Study Title: An Observational Study of TKI258 in Castration-Resistant Prostate Cancer Patients Evaluating Markers of FGF signaling in Bone Marrow Plasma.

Study Phase: Phase II Exploratory

Product Name: TKI 258

IND Number: 104,602

Indication: Castration-Resistant Prostate Cancer

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SYNOPSIS

Name of Finished Product:
TKI 258

Study Title:
An Observational Study of TKI258 in Castration-Resistant Prostate Cancer Patients Evaluating Markers of FGF signaling in Bone Marrow Plasma.

Study Phase: Phase II Exploratory

Primary Objective:

- To estimate overall survival and early response as characterized by a drop in PSA
- To identify the PSA modulation in 40 selected patients with advanced prostate cancer, and correlate PSA Modulation with changes in bone remodeling markers

Secondary Objective(s):

- To estimate the objective tumor response rate by RECIST criteria for subjects with measurable disease at baseline.
- To explore the potential association between serum PSA and bone turnover markers with bone marrow FGF R1 and FGF9 while on TKI 258
- To explore the predictive values of baseline FGF R1, FGF9, and FGF signaling in serum and those in the bone marrow before and during treatment with TKI258.
- To identify candidate mRNA gene expression changes in bone marrow biopsy aspirates following treatment with TKI258
- To collect and archive bone marrow biopsies and aspirates, serum and plasma in study patients for later hypothesis generating associations
- To explore FGF R expression following eight weeks of TKI 258

Study Design:
This is an observational study to explore the effect of TKI258 therapy on bone turnover markers (serum bone specific alkaline phosphatase and urinary N-telopeptides), and expression of FGF R 1, on both tumor and host cell compartments in bone marrow.

Study Population:
Approximately 40 patients are planned for enrollment.

Test Product, Dose, and Mode of Administration:
TKI258 500mg PO daily for 5 days, followed by a 2 day rest period. Each cycle is 28 days.

Duration of Treatment:

Patients will continue to receive TKI 258 until progression, unacceptable toxicity or withdrawal of consent

Statistical Methods:
This is a phase IIA activity trial of TKI 258 for treatment of castrate resistant prostate cancer with skeletal metastases. The two primary outcomes are survival time and early response as characterized by a drop in PSA as defined by Prostate Cancer Working Group 2 criteria. Based on a historical mean survival of time 8 months, a mean survival time on average > 10 months with TKI258 would be considered promising evidence of anti-disease activity. The planned sample size is 40 patients, with an anticipated accrual rate of 3

patients per month. Based on historical experience using carefully selected candidates with evidence for iliac involvement on bone scan, we anticipate that ~60% of patients will have positive biopsies. No early stopping rule in terms of the probability of PSA response will be employed because blocking the stromal-epithelial interactive pathway (SE-pathway) may produce clinical benefit independent of PSA modulation. Consequently, it may be the case that TKI258 does not cause significant reductions in PSA, but survival time is prolonged due to inhibition of disease progression. Given the short survival time of these patients and anticipated accrual rate of 3 patients per month, it also will not be feasible to implement an early stopping rule in terms of observed survival times. Based on an historical rate of 20% grade 3 or 4 toxicity with standard therapies the method of Thall and Sung (1998) will be used to monitor toxicity.

Unadjusted survival time will be estimated using the method of Kaplan and Meier (1958) and the effects of the following four potential prognostic covariates Inhibition of FGF signaling by bone marrow biopsy at 8 weeks, modulation of the bone markers (a) urinary NTX and (b) bone specific alkaline phosphatase, and baseline signature of FGF signaling in terms of FGF R-1, FGF R-3 and FGF 9 on Prob(PSA response) will be estimated using logistic regression, and on survival time will be estimated using the Cox model or an appropriate time-to-event regression model.

Preliminaries: This is a phase IIA activity trial of TKI258 for treatment of castrate resistant prostate cancer with skeletal metastases. The two primary outcomes are survival time and early response as characterized by a drop in PSA as defined by Prostate Cancer Working Group criteria (25).

Historical Experience and Goals: Based on the historical experience in which the mean survival time was 8 months, under a Bayesian model we assume that the unadjusted mean survival time with TKI258 follows an uninformative inverse gamma with mean 8 and variance 1000, equivalently with scale parameter 2.064 and shape parameter 8.512, denoted mE ~ IG(2.064, 8.512). A mean survival time on average > 10 months would be considered promising evidence of anti-disease activity. Formally, assuming that the historical mean survival mH ~ IG(52, 400), TKI258 will be considered promising if, based on the data from the trial, $Pr(mE > mH \mid data) > .95$. The planned sample size is 40 patients, with an anticipated accrual rate of 3 patients per month. In addition, the relationships between several potential prognostic covariates and the above clinical outcomes will be explored, as described below.

Monitoring Rules: No early stopping rule in terms of the probability of PSA response will be employed because it is not known whether blocking the stromal-epithelial interactive pathway (SE-pathway) will be related to clinical benefit. Consequently, it may be the case that PSA does not drop but survival time is prolonged due to inhibition of disease progression by TKI258. Given the short survival time of these patients and anticipated accrual rate of 3 patients per month, it will not be feasible to implement an early stopping rule in terms of observed survival times. However, based on an historical rate of 20% grade 3 or 4 toxicity with standard therapies, it will be assumed that p = Prob(grade 3 or 4

with TKI258) follows a beta prior with parameters (.20, .80). Using the method of Thall and Suung (26), based on the observed toxicity data, accrual to the trial will be stopped early if Pr(p > .20 | data) > .95, with this rule applied after successive cohorts f size 5. This rule says to stop the trial if [# patients with a grade 3 or 4 toxicity]/[# patients evaluated] is greater than or equal to 3/5, 5/10, 7/15, 8/20, 9/25, 11/30, 12/35.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANOVA	Analysis of variance
AP	Alkaline phosphatase
AST	Aspartate aminotransferase (SGOT)
bid	Twice daily
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Cell blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DHA	Directions for Handling and Administration
DHEA	Dihydroepiandrosterone
DHT	Dihydrotestosterone
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
FGF R	Fibroblast Growth Factor Receptor
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
Hct	Hematocrit
HEENT	Head, Eyes, Ears, Nose, Throat
Hgb	Hemoglobin

HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
LDH	Lactic dehydrogenase
LHRH	Luteinizing hormone-releasing hormone
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NDA	New Drug Application
PSA	Prostate Specific Antigen
qd	Once daily
qid	Four times daily
RBBB	Right bundle branch block
RBC	Red blood cell (count)
RH	Relative humidity
RTK	Receptor Tyrosine Kinase
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SSRIs	Serotinin reuptake inhibitors
tid	Three times daily
US	United States
WBC	White blood cell (count)

1.0 INTRODUCTION

1.1 Receptor Tyrosine Kinsases (RTKs) are involved in both 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 members of the RTKs are expressed on solid tumors and are involved in cancer cell growth and survival **(Collett and Erikson 1978; Takahaski, et al 1995)**. In some cases, mutations of these RTKs and their subsequent aberrant signaling are directly linked to the abnormal growth **(Mizuki, et al 2000; Deininger, et al 2000)**. In many other cases, expression and/or overexpression of these RTKs have been demonstrated; however, the exact role of these kinases in driving most cancerous growth is still unknown. Some tumors, however, are known to have their growth driven by a single mutation in a growth factor receptor kinase. These include FLT3 mutations in 20% to 30% of patients with AML **(Gilliland and Griffin 2002);** FGFR3 ectopic expression/mutation in 15% to 20% of patients with multiple myeloma **(Rasmussen, et al. 2003; Li, et al 2001)**; 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 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).** A recent publication has demonstrated that a 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 antitumor effects. TKI258 is a potent inhibitor of these three RTKs as well as other RTKs directly involved in tumor cell growth, particularly activating mutations of c-KIT and FLT3. Nonclinical studies were conducted with TKI258 free base or its lactate, mesylate, or hydrochloride salts. For consistency, these forms are collectively referred to as TKI258 in this document.

As mentioned above, the pathways and growth factors involved in angiogenesis and tumor cell growth are very complex and in many cases redundant. The first generation receptor kinase inhibitors to undergo clinical trials were in many cases specific inhibitors of a single receptor kinase. Compounds such as gefitinib (Iressa®) (EGFR), SU5416 (VEGF), and PTK787 (VEGF) are examples of some of the earlier, single targeted kinase inhibitors **(Arteaga 2003; Dancey and Sausville 2003).** A second generation kinase inhibitor, SU6668, hits a variety of kinase targets, including PDGFR, VEGFR, and FGFR. Other drug candidates such as ZD6474 (vandetanib),

SU11248 (sunitinib), and BAY43-9006 (sorafenib) were later developed to have activity against a variety of growth factor receptor kinases. Sunitinib (Sutent®) and sorafenib (Nexavar®) have recently been approved for the treatment of advanced renal cell carcinoma, an indication with a high level of VEGF-induced angiogenesis. Sunitinib was also approved in refractory GIST, a tumor type driven by activating mutations in c-KIT. The approval of these drugs provides clinical rationale for the development of additional multi-targeted receptor tyrosine kinase inhibitors with different target profiles. TKI258 is from a novel chemical series, inhibits multiple cancer or angiogenesis related kinases, and has favorable physicochemical and PK properties. TKI258 has potent activity in a variety of nonclinical tumor xenograft and targeted-tumor or angiogenesis animal models.

1.2 Background /Rationale

Androgen deprivation (AD) therapy induces a remission in 80% to 90% of patients with advanced prostate cancer and results in a median progression-free survival of 12 to 33 months, at which time; an androgen-independent phenotype usually emerges.

Androgen deprivation can be achieved surgically with orchiectomy, or medically using some form of drug treatment that lowers serum testosterone. Medical castration is commonly achieved with luteinizing hormone - releasing hormone (LHRH) agonists (for example, Lupron). The conventionally accepted definition of castration is a serum concentration of testosterone to less then 50 ng/dl. Additional anti-androgen therapies include classes of agents that: (1) block testosterone activity (for example, bicalutimide), (2) block adrenal synthesis of testosterone (for example, ketoconazole); or (3) synthetic estrogens (for example, DES). These agents are generally used to treat patients who demonstrate PSA and/or clinical progression while on Lupron monotherapy. Because many cancers continue to respond to these "second-line" hormonal strategies (given either singly or in combination) despite castrate levels of testosterone, this clinical state is referred to "castrate-resistant" disease (as opposed to "hormone-refractory" disease).

After failure of anti-androgen therapy, patients with castrate-resistant prostate cancer are routinely treated with cytotoxic chemotherapies. Two randomized trials testing docetaxel based regimens demonstrated PSA responses ranging from 40 to 50% but only a modest survival benefit of ~ 2 to 3 months. Chemotherapy was also associated with significant toxicities, including grade 3/4 neutropenia (~30%), infections (~6%), anemia (~5%), fatigue (~5%), dyspnea (~3%), nausea (~3%), diarrhea (~2%) and neuropathy (~1.5%). Based on these data, docetaxel-based chemotherapy is an option for patients with castrate-resistant disease but is not considered "standard of care". Current research efforts are now focused on identifying novel molecularly targeted therapies that will reduce morbidity and mortality from castrate-resistant disease and obviate (or at least delay) the use of cytotoxic chemotherapy.

The propensity for prostate cancer to metastasize to the skeleton has led investigates to speculate that the tumor microenvironment and the stromal-epithelial interactions within bone are critical for prostate cancer progression. Furthermore, the development

of castrate resistant disease is almost invariably associated with some extent of tumor infiltration into the bone marrow. There is evidence of increased expression of androgen converting genes in the castrate-resistant bone marrow tumor microenvironment.

MD Anderson Experimental observation:
We recently discovered that prostate cancer cells, especially those that had metastasized to bone, overexpress fibroblast growth factor 9 (FGF9), a discovery that prompted us to study how FGF9 participates in prostate cancer progression and metastasis. FGF9 (also known as glial activating factor) is a secreted, glycosylated 26-kDa protein that has mitogenic effects on a variety of different cell types. In the normal prostate, FGF9 is not expressed by prostate epithelial cells, but is expressed by prostate stroma cells [21]. We have recently found positive staining for FGF9 in prostate cancer cells in 24 of 56 primary tumors derived from organ-confined prostate cancer and in all the bone metastases cases studied (25 of 25) (Table 1 and Figure 1). Findings were confirmed by RT-PCR analysis of RNA obtained by laser capture microdissection of normal prostate epithelial cells and prostate cancer epithelial cells derived from two bone metastases (Figure 1a). This switch in the source of FGF9 from the stroma to the cancer cells could increase the availability of FGF9, thereby favoring prostate cancer growth or survival at metastatic sites **(Li, et al. 2008)**.

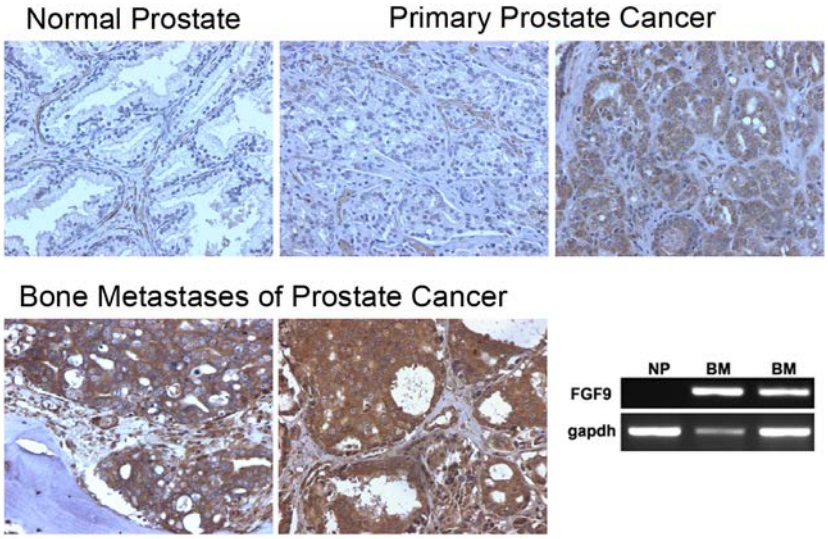


Figure 1a. Fibroblast growth factor 9 (FGF9) expression in a normal prostate and prostate cancer. Upper panels and lower left and middle panels, immunohistochemical staining with antibody to FGF9 in normal prostate, two cases of organ confined primary prostate cancer (one positive and one negative for FGF9 expression) and two cases of bone metastases of prostate cancer. Original magnification 200x. Lower right panel, reverse-transcription polymerase chain reaction analysis of FGF9 expression in normal prostate (NP) and two case of bone metastases of prostate cancer (BM). gapdh - glyceraldehyde-3-phosphate dehydrogenase.

