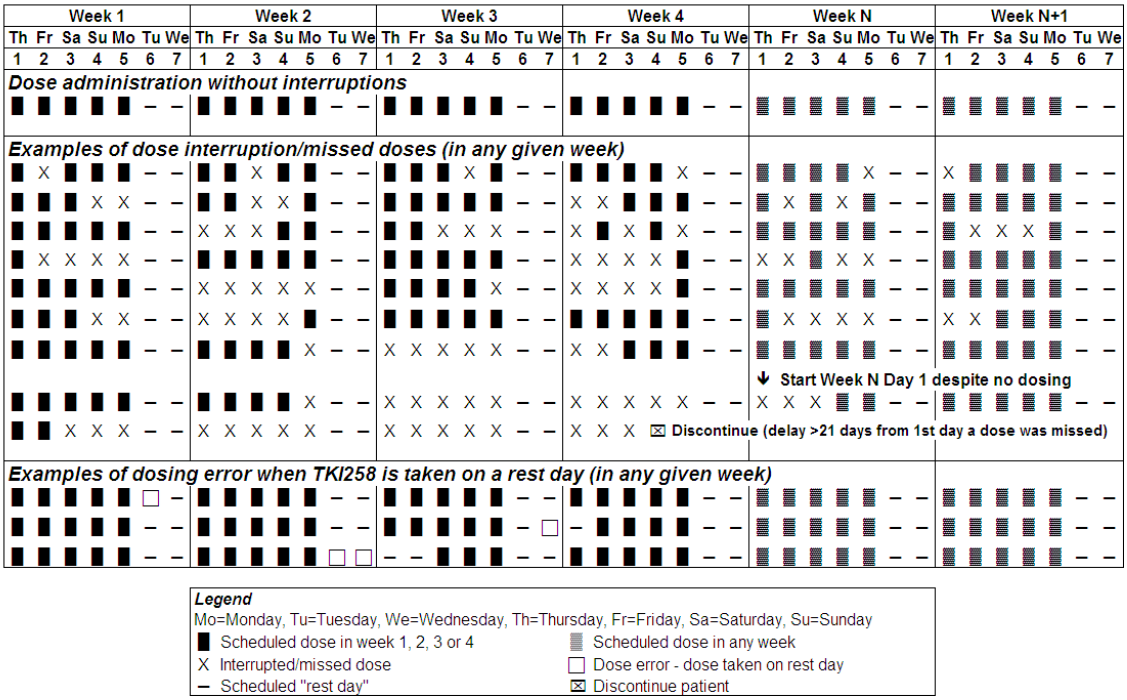
Figure 6-1 provides a general guideline of how treatment should be handled for dose interruptions, missed doses, and dose errors.

- During any given week, the study treatment is given on 5 days on/2 days off schedule.
- As soon as dosing can be resumed, every effort should be made to return to the original 5 days on/2 days off dosing schedule. Dosing should resume on the next day of planned dosing and dosing should be suspended on the days of rest (Day 6 and Day 7).
- In the case of dosing errors (e.g., if the study treatment is taken on the days of rest [Day 6 or Day 7] of a given week
    - For example, if the patient takes an additional dose on Day 6 of a given week, then the patient will rest on Day 7, and then will continue with the 5 days on/2 days off dosing schedule starting on Day 1 of the following week.
    - If the patient takes an additional dose on Day 7, then the patient should skip Day 1 of the following week and restart dosing the next day (Day 2) of the following week and

continues to take the doses intended for Days 3, 4 and 5 of that week and will rest on Day 6 and Day 7.

- If the patient takes additional doses on Day 6 and Day 7, then the patient will skip Day 1 and 2 of the following week and restart dosing on Day 3 of the following week and continues to take the doses intended for Day 4 and Day 5 of that week and will rest on Day 6 and Day 7.