To obtain preclinical evidence of the role of FGF9 in the osteoblastic progression of prostate cancer cells in bone, we used a new prostate cancer xenograft (MDA PCa 118b) derived from a bone metastases in a man with castrate resistant prostate cancer. MDA PCa 118b cells, which express high FGF9 levels, induce the proliferation of cocultured osteoblasts *in vitro* and can grow and induce a strong osteoblastic reaction in the bone of immunodeficient mice. We found that MDA PCa 118b–induced osteoblast proliferation *in vitro* was blocked by FGF9 antibody and that FGF9 induced the formation of new bone in an organ-culture assay. To assess *in vivo* the relevance of FGF9 in the osteoblastic bone growth of this model, we examined the effect of blocking FGF9 signals in mice injected with MDA PCa 118b cells into their femurs. We injected MDA PCa 118b ($1X10^6$) cells into the femurs of 20 SCID male mice. Ten mice were treated with neutralizing antibody against FGF9 (R&D (Clone 36912), 250 µg/mouse) i.v. twice weekly and another 10 mice were treated with IgG isotype (R&D, 250 µg/mouse) i.v. twice weekly. Treatment started the same day of cell injection and was performed for five consecutive weeks at which time tumor volumes in the femurs were determined by MRI analysis following established procedures [22]. MRI analysis of MDA PCa 118b tumors five weeks after cell injection demonstrated that the mice treated with FGF9 neutralizing antibody developed significant smaller tumors than controls did (P=0.011, Figure 1b). In order to assess whether the MDA PCa 118 induced bone reaction was also affected by FGF9 blockade, we subsequently monitor the tumor associated bone mass by weekly X-ray analysis and terminated the experiment 7 weeks after cell injection (2 weeks post end of treatment). We then performed specimen micro CT analysis (20 µm resolution) of tumor bearing bones and found a significantly lower bone volume in the femur of treated than in control mice (P=0.0057). Accordingly, histological analysis of tumor bearing bones demonstrated areas of woven bone in control but not in treated femurs (Figure 2). Taken together, these results suggest that FGF9 plays an important role in the osteoblastic progression of prostate cancer cells in bone **(Li et al. 2008)**.

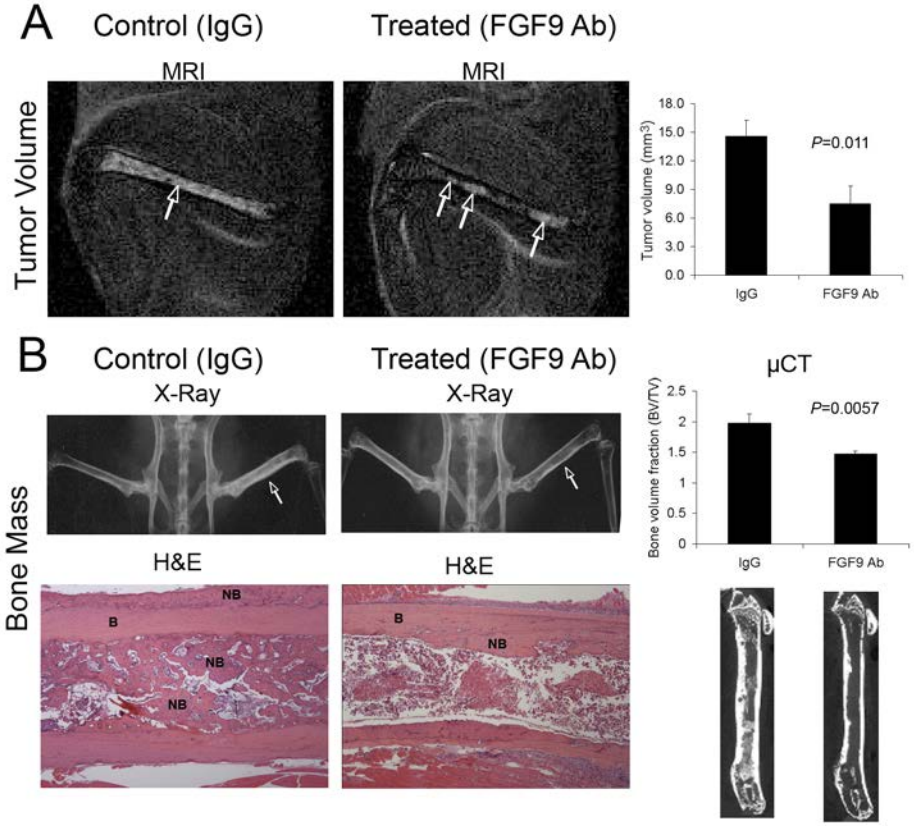


Figure 1b. Effects of FGF9 blockade on MDA PCa 118b bone growth and osteoblastic reaction *in vivo*. (**A**) Tumor volume. MDA PCa 118b tumor visualized and quantified by T2-weighted, fat suppressed MR. **Left and middle panels**: Representative axial MR images of mice injected with MDA PCa 118b cells in the femur and obtained after five weeks of treatment with FGF9 neutralizing antibody or IgG isotype. Arrows indicate tumor. Tumors were confined to the bone, spreading throughout the femur area in the IgG treated mice (control) and scattered in the bone area in the mice treated with FGF9 neutralizing antibody. **Right panel:** Volumes of regions of increased signal in the MDA PCa 118b injected femur measured by MR after five weeks of treatment were significantly higher in the control than in the treated mice (*P*=0,011). (**B**) Bone mass. **X-Ray** - Radiographs show mouse pelvis and rear limbs of mice 7 weeks after intrafemoral injection of MDA PCa 118b cells in the control and treatment groups. Arrows indicate area illustrated in the lower panels (H&E). **H&E**. H&E–stained sections of MDA PCa 118b bearing femurs. Note that the marrow cavity is fill with new bone (NB) in the femurs of the control but not the treated mice M, bone matrix; NB, new bone.

μCT - Effect of FGF9 blockade on bone volume fraction. Lower panel, cross-sectional views of both control and tumor-bearing bones.

Prostate cancer is a characterized by a unique bone marrow. Castrate resistance is almost invariably associated with some extent of infiltration of the bone marrow.

1.3 Drug and Dosing Information

TKI258 (dovitinib lactate) is an investigational new drug initially discovered and developed under the name of CHIR-258 by Chiron Corporation, now part of Novartis. TKI258 inhibits receptor tyrosine kinases (RTKs) involved in solid and hematologic cancers, as well as tumor angiogenesis. Based upon its potency as an inhibitor of Class III/IV/V RTK signaling both *in vitro* and *in vivo*, and pharmaceutical properties including high oral bioavailability in three species, TKI258 is being studied in clinical trials as a cancer therapeutic.

TKI258 has *in vitro* inhibitory activity against vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and platelet derived growth factor (PDGF) receptor kinases with IC50 values of approximately 10 nM. These structurally related receptors are important for the growth and survival of endothelial cells during tumor angiogenesis; PDGFR and FGFR are also believed to play a role in the proliferation of certain tumor cells and supporting stromal cells. Based on growth factor specific cell based assays and kinase assays, additional kinases such as stem cell factor receptor (c-KIT), FMS like tyrosine kinase 3 (FLT3), colony stimulating factor 1 (CSF 1R), tyrosine receptor kinase A (TrkA) and the Ret oncogene are also inhibited *in vitro* with IC50s below 10 nM (for c-KIT, FLT3, TrkA and RET) and below 40 nM (for CSF 1R). c-KIT and FLT3 have been implicated to play a role in leukemias; CSF 1R has been implicated in the activation of osteoclast progenitor cells, initiating bone resorption in multiple myeloma, and other cancers that are associated with bone metastasis. Distantly related RTKs and most serine/threonine kinases were not inhibited by TKI258.

As a result of inhibition of RTKs by TKI258, cellular functions are blocked, including activation of downstream-signaling molecules, cellular proliferation, and survival. In cultured human endothelial cells expressing VEGFR, TKI258 inhibits VEGF stimulated mitogenesis. In a FGF2 dependent model of angiogenesis, TKI258 potently inhibited neovascularization of Matrigel plugs *in vivo* with an average ED50 of 3 mg/kg. The effects on endothelial cells suggest that TKI258 may have potent antiangiogenic activity. Additionally, direct antiproliferative effects were observed in cell lines; those cells that expressed an RTK inhibited by TKI258 were most sensitive to the drug (MV4;11: an acute myeloid leukemia [AML] cell line driven by constitutively active FLT3; TF 1: a AML cell line driven by c-KIT; KMS11: a multiple myeloma line driven by an activating mutation in FGFR3; RT112 and RT4 bladder cancer cell lines overexpressing FGFR3; and the colon cancer cell line KM12L4a, driven by TPM3-TRKA translocation). Antitumor effects for this agent may therefore be conferred by antiangiogenesis, antistromal activity, and antiproliferative activity directed against tumor cells that directly express TKI258 targets.

The antitumor activity of TKI258 was evaluated in a variety of tumor xenograft models in athymic mice. In all models tested, TKI258 administered orally caused anti-tumor responses, ranging from growth inhibition and stasis to regression in tumor models driven by activating mutations of TKI258 targets. Furthermore, in a model of

disseminated disease, colonization of breast cancer cells in the livers of mice from a subcutaneous (SC) xenograft primary was significantly reduced by oral treatment with TKI258. To demonstrate that direct inhibition of RTKs in tumors was a primary mechanism of xenograft growth inhibition by TKI258, tyrosine phosphorylation of VEGFR2, PDGFRβ, FGFR3 and the downstream-signaling proteins AKT (also known as protein kinase B) and ERK (also known as MAPK) was shown to be inhibited following a single oral dose of TKI258. Inhibition was observed up to 24 hours (h) in some models. These results indicate that TKI258 may be useful in the treatment of disseminated disease and leukemia, as well as solid tumors and myeloma. The broad target profile of TKI258 is likely to contribute to its efficacy in many different types of tumor models by acting on endothelial cells and tumor cells.

The safety of TKI258 was evaluated on a daily dosing schedule in rats, dogs, and monkeys. The dose-limiting toxicity in all animal species tested was gastrointestinal irritation reflected in emesis, diarrhea, severely decreased food consumption, and severe body weight loss. There were no target organs identified for clinical monitoring other than GI irritation. At severely toxic doses, morbidity was attributed to emaciation. Comparison of plasma exposure between species for assessment of a safety margin was confounded by the time-dependent reduction in plasma exposure of TKI258 (as assessed by maximum plasma concentration [Cmax] and area under the concentration time curve [AUC] values) following repeated oral administration. Therefore, body surface area-normalized dosing between species provided the most accurate prediction of safety.

TKI258 is manufactured for use in clinical trials as a 100mg hard gelatin capsule. As of 10 September 2010, there were a total of 420 patients enrolled in the nine Phase I and three Phase II single agent clinical studies: CTKI258A1101 (1101) (advanced solid tumors), CTKI258A2101 (2101) (advanced solid tumors), CTKI258A2102 (2102) (acute myeloid leukemia [AML]), CTKI258A2103 (2103) and CTKI258A2104 (2104) (multiple myeloma [MM]), CTKI258A2105 (2105) (locally advanced or metastatic melanoma), CTKI258A2106 (2106) (advanced solid malignancies,) CTKI258A2107 (2107) advanced/ metastatic renal cell cancer (RCC), CTKI258A2112 (2112) (Phase 1, Bioavailability - FMI capsules), CTKI258A2116 (2116) (Phase I, Bioavailability - FMI tablets), CTKI258A2202 (2202) (Phase II, metastatic breast cancer) and CTKI258A2204 (2204) (Phase II, multiple myeloma). Clinical studies 2101, 2102, 2103, 2104, 2105 and 2106 have been discontinued and the 1101, 2107, 2112, 2116, 2201, 2202 and 2204 studies are ongoing. The maximum tolerated dose (MTD) of TKI258 for the continuous daily dosing regimen was defined at 400 mg/day (study 2105); the MTD for the intermittent dosing regimen of 5 days on/2 days off was defined at 500 mg/day (study 2107). The MTD has not been established in Japanese population (dose escalation is still ongoing for study 1101).

Adverse events (AEs) and laboratory data (hematology and chemistry) were available from 382 patients as of 10 September 2010. The five most commonly reported non-laboratory AEs were nausea, fatigue/asthenia, diarrhea, vomiting and

anorexia/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 continuous dosing regimen studies, five patients (3.5%) had grade 4 hemoglobin values, 7 patients (7.4%) had grade 4 absolute neutrophil count (ANC) values, 19 patients (14.6%) had grade 4 platelet counts, and 9 patients (6.9%) had grade 4 WBC values during study participation. The relatively higher incidence rate of grade 3/4 hematology abnormalities in the continuous daily dosing regimen was mainly due to acute myeloid leukemia (study 2102) and multiple myeloma (studies 2103 and 2104) patients. In global 5 days on/2 days off dosing regimen studies, 2 patients (1.3%) had grade 4 ANC values, 1 patient (0.5%) had grade 4 platelet counts, and no patients had grade 4 hemoglobin or white blood counts during study participation. Also, one patient (4.5%) had grade 4 hemoglobin in the Japanese 5 days on/2 days off dosing regimen study and no patients had grade 4 ANC, platelet or white blood cell counts.

Regarding biochemisty laboratory abnormailities, the most frquent lab test abnormalities observed were liver function test elevations (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkatine phoshatase, and total bilirubin). In most cases these changes were CTC grades 1 or 2. Overall CTC grade 3 or 4 liver function test abnormailites were seen in < 10% of patients treated with dovitinib. There was one fatal case of hepatoxicity (cholestatic liver injury); both the death and the heaptotoxicity were deemed related to dovitinib treatment by the investigator. As of the 10 September 2010 cutoff date, data from a total of 5196 ECGs (of which 3432 were post-treatment) were obtained from 360 patients across ten studies (2101, 2102, 2103, 2104, 2105, 2107, 2112, 2201, 2202, and 2204). The time-averaged changes from baseline ECG for each patient across different study days and dose groups were investigated. Outlier analyses were performed according to the ICH E14 guidance. The results of the analyses of the available ECG data do not reveal any effect of TKI258 on cardiac repolarization across days and doses of therapy, nor is there any specific outlier signal observed consistent with the central tendency finding.

In September 2009, an exposure ECG analysis was conducted through a mixed effect linear model using 546 matching ECG-TKI258 concentration data from 61 patients (studies 2105 and 2107 in which more timepoints with ECG monitoring and PK sample collection were availabe). The exposure-ECG analysis confirmed the conclusion of no-QTc prolonging signal from central tendency and outlier analyses.

Left ventricular ejection fraction (LVEF) data were available from 200 patients who had both pre- and post-treatment data from studies 2101, 2102, 2103, 2104, 2105, 2107, 2112, 2201, 2202 and 2204. Of these patients, 21 had ≥ 20% post-treatment LVEF decrease on ECHO or MUGA. Among the 21 patients, 11 patients had LVEF decrease to a value that was below 50%. The LVEF data were reviewed by an

independent cardiologist consultant. According to his assessment, based on the available data, TKI258 had no effect on the LVEF.

In summary, based on the available data, no consistent pattern of cardiac events related to TKI258 administration has been observed to date. More data will be collected to further assess the cardiac safety in relationship to TKI258 treatment. Although efficacy was not the primary end point for the dose escalation portion of the Phase I trials, preliminary efficacy data were obtained from some of the studies. Two metastatic renal cell cancer patients treated at 500 mg on a 5-day on/ 2-days off dosing regimen in study 2107 achieved confirmed partial response (PR). A FLT3-ITD acute myeloid leukemia (AML) patient who was treated at 100 mg/day in study 2102 achieved a morphologic complete remission with incomplete blood count recovery. Unfortunately the patient's peripheral blood count did not recover and the patient died unexpectedly due to a fungal infection, secondary to diseae progression. This patient stayed on the study for 69 days. A metastatic melanoma patient who was treated at 175 mg/day in study 2101 achieved a partial response at the end of cycle 11 and remained on treatment for 3.3 years (1217 days) before discontinued due to disease progression.

As of March 2010, pharmacokinetic data were available from 178 patients in studies CTKI258A2101, CTKI258A2102, CTK2582103/2104, CTKI258A2105, CTKI258A2106 and CTKI258A2107. Noncompartmental analysis was conducted on full plasma PK profiles of TKI258. Coefficients of variation in the PK parameters (Cmax and AUC_{24hr}) were between 16 and 111%. Cmax was observed at approximately 4 - 8 hours after dosing, and the concentration of TKI258 declined monoexponentially thereafter. Within the tested dose levels ranging from 25 to 600 mg/day, linear absorption of TKI258 was observed. TKI258 was extensively distributed to tissues.

Time-dependent PK of TKI258 was observed across all tested dose levels ranging from 25 to 600 mg/day. Following daily administration at dose below 400 mg, the auto-induction of CYP1A1/A2 resulted in lower plasma exposure of TKI258 on day 7 (steady state) than that observed on day 1. However, after increasing the daily dose to 400 - 600 mg, TKI258 plasma concentration on day 7 was found to be similar to or greater than that on day 1, suggesting a more pronounced accumulation of TKI258 at higher doses. In addition, an over-proportional increase in TKI258 plasma exposure was observed with doses from 400 to 600 mg/day. The maximum tolerated dose of TKI258 for the continuous daily dosing schedule was 400 mg (CTKI258A2105).

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 TKI258 exposure with dose escalation, an intermittent dosing schedule of 5 days on/2 days off was proposed for study CTKI258A2107. 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 schdule was 500 mg (CTKI258A2107). The human ADME study identified the major metabolites as C-hydroxyl metabolites (in feces) and N-oxide (in plasma). The ADME study demonstrated that majority of the total dose administered was recovered from feces, and less than 21% of the dose was recovered in urine.

No formal drug-drug interaction studies have been conducted. Available data from human as well as *in vitro* studies demonstrated that TKI258 has low or no inhibition potential for CYP450s. Therefore, TKI258 is not expected to cause inhibitory metabolic drug-drug interactions when co-administered with drugs metabolized by CYP450s. TKI258 induces CYP1A2, CYP2C9 and CYP2C19; hence co-administration with substrates of CYP1A2/2C9/2C19 could reduce the exposure of these substrates.

A relative bioavailability study (CTKI258A2112) was conducted to compare the final market image (FMI) capsule of TKI258 (monohydrate salt) with the clinical service form (CSF) capsule of TKI258 (anhydrate salt). PK data from 16 evaluable patients demonstrated that FMI capsule and the CSF capsule have comparable bioavailability. Therefore, FMI capsules will replace CSF capsules to be used in the new clinical studies moving forward. .

The effect of food on the bioavailability of TKI258 was studied in 19 patients with advanced solid tumors (CTKI258A2112 Arm 2; FMI capsule formulation). The PK of TKI258 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 TKI258 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 TKI258 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, TKI258 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.

Examples of a low-fat meal of approximately 500 calories and 20 grams of fat include: (1) 6 ounces (approximately 177 mL) of orange juice (except Seville), 8 ounces (approximately 237 mL) of 2% milk, 1 banana, ¾ cups of cereal, a slice of toast and 2 teaspoons (approximately 10 ml) of butter; (2) 1 cup of plain congee/porridge (approximately 240-250mL), 1 cooked salted duck egg **or** 1 preserved duck egg and 1 steamed pork bun; (3) 1 cup of steamed rice (186 g), 1 cup of miso soup (approximately 240-250mL), fried soybean curd (30 g) and 1 fried egg. If taken without food,

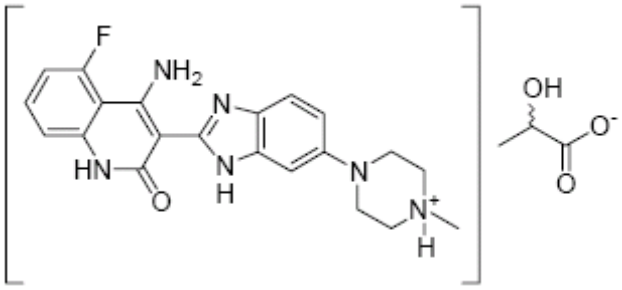
Plasma VEGF levels have been reported as a pharmacodynamic (PD) biomarker for drugs of anti-VEGF/VEGFR pathways such as bevacizumab (Avastin®), sunitinib (Sutent®) and PTK787/ZK222584. The preliminary PD data from study 2102 (AML) indicated that VEGF levels were increased in patients treated with TKI258 at 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 inhibitor such as sunitinib and sorafenib (Nexavar®).

Reduction of leukemic blasts either in bone marrow or in peripheral blood has proven to be a robust marker of tumor burden in clinical trials of FLT3 inhibitors and has been routinely monitored as a primary response marker. In study 2102, a total of 32 patients were enrolled at doses ranging from 50 - 600 mg. Of these 32 patients, 26 had measurable blasts. Of the 26 patients who had measurable blasts, 4 had blast increases without any reduction while on the study; 22 showed > 50% blast cell count reduction at some point during the study and 16 of these 22 patients sustained this level of reduction over the course of the study. The median duration of blast reduction for these 16 patients was 21 days (range 2 - 82). Of the 22 patients who had > 50% blast cell count reduction, 7 patients were FLT3-ITD and 15 patients were FLT3-WT.

1.3.1 Physical, chemical and pharmaceutical properties

TKI258 lactate salt (TKI258 or TKI258LC) is designated chemically as (4 Amino 5 fluoro 3 [6 (4 methyl 1 piperazinyl) 1H benzimidazol 2 yl] 2(1H) quinolinone mono DL lactate) and its structural formula is:



TKI258 is a yellow to orange and/or brownish tinged, nonhygroscopic solid that dissociates into TKI258 free base and lactic acid between 125 to 250°C. Its molecular formula is C21H21FN6O • C3H6O3 (molecular weight 482.5). TKI258 is freely soluble in water, DMSO, 1 methy 2 pyrrolidone, and acetic acid. In buffered aqueous solutions, depending on the prevailing pH, TKI258 reverts back to the appropriate

ionized species or free base. Since the degree of ionization is pH dependent, the solubility of TKI258 varies with pH (e.g., 6 µg/mL at pH 7 and 13.6 mg/mL at pH 2).

1.3.2 Clinical formulations

TKI258 is available in a capsule form. Each hard gelatin capsule contains TKI258 equivalent to 100 mg of TKI258 free base. The inactive ingredients for the TKI258 capsules are pregelatanized starch, colloidal silicon dioxide, microcrystalline cellulose, and magnesium stearate. The capsules are stored in a high-density polyethylene bottle. Each bottle will contain 30 capsules. The capsules should be stored between 15 to 30 °C (59 to 86 °F) in a secured, limited access area until required.

1.4 Pre-clinical studies

TKI258 was evaluated in a number of *in vitro* and *in vivo* nonclinical models to characterize its pharmacology, antitumor efficacy, pharmacokinetics, metabolism, and toxicology. TKI258 is an RTK inhibitor with potent antiangiogenic and antiproliferative activity. It targets type III, IV, and V RTKs, which include PDGFRβ, CSF 1R, KIT, FLT3, VEGFR, TrkA, RET and FGFRs. The biochemical and cell based potency against these receptors is in the nanomolar range. As a result of inhibition of target RTKs by TKI258, cellular functions are blocked, including activation of downstream-signaling molecules, cellular proliferation, and survival. Additionally, *in vivo* antitumor effects have been observed in a variety of nonclinical models representing solid and hematological cancers. The *in vivo* effects of TKI258 were shown to be a result of its dual mechanisms of action: antiangiogenesis and direct antitumor activity. Inhibition of angiogenesis (through inactivation of VEGFR, PDGFRβ, and FGFR on stroma and endothelium) was demonstrated by a reduction in hemoglobin concentration in subcutaneous Matrigel plugs, as well as reduced microvessel density in tumor xenografts after administration of TKI258. Direct inhibition of RTK activation on tumor cells (PDGFRβ, FLT3, and FGFR 1 & 3) was confirmed by a reduction in phosphorylation of these target RTKs, as well as signaling pathway components (ERK, STAT5, and AKT) in tumor xenografts **(Chase et al. 2007)**. Target inhibition was observed for as long as 24 h after a single high dose of TKI258. A decrease in tumor cell proliferation and induction of apoptosis, in combination with the antiangiogenic effect of TKI258, resulted in significant antitumor efficacy. The target profile of TKI258 is likely to confer activity in many different types of solid and hematologic tumor models by acting on both endothelial cells and tumor cells. In all human tumor xenograft models tested, including colon, prostate, myeloma, AML, breast, and ovarian, TKI258 had anti-tumor effects on both small and large established tumor xenografts.

TKI258 has high oral bioavailability in mice, rats, and monkeys, and moderate bioavailability in dogs. The agent clears rapidly from plasma with an elimination t1/2 of about 3 hours in mice, rats, dogs, and monkeys. TKI258 distributes widely to tissues, including tumor xenografts (in mice). After multiple dosing, TKI258 demonstrates a time dependent reduction in plasma exposure in rats, dogs, and monkeys, but not mice. Two major metabolites were identified *in vitro* and *in vivo* in

plasma from mice, rats, and monkeys. The N desmethyl TKI258 metabolite (generated by CYP3A4) has *in vitro* potency similar to that of TKI258, whereas the N oxide TKI258 metabolite (generated by FMO) is 5 to 10 fold less active.

TKI258 is metabolized by a number of enzymes, including CYP2C8, CYP2D6, CYP3A4, CYP1A1/2, FMO1, FMO3, and FMO5. Though no drug interactions have been studied clinically, drugs that inhibit or induce such enzymes may interact with TKI258. TKI258 demonstrated low inhibition potential (IC_{50} greater than 25 μM) in five major human hepatic cDNA derived CYP450 isozymes and in pooled human hepatic microsomes (CYP 3A4, 2D6, 2C19, 2C9, 1A2), suggesting that TKI258 is unlikely to cause significant inhibitory metabolic drug drug interactions when coadministered with drugs metabolized by the major CYP450s. The induction potential of TKI258 was evaluated in primary cultures of rat, dog, monkey and human hepatocytes. TKI258 treatment was not associated with the induction of CYP2B or CYP3A protein or enzyme activity in these species.