Figure 6-1 Example of treatment schedule, and permitted schedule adjustments



Criteria for interruption and re-initiation of Dovitinib treatment

If the administration of dovitinib must be interrupted because of an unacceptable toxicity, dovitinib dosing will be interrupted or modified according to rules described in Section 6.3.1 and Table 6-3. A patient who requires a dose interruption (regardless of the reason for the interruption) lasting >21 days (counting from the first day when a dose was missed) must discontinue the study treatment.

Table 6-3 Dovitinib related toxicity management guidelines

Toxicity intensity [a]	**Dose modification** [b, c]
Amylase and/or lipase elevations	
Asymptomatic Grade 1, 2 or 3	Maintain dose level
Asymptomatic Grade 4	Patients who develop grade 4 hyperlipasemia or hyperamylasemia without clinical or other evidence of pancreatitis should delay study treatment until resolved to ≤ grade 3, then re-start at the current dose level

Toxicity intensity [a]	Dose modification [b, c]
Cardiovascular	
Left ventricular systolic dysfunction	
Left ventricular ejection fraction (LVEF) ≥ 50%/LLN (ECHO), or ≥ 45%/LLN (MUGA)	Maintain dose level
LVEF < 50%/LLN (ECHO), or < 45%/LLN (MUGA), or Symptomatic due to drop in ejection fraction responsive to intervention	Delay study treatment until resolved to ≥ 50%/LLN (ECHO) or ≥45%/LLN (MUGA), then ↓ 1 dose level
Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support or heart transplant indicated	Discontinue study treatment
Other cardiovascular	
Grade 1 or 2	Maintain dose level
Grade 3	Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4	Discontinue study treatment
Gastrointestinal	
Diarrhea	At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated according to institutional standard of care
Grade 1 (despite maximal anti-diarrheal medication)	Maintain dose level
Grade 2 (despite maximal anti-diarrheal medication)	Delay study treatment, until resolved to ≤ grade 1, then re-start at the current dose level If diarrhea returns as ≥ grade 2, then suspend dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 3 or 4 (despite maximal anti-diarrheal medication)	Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level
Nausea	Suspend dose for CTCAE grade 2-3 nausea only if it could not be controlled despite the use of standard anti-emetics.
Grade 1 (despite standard anti-emetics)	Maintain dose level
Grade 2 (despite standard anti-emetics)	Delay study treatment, until resolved to ≤ grade 1, and then re-start at the current dose level. If nausea returns as ≥ grade 2, then suspend dose until resolved to ≤ grade 1, then ↓ 1 dose level.
Grade 3 (despite standard anti-emetics)	Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level
Vomiting	Suspend dose for CTCAE grade 2-4 vomiting only if it could not be controlled despite the use of standard anti-emetics.
Grade 1 (despite standard anti-emetics)	Maintain dose level
Grade 2 (despite standard anti-emetics)	Delay study treatment, until resolved to ≤ grade 1, and then re-start at the current dose level. If nausea returns as ≥ grade 2, then suspend dose until resolved to ≤ grade 1, then ↓ 1 dose level.
Grade 3 or 4 (despite standard anti-emetics)	Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level
Hand-foot syndrome	
Grade 1 or 2	Maintain dose level
Grade 3	Delay study treatment until resolved to ≤ grade 1 then ↓ 1 dose level
Grade 4	Discontinue study treatment