However, TKI258 treatment was associated with the induction of CYP1A1 and CYP1A2 protein and activity, as well as with the induction of UGT protein in dog, monkey and human hepatocytes. Therefore potent inhibitors/inducers of these enzymes, such as quinidine (a CYP2D6 inhibitor), fluvoxamine (CYP1A inhibitor), omeprazole (a CYP1A inducer), ketoconazole, itraconazole, erythromycin and glibenclamide (CYP3A4 inhibitors), as well as phenobarbital, phenytoin, carbamazepine and rifampicin (all CYP3A4 inducers), should be used with caution.

The safety of TKI258 was evaluated on a daily dosing schedule in rats, dogs, and monkeys for up to 28 consecutive days to determine target organ toxicity and the safe starting dose in clinical trials, and to provide information for clinical monitoring. A no- to minimal-effect level was approximately 60 mg/m², and 180 mg/m² approached the MTD after 28 days of daily dosing. The dose-limiting toxicity in all animal species tested was gastrointestinal irritation reflected in emesis, diarrhea, severely decreased food consumption, and severe body weight loss. There were no target organs identified for clinical monitoring other than GI irritation. At severely toxic doses, morbidity was attributed to emaciation. Comparison of plasma exposure between species for assessment of a safety margin was confounded by time-dependent reduction in plasma exposure of TKI258 (as assessed by Cmax and AUC values) following repeated oral administration. Therefore, body surface area-normalized dosing between species provided the most accurate prediction of safety.

1.5 Pharmacology

TKI258 demonstrated activity in a number of *in vitro* and *in vivo* models. It potently inhibits the activity of multiple RTKs including PDGFRβ, CSF 1R, KIT, FLT3, VEGFR, TrKA, RET, and FGFR. Inhibition of these RTKs impedes tumor growth and progression through different mechanisms, including both direct antitumor effects and effects on host tissues, such as endothelial cells and supporting stromal cells. Antiangiogenic effects are due to the pivotal role of these receptors and their growth factors in growth and maintenance of new blood vessels supplying the tumor. In

addition, inhibition of these receptors results in modulation of important downstream-signaling pathways that are essential for tumor cell proliferation and metastasis.

TKI258 inhibited angiogenesis in an FGF driven murine model of neovascularization with a minimum effective dose (MED) of 3 mg/kg/day (9 mg/m^2). Considerable antitumor activity (MED 4 to 10 mg/kg/day; 12 to 30 mg/m^2) was demonstrated in target driven tumor models. These included an AML xenograft model (MV4;11) with an FLT3 internal tandem duplication (ITD) mutation and an FGFR3 mutated multiple myeloma model (KMS11), both cell lines with constitutively active receptor tyrosine kinases known to be essential for tumor cell proliferation. Tumor regressions, including complete responses, were observed with doses of at least 10 mg/kg/day (30 mg/m^2) against established (300 mm^3) and very large tumors MV4;11 tumors (500 to 1000 mm^3). TKI258 also demonstrated tumor stasis at 50 mg/kg/day in the orthotopic RT112 bladder cancer model and regression at 60 mg/kg/day in the KMS11 multiple myeloma xenograft.

TKI258 treatment in additional oncology models of diverse tumor origin, including colon, myeloma, prostate, ovarian, lung, renal cell carcinoma and hepatocellular carcinoma, also resulted in tumor regression, stabilization, or growth inhibition. Spontaneous liver metastases were inhibited in a murine breast tumor model. Several dose scheduling studies have demonstrated similar efficacy with twice-daily, intermittent, or cyclic regimens compared with daily dosing in several models.

The biological activities of TKI258 have been determined *in vivo*. Inhibition of activity of downstream-signaling components of the target RTKs and reduced receptor phosphorylation have been demonstrated. Durable inhibition of kinase activity was demonstrated for 24hr after a high single dose of TKI258.

1.5.1 *In Vitro* pharmacology

TKI258 is an inhibitor of type III, IV, and V receptor tyrosine kinases (RTKs) that mediate both endothelial and tumor cell proliferation and survival. These growth factor receptors include FGFR subtypes 1, 2 and 3, three VEGFR subtypes (VEGFR 1, 2, and 3), PDGFRβ, CSF 1R, c-KIT, RET, TrkA, and FLT3. The biochemical activity against these receptors is in the low nanomolar range (IC50 = 1 to 40 nM) (Table 1-1).

Table 1-1 - In Vitro activity of TKI258

Target RTK	*In vitro* IC50 nM	Cell Proliferation EC_{50} nM	Target modulation EC_{50} nM	Target modulation EC_{90} nM
FLT3	1	13 (MV4;11 ITD) 315 (RS4;11 WT)	< 10 approximately 500	>10, <50 > 500, < 1000
KIT	2	Approximately 12 (TF-1, Moe7)	2	4-11
VEGFR1-3	8-15	13 (HMVEC)	approximately 10	approximately 20
FGFR3 FGFR1/2 FGFR4	5 20-40 2300	80 (KMS11 FGFR3 mut) 60 (RT112 FGFR3 overexpression; bladder) 160 (RT4 FGFR3 overexpression; bladder) 80 (HMVEC, FGFR1) 180 (LN427 FGFR1; GBM) 190 (SUM52: FGFR2 amplification and overexpression; breast) 903 (HUH7 FGFR4; HCC)	Not done	Not done
RET	7	Not Done	Not Done	Not Done
TrkA	9	27 (KM2L4a)	Not Done	Not Done
PDGFRB PDGFRα	30 150	211 (MG63 expresses PDGFR α & B)	30	150
CSF-1R	15	490 (MNFS-60)	100	650

RTKs belonging to other classes are either not inhibited or are much less responsive to inhibition by TKI258 (Table 1-2). For example, EGFR1, HER2, or Insulin Receptor (INSR) were inhibited in biochemical assays at IC50 values greater than 2.1 µM. TKI258 exhibited limited inhibitory activity against other intracellular kinases (IC50 values greater than 1 µM). Four additional tyrosine and serine threonine kinases (Fyn, Lck, RSK2, and Nek2) had IC50 values of less than 100 nM. Fyn and Lck have roles in T-cell signaling and proliferation, RSK2 is implicated in the activation of the mitogen activated kinase (MAPK) cascade and the stimulation of cell proliferation and differentiation, and Nek2 is a regulator of centrosome structure and function.

Table 1-2 - Kinase selectivity of TKI258 determined by *in vitro* kinase assays

	IC_{50} < 40 nM	IC_{50} < 0.5 µM	IC_{50} 1 - 10 µM	IC_{50} > 10 µM
RTKs	VEGFR1-3, FGFR1/3; PDGFRβ FLT3, KIT, RET, TrkA, CSF-1R	PDGFRα	EGFR1, INSR	HER2
	IC_{50} < 100 nM	IC_{50} < 1 µM	IC_{50} 1 - 10 µM	IC_{50} > 10 µM
Kinases (non-RTKs)	Fyn, Lck, Nek2, RSK2	c-abl, MEK1, Chk1, Chk2, PAR1	p60src, PKA, Ca^{2+}/CALM, CK1ε/δ, p70s6, raf, cdk4	GSK3, ERK1/2, p38-α,β,γ,δ; AKT 1/3; cdc2; PKC-α,β,γ, cdk2

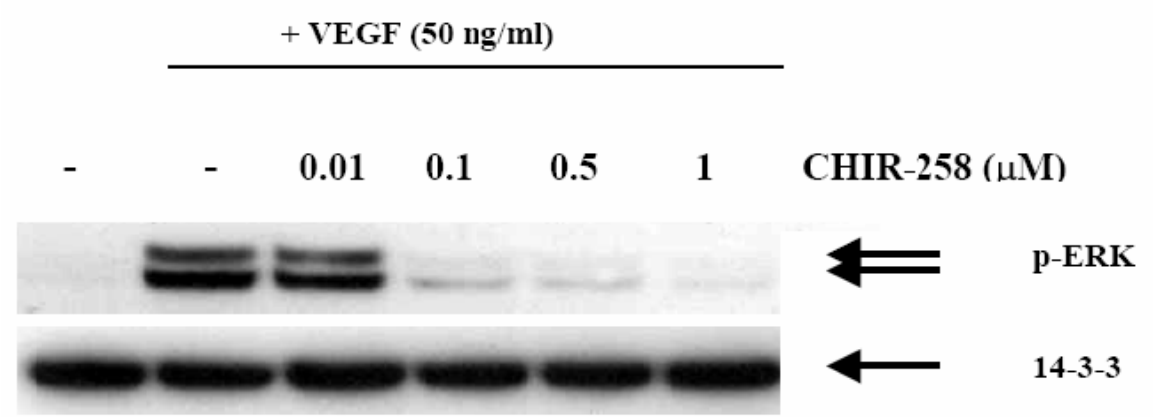
TKI258 was further profiled in a panel of enzyme, receptor, and transporter assays and did not demonstrate any effect on enzymes, excluding kinases, at concentrations below 10 µM. The antiproliferative activities of TKI258 were tested against a large number of cancer cell lines and primary nonmalignant cell lines in vitro (Table 1-3). In a subset of cancer cell lines and in endothelial cells, proliferation was inhibited with an EC50 value less than 60 nM, consistent with their dependence on an RTK targeted by TKI258; for example, t(4;14) translocation and FGFR3 activation in KMS11 cell line; expression of constitutively active FLT3 in MV4;11 cell line; VEGFR2 mediated proliferation in HMVEC; and c-KIT mediated proliferation in the TF 1 cell line). The EC50s for proliferation inhibition in primary normal cell lines were all greater than 1 µM.

Table 1-3 - Antiproliferative effects of TKI258 on cancer and normal cells

	EC_{50} < 60 nM	EC_{50} 0.2 µM	EC_{50} 0.4-1 µM	EC_{50} 1-10 µM	EC_{50} 10 µM
TKI258	MV4;11 (AML) KM12L4a (Trk expression) HMVEC (VEGF/VEGFR 2 mediated; endothelium) TF-1 (SCF/ c-KIT mediated; AML) KMS11 (FGFR3 mediated; multiple myeloma)	M-NFS-60 (MCSF/CSF-R1 mediated; murine myeloid)	RS4 (ALL) 4T1 (mouse breast cancer)	MDA-MB435 (breast cancer) SKOV3 (ovarian cancer) K562 (CML) Ku812 (CML) MOLT-4 (ALL) ARH77 (multiple myeloma) HCT116 (colon cancer) Du145 (prostate cancer) PC3 (prostate cancer) H209 (lung cancer) H226 (lung cancer) HT29 (colon cancer) SW620 (colon cancer) PrC (normal prostate epithelium) HMEC (normal mammary epithelium)	U87 (brain cancer)

The inhibitory activity of TKI258 on VEGF-mediated signaling pathways was evaluated in human microvascular endothelial cells (HMVEC). Immunoprecipitation and Western blot analysis demonstrated greater than 50% inhibition of phosphorylation of VEGFR2 after 1 hour of incubation with 100 nM TKI258. There was no change in total VEGFR2 levels. Consistent with inhibition of VEGFR2, the phosphorylation of the downstream-signaling molecule ERK/MAPK was also inhibited significantly after 1 hour with 100 nM TKI258 (Figure 1-4). Equivalent protein loading was confirmed by blotting for an abundant cellular protein, 14-3-3.

Figure 1-4 - Dose-dependent inhibition of ERK phosphorylation by TKI258 (CHIR-258) in VEGF-stimulated endothelial cells (HMVEC)



Inhibition of receptor activation (PDGFR, FGFR, FLT3) and reduced phosphorylation of downstream-signaling proteins (MEK, ERK, STAT5, and AKT) was demonstrated in several tumor cell lines expressing RTK targets of TKI258, including KMS;11 (mutant FGFR3 multiple myeloma) and KM12L4a (TPM3-TrkA expressing colon cancer cell line).

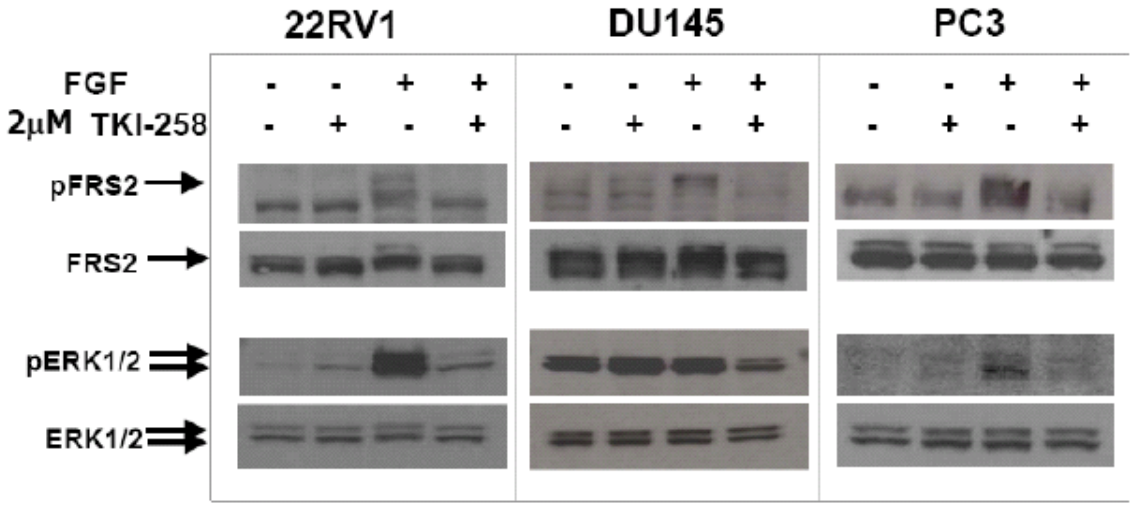
1.5.1.1 *In Vitro* Activity of TKI258 in Prostate Tumor Cells

Prostate cancer epithelial cells express all four types of FGF receptors (FGFR1 to 4) at variable frequencies. Expression of FGFR1 and FGFR4 is most closely linked to prostate cancer progression, while the role of FGFR2 remains controversial. Expression of FGFRs and other TKI258 targets were assessed by expression profiling of prostate tumor derived cell lines (not shown). FGFR1, 2, 3 and 4 were expressed at varying levels in prostate cell lines, with marked high expression of FGFR3 in 22RV1 cells and FGFR4 in MRI-HI-579 tumor xenograft samples. The cognate FGF ligands were also expressed, suggesting the possibility of autocrine activation of FGFR signaling. Prostate tumor cell lines and tumor xenograft samples also expressed other TKI258 targets such as VEGFR1 and 2, PDGFRβ, and FLT3.

Inhibition of FGF stimulated signaling was analyzed by western blot in several prostate cell lines (Figure 1-5). Concentrations of 2 uM TKI258 were able to completely inhibit the ligand induced phosphorylation of the adaptor protein FRS2

and signaling in the MAPK pathway (pERK) in 22RV1 and PC3 cells. DU145 cells showed pERK phosphorylation that did not increase after FGF stimulation but was reduced by TKI258.

Figure 1-5 - Inhibition of FRS2 and ERK phosphorylation in human prostate cell-lines by TKI258



Proliferation and/or survival of these established prostate tumor-derived cell lines and the patient derived prostate cell line PRXF1369 from Oncotest GmBH were inhibited by TKI258 in soft agar clonogenic assays. Table 1-6 shows the EC50 values for TKI258 inhibition in the clonogenic growth assay. Comparison of cell line sensitivity with expression profiling of FGFR1-4 showed that tumor cell sensitivity did not correlate with expression of a particular FGFR. The degree to which inhibition of FGFR contributes to the *in vitro* block in cell proliferation and how much of the proliferation effect is contributed by inhibition of other prostate tumor cell TKI258 targets, such as PDGFRβ, remains to be determined.

Table 1-6 - Inhibition of cell proliferation of human prostate cell lines by TKI258

Prostate Cancer-derived Cell Line	Clonogenic Assay EC50 (μM)	FGFR Expression by Western
PRXF1369	0.39	FGFR3
22RV1	0.52	FGFR1,2,3
DU145	1.86	FGFR1,3
MRI-H-1579	2.23	FGFR1,2,3,4
PC3M	2.66	FGFR1,2,3

1.5.2 *In vivo* pharmacology

The *in vivo* activity of TKI258 in nonclinical tumor models and an FGF murine Matrigel model was evaluated at multiple dose levels using daily administration (Table 1-7). Mice were randomized to treatment groups, and treatment began when

mean tumor volume was 100 to 200 mm3. TKI258 was formulated as a solution in water and was administered daily by oral gavage. Statistically significant tumor growth inhibition was observed in each study, and a minimum effective dose (MED) was determined from the dose response curve. TKI258 was also evaluated in an *in vivo* angiogenesis model in which Matrigel-containing FGF2 was placed subcutaneously in mice. TKI258 was administered daily for 8 days after which the Matrigel plugs were removed and the hemoglobin content measured.

Table 1-7 - *In Vivo* efficacy of TKI258 in mouse models

MED 3 - 10 mg/kg/day (9 - 30 mg/m^2)	MED 15 - 30 mg/kg/day (45 - 90 mg/m^2)	MED 40 - 65 mg/kg/day (120 - 200 mg/m^2)
Matrigel Angiogenesis: (FGF driven) AML: (MV;411, FLT3 ITD) Myeloma: (KMS11, FGFR3 mutant)	2 colon (KM12L4a, HCT116) 2 prostate (DU145, PC3) 1 ovarian (SKOV3ip1) Spontatneous liver mets (4T1 murine breast tumor model)	1 epidermoid (A431) 3 leukemic (K562 CML, MOLT4 and RS4 ALL) 1 small cell lung (H526)
Note: TKI258 was administered once daily by oral gavage for 8-30 days depending on the model. Model and tumor cell lines used are listed under their respective minimum effective dose (MED) range for TKI258. All tumor cell lines are human except 4T1, which is derived from a mouse breast tumor.		

The most potent antitumor activity of TKI258 (MED of 3 to 10 mg/kg/day; 9 to 30 mg/m2/day) was observed in RTK target-driven tumor models (e.g., KMS11 FGFR3 mutant multiple myeloma and MV4;11 FLT3-ITD mutant AML). In these cases, the mutations in the target RTK are known to drive disease progression and to be associated with poor clinical prognosis.

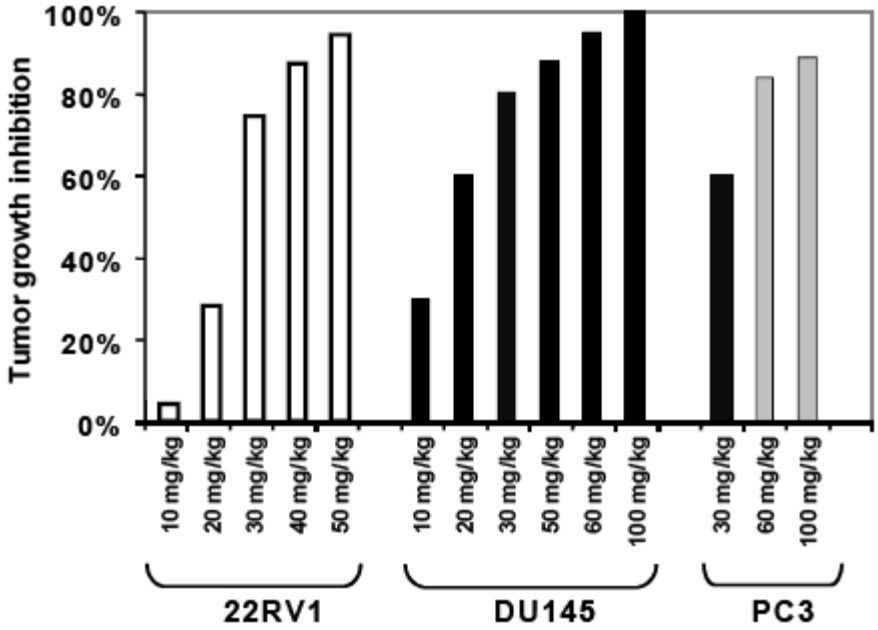
For *in vivo* studies mentioned in Section 1.4.2, tumor growth inhibition (TGI) was calculated as % (mean tumor volume of treated group /mean tumor volume of control group)-1.

1.5.2.1 *In Vivo* Activity of TKI258 in Prostate Tumor Models

The antitumor activity of TKI258 was evaluated in the human prostate tumor xenograft models PC3, DU145 and 22RV1. In single agent tumor growth inhibition studies, TKI258 was administered at daily oral doses ranging from 10 to 100 mg/kg, with tumor growth inhibition seen at doses above 20 mg/kg. In general TKI258 was well tolerated at the lower doses. Daily dosing at 100 mg/kg incurred significant body weight loss requiring cessation of dosing in most studies.

Tumor growth inhibition (%TGI) determined from several studies in DU145, PC3 or 22RV1 is summarized in Figure 1-8. In these studies, subcutaneous DU145, PC3 or 22RV1 human prostate tumors in male nude mice (300-500 mm3) were treated with vehicle (p.o. daily x 15- 21 days) or TKI258 (p.o., daily x 21 days) at the indicated doses. Data represent mean tumor growth inhibition compiled from multiple independent studies, with n = 10 mice/group/study.

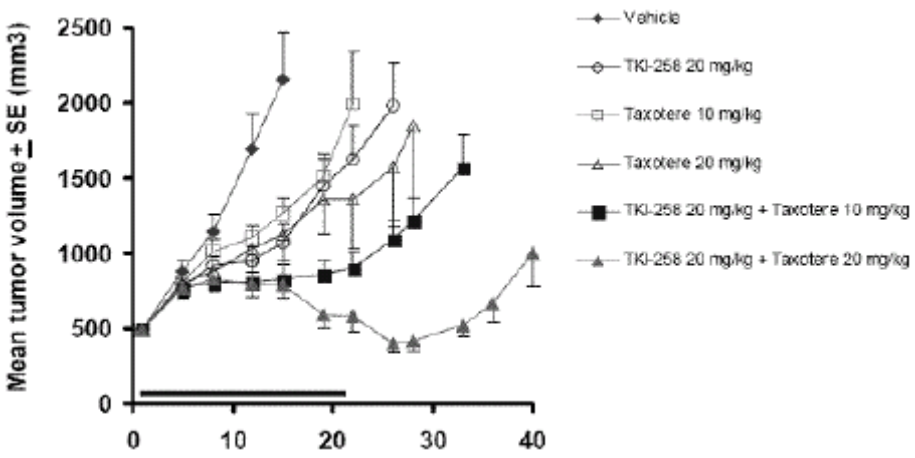
Figure 1-8 - Mean tumor growth inhibition



The effect of TKI258 in combination with Taxotere (docetaxel) was evaluated in the DU145 and 22RV1 tumor models. Suboptimal doses of single agents were used in these studies in order to reveal potential combination effects.

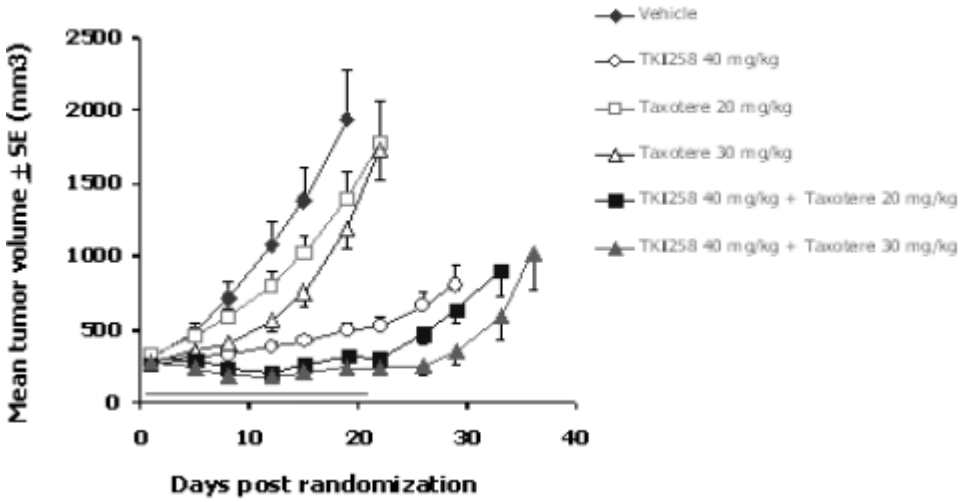
In the DU145 model, mice treated with a combination of TKI258 and Taxotere showed substantially greater tumor inhibition (> 86% TGI) compared to single agent TKI258 (60% TGI) or Taxotere (47 or 69% TGI) treatment at the end of 3 weeks (Figure 1-9). Tumor shrinkage occurred by day 18 in response to combined treatment with a response greater than either agent alone. The durability of response of was also evident from the analyses of tumor growth delay (to 1500mm^3), where, combination of TKI258 and Taxotere not only significantly suppressed tumor growth but also increased growth delay of the tumors (TKI258 + Taxotere >37days vs. TKI258 = 8 days or Taxotere = 15 days. Maximum average body weight loss in the groups treated with TKI258 ranged from 7-10%, while in the Taxotere monotherapy groups the maximum body weight loss was 10% at the lower dose and 20% at the higher dose. The combinations of Taxotere and TKI258 were relatively well-tolerated with no more than 10% maximum average body weight loss.

Figure 1-9 - Response of subcutaneous DU145 prostate tumor to TKI258 and Taxotere in nude mice



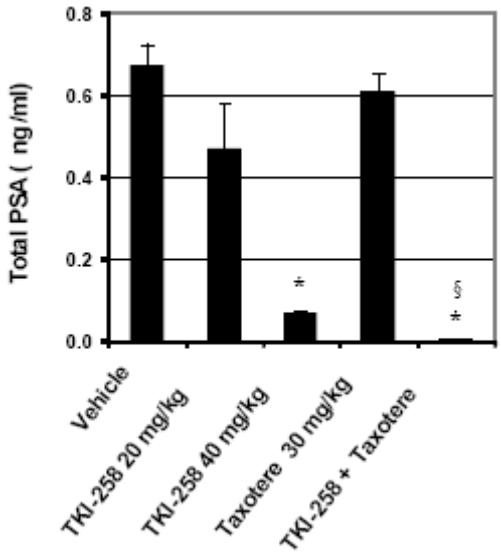
TKI258 was also evaluated in combination with Taxotere in the androgen-receptor positive 22RV1 prostate xenograft model. Combination therapy of TKI258 (40 mg/kg) and Taxotere (20 or 30 mg/kg) produced pronounced tumor inhibition and delayed time to tumor regrowth compared to monotherapies (> 98% inhibition; $p<0.001$ vs. vehicle; see Figure 1-10). In this study TKI258 was well tolerated as monotherapy, with average body weight loss of 0 and 2 % respectively for the 30 and 40 mg/kg groups. In the Taxotere monotherapy group's maximal body weight loss was 2 and 5%, respectively for the 20 mg/kg and 30 mg/kg groups. In the combination group's maximal average body weight loss ranged from 5 to 7 %.