Toxicity intensity [a]	**Dose modification** [b, c]
Hematologic	
Febrile neutropenia (Grade 3 or 4) (Per protocol) fever of unknown origin without clinically or microbiologically documented infection (ANC <1.0 x 10^9/L, fever ≥ 38.5°C)	Delay study treatment until resolved, then ↓ 1 dose level
≥ Grade 3 anemia judged to be a hemolytic process secondary to study treatment	Discontinue study treatment.
≥ Grade 3 lymphopenia considered clinically significant	Requires dose interruption until resolved to ≤ grade 1, then ↓ dose level.
Neutropenia /Neutrophil count decreased	
Grade 1 or 2	Maintain dose level
Grade 3 Grade 4	Delay study treatment until resolved to ≤ grade 2, then: If resolved by ≤ 7 days after suspending dovitinib, maintain dose level If resolved by > 7 days after suspending dovitinib, ↓ 1 dose level
Thrombocytopenia / Platelet count decreased	
Grade 1 or 2	Maintain dose level
Grade 3	Delay study treatment until resolved to ≤ grade 1, then: If resolved by ≤ 7 days after suspending dovitinib, maintain dose level If resolved by > 7 days after suspending dovitinib, ↓ 1 dose level
Grade 4	Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level
Pancreatitis	
Grade 1 or 2	Maintain dose level
Grade 3 or 4	Discontinue study treatment
Renal	
Serum creatinine	
Grade 1 or 2	Maintain dose level
Grade 3	Delay study treatment until resolved to ≤ grade 1 or baseline, then ↓ 1 dose level
Grade 4	Discontinue study treatment
Other clinically significant adverse events	
Grade 1 or 2	Maintain dose level
Grade 3 (except hyperlipidemia[d])	Delay study treatment until resolved to ≤ grade 1 or baseline, then maintain dose level or ↓ 1 dose level at the discretion of the investigator
Grade 4	Delay study treatment until resolved to ≤ grade 1 or baseline, then ↓ 1 dose level or discontinue dovitinib at the discretion of the investigator
All dose modifications should be based on the worst preceding toxicity.	
[a] Common Terminology Criteria for Adverse Events (CTCAE)) v4.0	
[b] Patients are allowed two dose reductions: a dose reduction from 400 mg to 300 mg, and, if necessary, a dose reduction from 300 mg to 200 mg.	
[c] If a patient requires a dose interruption of > 21 days starting from the first day a dose was missed, then the patient must be discontinued from the study treatment. Patients who discontinue the study treatment for a study related adverse event including an abnormal laboratory value must be followed at least once a week for 28 days and subsequently at 28 days intervals until resolution or stabilization of the event, whichever comes first.	

Toxicity intensity [a]	Dose modification [b, c]
[d] Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using standard therapies. Fluvastatin and Rosuvastatin may have potential of drug to drug interactions with dovitinib, and other statins may interact with abiraterone acetate. If statins are prescribed, close clinical monitoring including serum lipids is required since dovitinib could reduce the exposure of statins. Statins should be prescribed according to product label/data sheets for HMG-CoA reductase inhibitors. Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state. Grade 2 or higher hypercholesterolemia or Grade 2 or higher hypertriglyceridemia should be treated with fibrate, or appropriate lipid-lowering medication in addition to diet.	
[e] LFTs include albumin, GGT, ALT, AST, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated [quantification of isoenzymes], if alkaline phophatase ≥ Grade 2).	

6.4 Permitted Concomitant Therapy

6.4.1 CYP450 inducers, inhibitors and substrates

Dovitinib and abiraterone acetate have not yet been given together. Dovitinib is metabolized mainly by CYP1A1/2 and FMO, while abiraterone acetate is metabolized mainly by CYP3A4 and SULT2A1. Thus, the potential for drug interaction when administering both drugs at the same time is relatively low.

Though no drug interactions have been studied clinically, drugs that inhibit (ciprofloxacin, clinafloxacin, enoxacin, fluvoxamine, oltipraz, propranolol, rofecoxib, thiabendazole, and zafirlukast) or induce CYP1A1/2 (omeprazole and tobacco) may interact with dovitinib and should be used with caution.