Figure 1-10 - Combination therapy of TKI258 and Taxotere in the subcutaneous 22RV1 prostate tumor model in nude mice



22RV1 tumor xenografts *in vivo* secrete PSA, permitting analysis of the effect of TKI258 and Taxotere on total serum PSA levels in tumor-bearing nude mice (Figure 1-11). Basal levels of total serum PSA were undetectable in naïve, non-tumored male mice. The mean total PSA level was 0.67 ng/ml in serum of vehicle-treated mice bearing 22RV1 tumors of approximately 2cm3. Treatment with TKI258 at 20 or 40 mg/kg produced a dose-dependent decrease of total serum PSA levels, with statistically significant inhibition in total PSA observed with 40 mg/kg (0.07 ng/ml vs. vehicle or Taxotere; $p<0.001$). Taxotere therapy (30 mg/kg) did not change total serum PSA levels compared to vehicle treatment ($p>0.05$). Substantial reduction in total PSA levels was observed with combined TKI258 and Taxotere therapy ($p<0.001$ vs vehicle or single agents). The decrease in total serum PSA levels with combination therapy correlated well with tumor growth inhibition (see Figure 1-11).

Figure 1-11 - PSA levels in serum following combination therapy of TKI258 and Taxotere in the subcutaneous 22RV1 prostate tumor model in nude mice



1.5.3 Safety Pharmacology

An *in vitro* HERG assay and *in vivo* monkey safety pharmacology studies were performed and described below. Additional cardiovascular safety measurements were part of the GLP dog study [Study No. N103753]. There was no effect on cardiovascular parameters during 28 days of dosing in the dog. A GLP oral safety pharmacology study in rats was also performed to evaluate effects on CNS and respiratory function [Study No. 0770153]. TKI258 at 100 mg/kg did not have any effects on CNS functional observation battery (FOB) and respiratory function.

Effects on HERG were evaluated in GLP [Study No. SPH03-029] "Effects of CHIR-258LC on HERG Tail Current Recorded from Stably Transfected HEK293 Cells" (Table 1-12). The purpose of this study was to assess the effect of TKI258 on the human ether-a go-go-related gene (HERG)-encoded channel tail current recorded from human embryonic kidney 293 (HEK293) cells stably transfected with HERG

complementary DNA. TKI258 was tested at 0.1, 0.3, 1, 3, and 10 µM along with a positive control (E-4031) previously validated in the assay. Single cells were continuously exposed in the bath solutions to TKI258, the positive control or vehicle, for the duration of the measurements. The concentration-response curve was fit with a sigmoidal function. The IC25 and IC50 values were estimated from the best-fit results. No statistically significant inhibition in HERG tail current was observed at concentrations below 1 µm. The IC25 and IC50 values were 2.5 and 6.6 µM, respectively. The positive control used produced an 84% decrease in tail current at 100 nM.

Table 1-12 - In vitro safety pharmacology studies

Study type (Study no.)	Test system	Concentrations of TKI258	Major findings
HERG SPH03-029	HEK293 cells	0.1, 0.3, 1.0, 3.0 and 10 µM; 100 nM E-4031 (positive control)	IC_{50}: 6.61 µM.

HEK cells = human embryonic kidney cells

In GLP [Study No. UBAW-0200] "A Cardiovascular Safety Study of CHIR154258 Administered to Naïve Telemetered Cynomolgus Monkeys", a group of telemetered cynomolgus monkeys, 3 per sex, received single escalating oral gavage doses of vehicle and 30, 100, and 300 mg/kg (370, 1222, and 3700 mg/m2) TKI258 (Table 1-13). Doses were escalated weekly. The dose levels chosen for this study were at or above dose levels that produced lethality in the multiple daily dose GLP monkey study. Monkeys were monitored for changes in heart rate, blood pressures (systolic, diastolic, and mean), body temperature, and electrocardiogram parameters 1.5 hours prior to dosing and for 24 hours post dosing.

Emesis occurred with a dose dependent increase in frequency and duration starting at ≥ 100 mg/kg. Heart rates were decreased in all animals (10 to 30 bpm) following treatment with TKI258 at all dose levels compared with vehicle administration beginning 8 to 10 hours post dose administration. This response was not dose dependent and was similar at all 3 dose levels. Several animals demonstrated an increase in mean arterial blood pressure during the period of decreased heart rate. One of the six treated animals had a potentially biologically significant prolongation of QTc interval (22 to 39 msec) at each dose of CHIR-258LC. This finding occurred within a very narrow time period at night. This particular animal had wide variations in heart rate making QTc interval determination difficult to interpret. The relevance of these findings at such high single dose levels compared to tolerated multiple doses at 5 mg/kg (60 mg/m2) in the monkey is not known. Although decreased heart rates were observed, this observation did not appear to be dose related. Cardiac arrhythmias, conduction disturbances, or quantitative ECG abnormalities (including QTc prolongation) were not consistently observed following the oral administration of TKI258 at any of the dose levels tested.

Table 1-13 - in vivo safety pharmacology studies

Species (strain) (Study no.)	Route of administration (vehicle/ formulation)	Organ systems evaluated	Doses (mg/kg)	Gender and no. per group	Remarks / major findings
Cynomolgus monkey (UBAW-0200)	Oral gavage of lactate solution	Cardiovascular (telemetry)	0, 30, 100, 300 weekly dose escalation	3/sex	No definitive effect on quantitative ECG abnormalities. Decreased heart rate was observed in treated animals 8 to 10 hours post dose. One of the six animals demonstrated a potentially biologically significant prolongation of QTc during the brief period of decreased heart rate.
Wistar rat [Study No. 0770153]	Oral gavage of TKI258 lactate salt in sterile water for injection	CNS (FOB) Respiratory (plethysmography)	0 and 100 mg/kg single dose	10 males/ group	No effect on CNS or respiratory function

1.5.4 Development of pharmacodynamic monitoring of TKI258 activity for use in clinical trials

The rationale for utilizing biomarker or pharmacodynamic marker evaluation in phase 1 clinical trials of TKI258 is to evaluate target modulation in patients as an indicator of the biological effect of the compound. An objective of these studies is to identify dose and plasma exposures necessary for inhibiting targets of TKI258. These results will support selection of optimal dose and schedule for clinical use of TKI258.

Potential pharmacodynamic markers that may be utilized to assess target modulation by TKI258 in clinical specimens were explored nonclinically, as described earlier. In addition to inhibition of target receptor phosphorylation, inhibition of downstream-signaling components of the target RTKs were demonstrated in tumor xenografts. In both cell lines and xenografts, TKI258 inhibited phosphorylation of FLT3 in AML models and FGFR3 in multiple myeloma models. ERK and STAT5 phosphorylation were also shown to be reduced in several models.

1.5.5 Distribution

Following a single oral dose of radiolabeled compound to rats, TKI258 was widely distributed with highest concentrations of the radiolabel observed in the harderian gland, liver, renal medulla, spleen, adrenal gland, and kidneys (30 to 100 fold higher than plasma). The radioactivity in both tissues and plasma peaked within 4 hours after dosing and was significantly lower at 24 hours after dosing.

In murine xenograft models, oral dosing with TKI258 demonstrated extensive distribution to tumors relative to plasma or normal tissue (up to 200 fold higher at 48 hours after cessation of dosing). Plasma or normal tissue concentrations declined rapidly relative to those in tumors, suggesting that TKI258 may be preferentially retained in tumors. TKI258 was highly bound to plasma proteins (90.8% to 98.2%), mainly to albumin, and its binding was independent of concentration (0.5 to 10 μg/mL) and gender in mouse, rat, dog, monkey, and human plasma.

The blood cell to plasma partitioning ratios of TKI258 ranged from 1.45 to 2.64 and were, in general, independent of concentration and gender in mouse, rat, dog, monkey, and human blood. These results indicate that the majority of TKI258 in blood was associated with blood cells.

1. 5.6 Metabolism

TKI258 is metabolized mainly by CYP1A1/2 and FMO. FMO is not readily induced or inhibited by any other agents, therefore the drug-drug interactions between TKI258 and FMO inducers/inhibitors are of lesser concern. To a lesser extent, TKI258 could be metabolized by CYP3A4, CYP2C8, and CYP2D6 enzymes.

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 TKI258 and should be used with caution.

1.5.6.1 *IN VITRO* STUDIES

The induction potential of TKI258 was evaluated in primary cultures of rat, dog, monkey and human hepatocytes. TKI258 treatment was not associated with the induction of CYP2B or CYP3A protein or enzyme activity in these species. However, TKI258 treatment was associated with the induction of CYP1A1 and CYP1A2 protein and activity, as well as with the induction of UGT protein in dog, monkey and human hepatocytes.

In vitro, TKI258 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 as listed below should also be used with caution:

• 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.

1.5.6.2 *IN VIVO* STUDIES

After a single intravenous or oral dose of radiolabeled (14C) TKI258 to rats and monkeys ([Studies No. 6549 177] and [-178], respectively), unchanged TKI258 and its N des methyl metabolite accounted for most of the radioactivity in plasma. In other studies, N desmethyl TKI258 and TKI258 N oxide were the two major metabolites detected in plasma from mice, rats, dogs, and monkeys following single or multiple oral doses of TKI258. The ratios of plasma concentrations of each of these two metabolites to unchanged TKI258 were comparable after single and multiple dose administration in each species examined, suggesting that the time dependent kinetics (observed in rats, dogs, and monkeys) is likely independent of the formation of these two metabolites. An additional mono-hydroxy metabolite was found in plasma and urine samples from dogs after a single oral dose. The proportion of this metabolite relative to unchanged TKI258 increased after multiple dosing suggesting possible induction of metabolic enzymes responsible for the formation of the hydroxylated metabolite. Such a hydroxy metabolite was not identified in plasma, urine, and feces from rats, or in plasma and urine from monkeys.

Livers collected from rats treated with once daily oral doses of 30, 50, or 80 mg/kg/day TKI258 for 14 days exhibited only a modest (3.7 to 4.7 fold) increase in CYP1A1/2 and CYP2A1 activities compared to those from control animals. However, about a 9 to 17 fold increase in uridyl glucuronosyl transferase (UGT) activity was observed in the treated animals compared to those in the control group. In a similar study in monkeys, livers collected after multiple oral dosing with TKI258 (5, 30, or 80 mg/kg/day; [Study No. 02 3008]) demonstrated up to a 15 fold increase in CYP450 1A1/2 and a modest 3.2 fold increase in thyroxine glucuronidation compared to those from control animals.

In another study, significant differences were observed in the metabolic profiles of rat bile after single oral dose of TKI258 compared to that after multiple oral doses. After a single oral dose (20 mg/kg), unchanged parent, the N desmethyl (minor), and the N oxide (major) metabolites were detected in the rat bile. After multiple dosing (20 mg/kg/day for 7 days), several conjugated metabolites, including conjugated products of hydroxylated TKI258, were observed. It is noteworthy that the mono hydroxylated metabolite or the conjugated metabolites were not identified in plasma, urine, and feces from rats.

Therefore, taken together, these results suggest that after a single oral dose, TKI258 appears to be primarily metabolized by N demethylation and N oxidation, with a minor contribution of the hydroxylation pathway. However, after multiple oral dosing, the metabolism of TKI258 increases, possibly due to induction of metabolic enzymes responsible for the formation of the hydroxylated and conjugated metabolites. Such an increase in the metabolic rate may explain the time dependent reduction in TKI258 exposure following repeated oral dosing.

1.6 Human studies

All data presented in this section are preliminary. All clinical studies described in this TKI258 (dovitinib) Investigator's Brochure (edition 8) have been designed and implemented in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles described in the Declaration of Helsinki.

Description and status of clinical studies with TKI258
TKI258 is being studied as a single agent in ten Phase I and three Phase II clinical trials designed to characterize safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity.

Table 1-14 provides detailed description and status of clinical trials with TKI258. As of 10 September 2010, a total of 420 patients have received single agent TKI258. Among them, 35 patients (advanced solid tumors) were treated in study 2101 (dose range: 25 - 175 mg continuous once daily), 32 patients (acute myeloid leukemia) were treated in study 2102 (dose range: 50 - 600 mg continuous once daily), 21 patients (multiple myeloma) were treated in study 2103 (dose range: 50 - 500 mg continuous once daily), 7 patients (multiple myeloma) were treated in study 2104 (dose range: 100 - 325 mg continuous once daily), 47 patients (locally advanced or metastatic melanoma) were treated in study 2105 (dose range: 200 – 500 mg continuous once daily), 13 patients (advanced solid malignancies) were treated in study 2106 (4 enrolled into the ADME [absorption, distribution, metabolism and excretion] part using TKI258 at 500 mg single radiolabelled dose on day 1 followed by 400 mg continuous once daily starting from day 15, and 9 enrolled into the extension part using TKI258 at 400 mg continuous once daily), 78 patients (locally advanced/metastatic renal cell cancer) were treated in study 2107 (dose range: 500 - 600 mg for 5 days on/2 days off), 23 patients

Table 1-14 - Summary of clinical trials conducted with TKI258 as of 10 September 2010

Study No. / Phase	Indication / Country or Region	Objectives[a]	Dosing Schedule and Duration	Total Daily Dose[b] (mg/day)	Number of Patients[c]	
					Enrolled / Evaluable for MTD[d]	With DLT During Cycle 1[e] (Event[f])
TKI258 2101 Phase I	Advanced solid tumors / UK	Primary: DLT, MTD & safety profile Secondary: PK, PD, antitumor activity & urinary metabolic profiling	Initial regimen (Schedule A) (15 pts): once daily for 7 days followed by 7-day rest period. Revised regimen (Schedule B) (20 pts): once daily for 7 days followed by 7-day rest period, then continuous dosing in 28-day cycles.	25 (schedule A) 50 (schedule A) 75 (schedule A) 100 (schedule A) 100 (schedule B) 125 (schedule B) 175 (schedule B)	3/3 4/4 4/4 4/3 6/6 7/7 7/6 Total: 35/33	0 0 0 0 0 0 1 (Gr 3 Gamma glutamyltransferase increase) Total: 1
TKI258 2102 Phase I	Acute myeloid leukemia / UK & US	Primary: DLT, MTD & safety profile Secondary: PK, PD & antitumor activity	Once daily for 7 days followed by 7-day rest period, then continuous dosing in 28-day cycles.	50 100 200 400 600 600 (capsules)	3/3 5/5 4/3 6/5 4/0 10/5 Total: 32/21	0 0 0 0 0 2 (Gr 3 Nausea/Vomiting[g], Gr 4 Neutropenia) Total: 2

Study No. / Phase	Indication / Country or Region	Objectives[a]	Dosing Schedule and Duration	Total Daily Dose[b] (mg/day)	Number of Patients[c]	
					Enrolled / Evaluable for MTD[d]	With DLT During Cycle 1[e] (Event[f])
TKI258 2103[h] Phase I	Relapsed & Refractory multiple myeloma / US	Primary: DLT, MTD & safety profile Secondary: PK, PD & antitumor activity	Initial regimen for original protocol and Amend # 1-4 (20 pts including a pt at 500 mg): Once daily for 14 days followed by 7-day rest period (cycle 1), then continuous dosing in 28-day cycles (cycle 2, etc.). Revised regimen Amend #5 (1 pt at 500 mg): Continuous once daily dosing in 28-day cycles starting from cycle 1.	50 100 200 325 325 (capsules) 500 (capsules)	3/3 3/3 7/6 1/0 5/5 2/2 Total: 21/19	0 0 2 (Gr 4 Neutropenia, Gr 3 Anorexia) 0 1 (Gr 3 Hypokalemia) 1 (Gr 4 Fatigue) Total: 4
TKI258 2104[h] Phase I	Relapsed & Refractory multiple myeloma / UK	Primary: DLT, MTD & safety profile Secondary: PK, PD & antitumor activity	Initial regimen for original protocol and Amend #1 (6 pts): continuous twice daily dosing in 28-day cycles starting from cycle 1. Revised regimen for Amend #2-3 (1 pt at 325 mg): Once daily for 14 days followed by 7-day rest period (cycle 1), then continuous once daily dosing in 28-day cycles (cycle 2, etc.). Planned regimen for Amend #4 (no pts): Continuous once daily dosing in 28-day cycle starting from cycle 1.	100 (50 bid) 200 (100 bid) 325 (qd capsules)	4/3 2/1 1/1 Total: 7/5	0 0 1 (Delayed recovery from AST/ALT elevation) Total: 1

Study No. / Phase	Indication / Country or Region	Objectives[a]	Dosing Schedule and Duration	Total Daily Dose[b] (mg/day)	Number of Patients[c]	
					Enrolled / Evaluable for MTD[d]	With DLT During Cycle 1[e] (Event[f])
TKI258 2105 Phase I/II	Locally advanced or metastatic melanoma / US	Primary: DLT, MTD & safety profile Secondary: PK, PD & antitumor activity	Initial regimen for original protocol and Amend #1-2 (17 pts: 2x200, 2x300, 6x400, 7x500): Once daily continuous dosing in 28-day cycles. Revised regimen for Amendment # 3 (30 pts at 400): 2-day PK run-in (TKI258 on day 1; no drug on day 2) added prior to 28-day cycles of dosing.	Escalation : 200 300 400 500 Expansion : 400	 2/2 2/2 16/11 7/7 (escalation) Total: 27/22 20 (entire study) Total: 47	 0 0 3 (Gr 3 Nausea, Gr 3 Fatigue x 2) 3 (Gr 3 Fatigue, Gr 4 Fatigue, Gr 3 Diarrhea) Total : 6 N/A
TKI258 2106 (ADME Trial)	Advanced Solid tumors / Netherlands	Primary: (Cohort 1) ADME & PK; (Cohort 2) safety profile Secondary: (Cohort 1) safety, tolerability, & antitumor activity; (Cohort 2) antitumor activity	Cohort 1: 500 mg [^{14}C] TKI258 single dose on day 1, followed by 400 mg Once daily continuous dosing starting from day 15 in 28-day cycles. Cohort 2: 400 mg once daily continuous dosing in 28-day cycles.	500 [^{14}C] / 400 400	Cohort 1: 4 Cohort 2: 9 Total: 13	N/A N/A

Study No. / Phase	Indication / Country or Region	Objectives[a]	Dosing Schedule and Duration	Total Daily Dose[b] (mg/day)	Number of Patients[c]	
					Enrolled / Evaluable for MTD[d]	With DLT During Cycle 1[e] (Event[f])
TKI258 2107 Phase I/II	Advanced/ metastatic renal cell cancer / US, EU, Taiwan	Primary: (Phase I) DLT, MTD & safety; (Phase II) antitumor activity Secondary: (Phase I) PK, PD & antitumor activity; (Phase II) PK, PD & safety	Once daily dosing for 5 days followed by 2 days rest in 28-day cycles.	Escalation: 500 600 Expansion: 500	 15/15 5/5 (escalation) Total: 20/20 58 (entire study) Total: 78	 1 (Gr 2 Sinus bradycardia) 2 (Gr 3 Asthenia, Gr 4 Hypertensive crisis) Total: 3 N/A
TKI258A2112 Phase I	Advanced solid tumors / US	Primary: BA of FMI capsule vs CSF capsule; food effect Secondary: Safety, preliminary anti-tumor activity	Relative bioavailability (BA) arm: 500 mg on Day 1 and Day 9 followed by 2-9 days rest; then once daily dosing for 5 days followed by 2 days rest in 28-day cycles. Food effect arm: 300 mg once daily for 22 days followed by 2-9 days rest; then once daily dosing for 5 days followed by 2 days rest in 28-day cycles.	BA arm : 500	23	N/A

Study No. / Phase	Indication / Country or Region	Objectives[a]	Dosing Schedule and Duration	Total Daily Dose[b] (mg/day)	Number of Patients[c]	
					Enrolled / Evaluable for MTD[d]	With DLT During Cycle 1[e] (Event[f])
TKI258A2116 Phase I	Advanced solid tumors / US	Primary: BA of FMI tablet vs CSF capsule; food effect Secondary: Safety, preliminary anti-tumor activity	Relative bioavailability (BA) arm: 500 mg on Day 1 and Day 9 followed by 2-9 days rest; then once daily dosing for 5 days followed by 2 days rest in 28-day cycles. Food effect arm: 300 mg once daily for 22 days followed by 2-9 days rest; then once daily dosing for 5 days followed by 2 days rest in 28-day cycles.	BA arm : 500	17	N/A
TKI258A2201 Phase II	Advance urothelia carcinoma / US, Canada, EU, Asia (Taiwan)	Primary: ORR by local assessment (mutant and wild type) Secondary: ORR by central assessment (mutant and wild type) PFS, DCR, safety & tolerability	Once daily dosing for 5 days followed by 2 days rest in 28-day cycles.	500	37	N/A
TKI258 2202 Phase II	Metastatic breast cancer / US, Canada, EU	Primary: ORR Secondary: DCR, PFS, safety, tolerability & PK	Once daily dosing for 5 days followed by 2 days rest in 28-day cycles.	500	76	N/A
TKI258A2204 Phase II	Relapsed & Refractory multiple myeloma / US, Canada, EU, Australia, Turkey	Primary: Extended ORR Secondary: Safety, ORR as per IMWG, PFS, PK	Once daily dosing for 5 days followed by 2 days rest in 28-day cycles.	500	12	N/A
TKI258 1101 Phase I (Japan)	Advanced solid tumors / Japan	Primary: DLT, MTD & safety profile Secondary: PK, PD & antitumor activity	Once daily dosing for 5 days followed by 2 days rest in 28-day cycles.	100 200 300 400	3/3 3/3 7/6 9/9 Total: 22/21	0 0 1 (Gr3 Anorexia) 2 (Gr 3 Nausea/Vomiting, Gr 3 Liver function disorders) Total: 3
				Grand Total:	**420**	

Study No. / Phase	Indication / Country or Region	Objectives[a]	Dosing Schedule and Duration	Total Daily Dose[b] (mg/day)	Number of Patients[c]	
					Enrolled / Evaluable for MTD[d]	With DLT During Cycle 1[e] (Event[f])

[a] ADME = absorption, distribution, metabolism and excretion; DCR = disese control rate; DLT = dose limiting toxicity; MTD = maxium tolerated dose; ORR = overall resonse rate; PD = pharmacodynamics; PFS = progression free survival; PK = pharmacokinetics; BA = bioavailability.

[b] Patients received powder in bottle (PIB) formulation in the 2101, 2102, 2103 and 2104 studies unless capsules are indicated. CSF capsules were used for the 2102 (600 mg/day cohort), 2103 (325 and 500 mg/day cohorts), 2104 (325 mg/day cohort), 2105, 2106, 2107, 2112, 2116, 2201, 2202, 2204 and 1101 studies. In addition, FMI capsules were used in the 2112 study and FMI tabets used in the 2116 study.

[c] Enrollment was as of 10 September 2010. Patients who received at least 1 dose of TKI258 were considered enrolled.

[d] Evaluble for MTD is only applicable to the dose escalation studies. For dose escalation studies, patients who completed cycle 1 or experienced DLT during cycle 1 were considered evaluable for the MTD determining population.

[e] Definition of cycle 1 for dose finding studies:

2101 Schedule A: 7-day on and 7-day off for 28 days; Schedule B: 7-day on, 7-day off then followed by 14-day on (28 days).

2102: 7-day on, 7-day off then followed by 14-day on (28 days).

2103 / 2104: (1) Prior to Amend#5 (2103) / prior to Amend#4 (2104): 14-day on and 7-day off (21 days).

(2) Amend#5 (2103) / Amend#4 (2104): once daily for 28 days.

2105: Prior to Amend#3 the DLT observation period included only the first 14 days of cycle 1; starting with Amend#3 the DLT observation period included the first 30 days of treatment (PK run-in days 1 -2 and cycle 1 days 1-28). All DLTs have been reassessed as per the amendment 3 definition.

2107: 5-day on, 2-day off for 28 days.

1101: Dose determination period include two days of PK run-in prior to the cycle 1, 5-day on 2-day off for 28 days.

[f] The following events were reported in study 2101 as DLTs that occurred after cycle 1: 100 mg: grade 3 hypertension on cycle 2 day 8; 175 mg: grade 3 anorexia on cycle 2 day 9 and grade 3 alkaline phosphatase increase on cycle 2 day 29.

[g] The grade 3 nausea and grade 3 vomiting occurred 2 hours after receiving the first dose of TKI258 at 600 mg. The symptoms elapsed for 10 days and the patient was discontinued from the study without further dosing.

[h] 2103 and 2104 were merged for cohort enrollment. The first merged cohort was 325 mg.

1.7 Adverse Events

1.7.1 Common adverse events (AEs; greater than or equal to 10%)

Table 1-15 to Table 1-17 summarize the most commonly reported adverse events (AEs) regardless of relationship to TKI258 treatment, which are defined as events that occurred in ≥ 10% of the patients who received TKI258 based on AE data in the clinical database as of the 10 September 2010 cutoff date.

The five most commonly reported non-laboratory AEs were nausea, fatigue/asthenia, diarrhea, vomiting and anorexia/decreased appetite for all 3 data groups (continuous daily dosing, global 5 days on/2 days off, and Japanese 5 days on/2 days off (study 1101)). Commonly reported AEs were reversible and manageable; most were mild or moderate in severity (CTCAE grade 1 or 2).

Table 1-15 Commonly reported adverse events (occurring in greater than or equal to 10% patients) regardless of study drug relationship, by preferred term and treatment group (continuous daily dosing: studies 2101, 2102, 2103, 2104, 2105 and 2106)

Preferred Term	<400mg (N=77) n (%)	400mg (N=51) n (%)	500-600mg (N=27) n (%)	All (N=155) n (%)
Nausea	50(64.9)	40(78.4)	22(81.5)	112(72.3)
Fatigue	45(58.4)	37(72.5)	20(74.1)	102(65.8)
Diarrhoea	40(51.9)	37(72.5)	20(74.1)	97(62.6)
Vomiting	33(42.9)	28(54.9)	17(63.0)	78(50.3)
Anorexia	26(33.8)	14(27.5)	7(25.9)	47(30.3)
Headache	28(36.4)	7(13.7)	8(29.6)	43(27.7)
Constipation	19(24.7)	12(23.5)	9(33.3)	40(25.8)
Dyspnoea	21(27.3)	11(21.6)	8(29.6)	40(25.8)
Pyrexia	20(26.0)	10(19.6)	4(14.8)	34(21.9)
Dysgeusia	19(24.7)	13(25.5)	1(3.7)	33(21.3)
Rash	12(15.6)	15(29.4)	3(11.1)	30(19.4)
Weight decreased	10(13.0)	14(27.5)	5(18.5)	29(18.7)
Abdominal pain	15(19.5)	7(13.7)	5(18.5)	27(17.4)
Dizziness	9(11.7)	10(19.6)	8(29.6)	27(17.4)
Back pain	12(15.6)	8(15.7)	5(18.5)	25(16.1)
Anaemia	18(23.4)	3(5.9)	3(11.1)	24(15.5)
Dry mouth	12(15.6)	8(15.7)	3(11.1)	23(14.8)
Cough	11(14.3)	8(15.7)	3(11.1)	22(14.2)
Dehydration	6(7.8)	8(15.7)	8(29.6)	22(14.2)
Oedema peripheral	8(10.4)	6(11.8)	8(29.6)	22(14.2)
Pain in extremity	12(15.6)	4(7.8)	6(22.2)	22(14.2)
Urinary tract infection	9(11.7)	8(15.7)	5(18.5)	22(14.2)
Abdominal pain upper	7(9.1)	11(21.6)	3(11.1)	21(13.5)
Dyspepsia	9(11.7)	7(13.7)	3(11.1)	19(12.3)
Thrombocytopenia	11(14.3)	3(5.9)	5(18.5)	19(12.3)