In vitro, dovitinib has a potential to induce CYP1A2 activity 2- to 14-fold, as well as CYP2C9 and CYP2C19 activity to a lesser extent (< 3- to 4-fold). Therefore, CYP1A2, CYP2C9, and CYP2C19 substrates listed below should also be used with caution (list is not all-inclusive):

- CYP1A2 substrates: clozapine, cyclobenzaprine, imipramine, mexiletine, naproxen, riluzole, tacrine,and theophylline.
- CYP2C9 substrates: losartan, irbesartan, diclofenac, ibuprofen, piroxicam, tolbutamide, glipizide, celecoxib, fluvastatin, naproxen, phenytoin, rosiglitazone, sulfamethoxazole, tamoxifen, tolbutamide, torsemide, and warfarin.
- CYP2C19 substrates: diazepam, phenytoin, phenobarbital, lansoprazole, omeprazole, pantoprazole, rabeprazole, amitriptyline, clomipramine, clopidogrel, cyclophosphamide and progesterone.

It is recommended to avoid concomitant medications that are known to cause hepatotoxicity.

Patients should also avoid use of St. John's Wort and should not consume grapefruit juice while receiving treatment with dovitinib.

Oral contraceptives are generally metabolized by CYP3A4/2C9, and also act as a moderate inhibitor of CYP1A2, therefore should not be used. Thus, patients who are sexually active and are using oral contraceptives as a method of contraception should change to other highly effective contraceptive methods during the study participation.

6.4.2 Effects of Abiraterone acetate on Drug Metabolizing Enzymes

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

In vitro, abiraterone acetate was shown to inhibit the hepatic drug-metabolizing enzyme CYP2C8. There are no clinical data on the use of abiraterone acetate with drugs that are substrates of CYP2C8.

Drugs that Inhibit or Induce CYP3A4 Enzymes:

Based on *in vitro* data, abiraterone acetate is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during abiraterone acetate treatment.

A comprehensive list of drugs that may interact with the pathways discussed above may be found at the following web address: http://medicine.iupui.edu/flockhart

6.4.3 Permitted Treatments during the Study Include, but are not limited to the Following:

- Nausea management: consistent, prophylactic use of antiemetics, and Zofran and the newer centrally acting agents is recommended for nausea management.
- Pain medication to allow the patient to be as comfortable as possible.
- Localized radiotherapy and treatment with bisphosphonates for pre-existing, painful bone metastases is permitted only if evidence of radiological progression is not present. Treatment with bisphosphonates must begin before the study treatment is initiated.
- Nutritional support or appetite stimulants (e.g. megestrol).
- Oxygen therapy and blood products or transfusions.
- Prophylactic anti-emetics are allowed for patients who, at the discretion of the investigator, have experienced ≥ grade 1 nausea or vomiting.
- Hematopoietic growth factors should be used according to the guidelines established by the American Society of Clinical Oncology (ASCO) or as dictated by local practice. The ASCO guidelines are available [http://jco.ascopubs.org/cgi/content/full/24/19/3187].
- The administration of anticoagulation and antiaggregation agents (e.g. eptifibatide, epoprosterol, dipyridamole, fondaparinix) should be allowed except prasugrel, due to its

potential drug-drug interaction with dovitinib. Prasugrel is primarily metabolized by the CYP3A4 and CYP2B6 and to a lesser extent by the CYP2C9 and CYP2C19. Co-administration of dovitinib (an inducer of CYP2C9 and CYP2C19) with prasugrel is likely to reduce the exposure of prasugrel.

- Caution should be employed when prescribing statin drugs as they may interact with both study agents.

6.4.4 The Following Concomitant Treatments are Not Allowed during the Study:

- Concurrent use of isoniazid, labetalol, tolcapone, and felbamate are not permitted, since alternative less hepatotoxic drugs are available to use.
- Concurrent use of other investigational drugs is not permitted
- The administration of other antineoplastic therapy (e.g. chemotherapy, hormone therapy other than LHRH agonist/antagonists, immunotherapy, targeted therapy, monoclonal antibodies and radiation therapy) is not permitted. Patients requiring radiation therapy after the start of the study are considered as having progression of disease and must discontinue study treatment. Palliative radiation for local peripheral metastases is allowed, but the need for such therapy may be an indication of disease progression and should be discussed with Novartis prior to administration.

Important reminders:

- All medications and non-drug therapies (including physical therapy, oxygen and blood transfusions) administered to the patient prior to (within 30 days of the first dose of study drug) or during the course of the study, and until 30 days after the last dose of study drug should be documented.
- In addition to receiving the study treatment, all patients should receive best supportive care (BSC), as per standard local practice for the treatment of pre-existing medical conditions or adverse events that may arise during the study. BSC is defined as drug or non-drug therapies, nutritional support, physical therapy or any other treatment alternative that the investigator believes to be in the patient's best interest, but excluding other antineoplastic treatments.
- Patients must be instructed not to take additional medications (including over-the-counter products and herbal/alternative medications during the study without prior consultation with the investigator.
- Patients taking chronic medications should be maintained on the same dose and schedule throughout the study period, if medically feasible and the drugs noted on the CRF.

10 Statistical Methods and Data Analysis

This is a single arm, open label, phase II trial with a primary objective to assess the safety and tolerability of dovitinib (TKI258) plus Abiraterone Acetate in patients with Metastatic Castrate-Resistant Prostate Cancer (mCRPC). Secondary objectives are to assess progression-free survival and overall survival in treated patients.

A maximum of 60 patients will be enrolled in the study at an estimated accrual rate of 3 patients per month. The sample size and power calculation are based on the change of gene expressions (i.e. AR, CYP17, FGFR1) or soluble CAF (e.g. FGF23) before and after therapy, which can be characterized based on effect size (i.e. mean difference of gene expression or

CAF divided by the standard deviation). Considering subjects with baseline and Week 8 laboratory results derived from bone marrow samples, a sample of 30 subjects provides 82% power to detect a change of gene expression or CAF with an effect size of at least 0.55, using a two sided paired t-test, at a 0.05 significance level. A total of 60 subjects will be accrued to obtain at least 30 evaluable patients based on the prediction that the yield of evaluable bone marrow samples with prostate cancer cells is approximately 50%. nQuery Advisor 7.0 was used for this sample size calculation.

With a total sample size of 60, if the trial did not stop early and if we observe 12 patients with grade 3 or greater toxicities, then the posterior 95% credible interval of the estimated toxicity rate is (0.12, 0.32) , assuming a prior of beta(1,1).

Safety monitoring:

Toxicity is defined as grade 3 or greater toxicities related to the treatment during the treatment course. It will be monitored using the method of Thall, Simon, and Estey [17]. Historical data showed that the rate of drug related grade 3 or greater toxicities was approximately 20%. A non-informative flat prior distribution of Beta (1, 1) was chosen for the toxicity rate of the combination therapy in this study.

The interim monitoring will be first conducted after the first 5 patients have been evaluated, and will be implemented in cohort size of 5. The monitoring rule for toxicity is $Pr(qE, Tox > 0.2| data) > 0.95$, where qE, Tox is the proportion of any grade 3 or greater toxicities. That is, the trial will be terminated if there is a more than 95% chance that the average rate of grade 3 or greater toxicities is more than that of historical control.

The stopping boundaries corresponding to this toxicity monitoring rule are shown in Table 1. For example, accrual will be stopped if all 3 or more patients experience toxicities among the first 5 patients treated, or if 5 or more patients experience toxicities in the first 10 patients.

The operating characteristics are summarized in Table 2. Multc Lean Desktop (version 2.0.0) was used to generate the toxicity stopping boundaries and the OC table. In order to utilize the software for the design, a beta (200,800) prior was assumed for the historical control toxicity rate, which is a close approximation to a fixed 20% toxicity rate, as specified in the stopping rule.

Table 1. Toxicity stopping boundaries.

Number of patients evaluated (in cohorts of 5)	**Stop the trial if number of patients with grade 3 or greater toxicities is**
5	3-5
10	5-10
15	6-15
20	7-20

25	9-25
30	10-30
35	11-35
40	13-40
45	14-45
50	15-50
55	16-55

Table 2. Operating characteristics for toxicity monitoring among all 60 patients.

True toxicity rate	Prob(stop the trial early)	Average sample size
0.10	0.012	59.4
0.15	0.058	57.3
0.20	0.196	52.2
0.25	0.453	43.1
0.30	0.731	32.4
0.35	0.909	23.1
0.40	0.980	16.7

Futility monitoring:

The Bayes factor single arm time-to-event model by Johnson & Cook [18] will be used to monitor the time to progression. Based on historical data, the median progression-free survival time for the standard of care is 4.0 months (mean TTE = 5.77 months), and we expect that the treatment would prolong the median progression-free survival to be 6 months (mean TTE = 8.66 months). Using this Bayesian hypothesis test-based design, we assume the median progression-free survival time is 4.0 months under the null hypothesis (H0), and the median progression-free survival time is 6 months under the alternative hypothesis (H1).

We assume that the sample distribution of progression-free survival time follows an exponential distribution, and use an inverse moment prior for mean progression-free survival time under the alternative hypothesis. A monthly accrual rate of 3 patients per month is assumed for the design.

Stopping Rules:

We implement one stopping rules during the trial, that is we will stop the trial for inferiority if the posterior probability of the alternative hypothesis is less than 0.06, i.e. $Pr(H1|Data) < 0.06$.

Operating Characteristics:
The operating characteristics of the design were produced using the MD Anderson Cancer Center Department of Biostatistics software **BayesFactorTTE**, version 1.1.

Table 3: Operating characteristics for Futility monitoring

Simulation Results

Scenario	True median (mean) TTE	Pr(Stopping for H0)	Average # patients treated (10%, 25%, 50%, 75%, 90%)
1	3 (4.33)	0.996	27.2 (17, 20, 25, 33, 40)
2	4 (5.77)	0.754	41.31 (22, 29, 40, 60, 60)
3	6 (8.66)	0.062	58.55 (60, 60, 60, 60, 60)
4	7 (10.1)	0.014	59.63 (60, 60, 60, 60, 60)

Note:H0 = null hypothesis; H1 = alternative hypothesis

For example, if the true median PFS time is 4.0 months (Scenario 2, the null hypothesis), the trial will stop with a probability of 75.4% in favor of the null hypotheses. The average number of patients (10%, 90%) treated is 41.31 (22, 60). If the true median PFS time is 6 months (Scenario 3, the alternative hypothesis), the trial will stop with a probability of 6.2% in favor of the null hypotheses. The average number of patients (10%, 90%) treated is 58.55 (60, 60).

Stopping Boundaries:

The entire simulation output from BayesFactorTTE is attached as the Appendix, including stopping boundaries for inferiority. The futility monitoring will be conducted through the Clinical Trial Conduct website (https://biostatistics.mdanderson.org/ClinicalTrialConduct/) maintained by the Department of Biostatistics. The Clinical Trial Conduct website resides on a secure server, and access is gained through usernames and passwords provided to personnel responsible for enrolling patients and updating patient data.

Trial Conduct:

Analysis

Unless otherwise specified, categorical variables will summarized as counts and percentages, and continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum). To evaluate the safety endpoint, the incidence rate of grade 3 or greater toxicities will be estimated, along with the 95%

credible interval. For the efficacy endpoint of PFS, we will calculate the Bayes factor, which represents the odds in favor of the alternative hypothesis. We will also use the Kaplan-Meier method to estimate the probabilities of PFS and OS. For exploratory purpose, we will use paired t-test to assess the biomarker change between baseline and 8-week post treatment. Cox proportional hazards regression models will be fit to assess the association between biomarker change and the efficacy endpoints of PFS and OS.

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