Table 1-16 **Commonly reported adverse events (occurring in greater than or equal to 10% patients) regardless of study drug relationship, by preferred term and treatment group (5 days on/2 days off dosing: study 2107, 2112*, 2201*, 2202, 2204*)**

Preferred Term	500mg (N=200) n (%)	600mg (N=5) n (%)	All (N=205) n (%)
Diarrhoea	130(65.0)	3(60.0)	133(64.9)
Nausea	121(60.5)	5(100)	126(61.5)
Vomiting	111(55.5)	4(80.0)	115(56.1)
Asthenia	89(44.5)	4(80.0)	93(45.4)
Decreased appetite	76(38.0)	2(40.0)	78(38.0)
Headache	47(23.5)	3(60.0)	50(24.4)
Fatigue	48(24.0)	0(0.0)	48(23.4)
Dyspnoea	43(21.5)	1(20.0)	44(21.5)
Constipation	40(20.0)	0(0.0)	40(19.5)
Dysgeusia	36(18.0)	1(20.0)	37(18.0)
Abdominal pain	34(17.0)	1(20.0)	35(17.1)
Rash	31(15.5)	2(40.0)	33(16.1)
Hypertension	30(15.0)	1(20.0)	31(15.1)
Weight decreased	29(14.5)	1(20.0)	30(14.6)
Abdominal pain upper	29(14.5)	0(0.0)	29(14.1)
Cough	26(13.0)	3(60.0)	29(14.1)
Anaemia	26(13.0)	0(0.0)	26(12.7)
Dry skin	25(12.5)	1(20.0)	26(12.7)
Oedema peripheral	26(13.0)	0(0.0)	26(12.7)
Dizziness	23(11.5)	0(0.0)	23(11.2)
Dry mouth	23(11.5)	0(0.0)	23(11.2)
Pyrexia	19(9.5)	3(60.0)	22(10.7)
Stomatitis	22(11.0)	0(0.0)	22(10.7)
Myalgia	20(10.0)	1(20.0)	21(10.2)

*CTCAE version 4.0 was used in these studies

Table 1-17 **Commonly reported adverse events (occurring in greater than or equal to 10% patients) regardless of study drug relationship, by preferred term and treatment group (5 days on/2 days off dosing: study 1101)**

Preferred Term	<300mg (N=6) n (%)	300mg (N=7) n (%)	400mg (N=9) n (%)	All (N=22) n (%)
Diarrhoea	5(83.3)	5(71.4)	9(100)	19(86.4)
Nausea	3(50.0)	6(85.7)	8(88.9)	17(77.3)
Decreased appetite	2(33.3)	5(71.4)	7(77.8)	14(63.6)
Fatigue	4(66.7)	4(57.1)	5(55.6)	13(59.1)
Vomiting	1(16.7)	5(71.4)	7(77.8)	13(59.1)
Blood alkaline phosphatase increased	2(33.3)	5(71.4)	5(55.6)	12(54.5)
Hypertension	1(16.7)	4(57.1)	4(44.4)	9(40.9)
Lymphopenia	2(33.3)	5(71.4)	2(22.2)	9(40.9)
Weight decreased	0(0.0)	3(42.9)	5(55.6)	8(36.4)
Headache	1(16.7)	0(0.0)	5(55.6)	6(27.3)
Hepatic function abnormal	2(33.3)	1(14.3)	3(33.3)	6(27.3)
Hypertriglyceridaemia	0(0.0)	2(28.6)	4(44.4)	6(27.3)
Hypoalbuminaemia	0(0.0)	3(42.9)	3(33.3)	6(27.3)
Rash	1(16.7)	3(42.9)	2(22.2)	6(27.3)
Blood triglycerides increased	2(33.3)	1(14.3)	2(22.2)	5(22.7)
Cancer pain	2(33.3)	2(28.6)	1(11.1)	5(22.7)
Dysgeusia	1(16.7)	2(28.6)	2(22.2)	5(22.7)
Leukopenia	1(16.7)	2(28.6)	2(22.2)	5(22.7)
Pyrexia	1(16.7)	2(28.6)	2(22.2)	5(22.7)
Stomatitis	0(0.0)	0(0.0)	5(55.6)	5(22.7)
White blood cell count decreased	0(0.0)	2(28.6)	3(33.3)	5(22.7)
Alanine aminotransferase increased	1(16.7)	0(0.0)	3(33.3)	4(18.2)
Constipation	2(33.3)	2(28.6)	0(0.0)	4(18.2)
Neutrophil count decreased	0(0.0)	2(28.6)	2(22.2)	4(18.2)
Palmar-plantar erythrodysaesthesia syndrome	0(0.0)	2(28.6)	2(22.2)	4(18.2)
Anaemia	0(0.0)	2(28.6)	1(11.1)	3(13.6)
Aspartate aminotransferase increased	1(16.7)	0(0.0)	2(22.2)	3(13.6)
Blood albumin decreased	1(16.7)	1(14.3)	1(11.1)	3(13.6)
Blood fibrinogen increased	1(16.7)	1(14.3)	1(11.1)	3(13.6)
C-reactive protein increased	0(0.0)	1(14.3)	2(22.2)	3(13.6)
Dizziness	0(0.0)	2(28.6)	1(11.1)	3(13.6)
Dry mouth	1(16.7)	0(0.0)	2(22.2)	3(13.6)
Haemoglobin decreased	0(0.0)	1(14.3)	2(22.2)	3(13.6)
Myalgia	0(0.0)	0(0.0)	3(33.3)	3(13.6)
Neutropenia	0(0.0)	1(14.3)	2(22.2)	3(13.6)
Pharyngitis	0(0.0)	1(14.3)	2(22.2)	3(13.6)
Platelet count decreased	0(0.0)	1(14.3)	2(22.2)	3(13.6)
Thrombocytopenia	0(0.0)	1(14.3)	2(22.2)	3(13.6)

1.7.2 CTCAE grade 3 and grade 4 adverse events regardless of study drug relationship (greater than or equal to 2%)

The majority of these events were grade 3 across all dosing regimens. In the continuous dosing regimen studies, grade 4 events included 5 cases of fatigue, 2 cases of pyrexia, 1 case of deep vein thrombosis, 5 cases of pulmonary embolism, 2 cases of neutropenic sepsis, and 1 case of pain in extremity. In the global 5 days on/2 days off dosing regimen studies, grade 4 events included 3 cases of pumonary embolism and 1 case of stomatitis. In the Japanese 5 days on/2 days off dosing regimen study (1101), there were no grade 4 events for these AEs.

1.7.3 Laboratory Data

The majority of the hematology laboratory abnormalities were grade 1 or 2 events across all dosing regimens. In continuous dosing regimen studies, five patients (3.5%) had grade 4 hemoglobin values, 7 patients (7.4%) had grade 4 ANC values, 19 patients (14.6%) had grade 4 platelet counts, and 9 patients (6.9%) had grade 4 WBC values during study participation.

The relatively higher incidence rate of grade 3/4 hematology abnormalities in the continuous daily dosing regimen was mainly due to acute myeloid leukemia (study 2102) and multiple myeloma (studies 2103 and 2104) patients. In global 5 days on/2 days off dosing regimen studies, 2 patients (1.3%) had grade 4 ANC values, 1 patient (0.5%) had grade 4 platelet counts, and no patients had grade 4 hemoglobin or white blood counts during study participation. Also, one patient (4.5%) had grade 4 hemoglobin in the Japanese 5 days on/2 days off dosing regimen study and no patients had grade 4 ANC, platelet or white blood cell counts during study participation.

The majority of the chemistry laboratory abnormalities were also grade 1 or 2 events across all dosing regimens. In continuous dosing regimen studies, only 1 patient (0.7%) had grade 4 creatinine value and 2 patients (1.6%) had grade 4 triglyceride values. There were no grade 4 abnormalites observed in cholesterol or amylase laboratory values in the continuous dosing regimen. In global 5 days on/2 days off dosing regimen studies, 2 patients (1.2%) had grade 4 triglycerides and 2 patients (1.1%) had grade 4 cholesterol values. There were no grade 4 abnormalites observed in amylase or creatinine laboratory values in this dosing regimen. Also, there were no grade 4 chemistry laboratory abnormalities observed in Japanese patients.
The majority of the liver function test laboratory abnormalities were also grade 1 or 2 events across all dosing regimens. In the continuous dosing regimen studies, there were no grade 4 laboratory values observed in AST, ALT, total bilirubin or alkaline phosphatase. In global 5 days on/2 days off dosing regimen studies, there were no grade 4 AST laboratory values;

however, 1 patient (0.5%) had a grade 4 ALT value, 1 patient (1.1%) had a grade 4 total bilirubin value, and 3 patients (1.6%) had a grade 4 alkaline phosphatase values. In the Japanese 5 days on/2 days off dosing regimen study, only 1 patient (4.5%) had grade 4 total bilirubin values and no grade 4 values were observed in the AST, ALT or alkaline phosphatase values during study participation.

1.7.4 Hepatic dysfunction as defined by laboratory criteria

As of the 10 September 2010 data cut-off, there were 12 cases with hepatic dysfunction, defined as total bilirubin >2X ULN and AST or ALT > 3X ULN. From the Novartis perspective, in 6 of these cases, data available do not provide any evidence supporting a causal relationship of hepatic dysfunction and dovitinib treatment. The cause of liver injury in these patients was progression of underlying metastatic liver disease, with signs suggestive of pre-existing cholestatic liver injury in 5 out of 6 patients.

For 6 out of 12 patients, a contribution of dovitinib treatment to liver injury cannot be excluded, based on time relationship of onset or worsening of elevated enzyme activities to study treatment and improvement of enzyme activities after stop/interruption of treatment.

None of the above cases qualifies as a "Hy's law" case (Rueben 2004). All of the cases demonstrate a clear cholestatic component, only 2 of 12 cases would qualify as mixed type cholestatic/hepatocellular injury, the remaining 10 cases are of cholestatic injury type. Moreover, factors confounding any qualification as "Hy's law" were present in all 12 patients in terms of underlying disease (malignancy, 10 of 11 solid tumor cases with liver metastases at baseline), and in 10 of 12 patients in terms of concomitant medication. One heavily pre-treated, advanced breast cancer patient with liver, bone and lymph nodes metastases was assessed by the investigator as having drug-related cholestatic hepatic injury leading to death. Confounding factors were present in this fatal case including liver metastases and concomitant medications. Of the remaining 11 patients: 1 patient remains on study, for 1 patient there is no available survival data, and in 9 patients, the deaths were due to disease progression.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To estimate overall survival and early response as characterized by a drop in PSA
- To identify the PSA modulation in 40 selected patients with advanced prostate cancer, and to correlate PSA Modulation with changes in bone remodeling markers.

Secondary Objectives

The secondary objectives of this study are:

- To estimate the objective tumor response rate for subjects with measurable disease at baseline.
- To explore the potential association between serum PSA and bone turnover markers with bone marrow FGF R 1 and FGF9 while on TKI 258
- To explore the predictive values of baseline FGF R 1, FGF9, and FGF signaling in serum and those in the bone marrow before and during treatment with TKI258
- To identify candidate mRNA gene expression changes in bone marrow biopsy aspirate following treatment with TKI258
- To collect and archive bone marrow biopsies and aspirates, serum and plasma in study patients for later hypothesis generating associations
- To explore FGF R expression following eight weeks of TKI 258.

3.0 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an observational study to explore the effect of TKI258 therapy on bone turnover markers (serum bone specific alkaline phosphatase and urinary N-telopeptides), and expression of FGF R 1, on both tumor and host cell compartments in bone marrow.

3.2 Study Duration and Dates

In this oncology study, patients will receive study treatment until clinical disease progression.

4.0 STUDY POPULATION SELECTION

Approximately 40 medically or surgically castrated male patients with metastatic castration-resistant prostate cancer (CRPC) will be enrolled from one study site.

4.1 Inclusion Criteria

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

1) Histologically proven adenocarcinoma of the prostate with evidence for skeletal metastases on bone scan and/or CT scan.
2) Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2. (Karnofsky Performance Status $\geq$ 50%) (Appendix F)
3) Serum testosterone levels $\leq$ 50ng/ml

4) Ongoing gonadal androgen deprivation therapy with LHRH analogues or orchiectomy. Patients, who have not had an orchiectomy, must be maintained on standard dosing of LHRH analogue therapy at appropriate frequency for the duration of the study
5) Progression of disease despite androgen ablation (either documented osseous or soft tissue metastatic disease progression or by PSA criteria progression).
   a) Definition of Progressive disease by PSA evidence: a PSA level of at least 5 ng/ml which has risen on at least 2 successive occasions, at least 2 weeks apart. The participant will need a baseline test and a test to show that the PSA has increased.
6) Discontinue diethylstilbestrol (DES) for ≥ 4 weeks and antiandrogens ≥ 6 weeks prior to study drug.
7) Discontinue any steroids prescribed to specifically treat prostate cancer (for e.g as a secondary hormonal manipulation or for cord compression) ≥ 4 weeks prior to study drug. Steroids chronically prescribed for a non-cancer-related illness (e.g. asthma or COPD) that is well controlled with medical management are permissible to an equivalent of ≤10 mg Prednisone daily.
8) Antiandrogen Withdrawal: Patients who are receiving an antiandrogen as part of primary androgen ablation must demonstrate disease progression following discontinuation of antiandrogen. Disease progression after antiandrogen withdrawal is defined as 2 consecutive rising PSA values, obtained at least 2 weeks apart, or documented osseous or soft tissue progression.
9) For patients receiving flutamide, at least one of the PSA values must be obtained 4 weeks or more after flutamide discontinuation.
10) For patients receiving bicalutamide or nilutamide, at least one of the PSA values must be obtained 6 weeks or more after antiandrogen discontinuation
11) Laboratory Requirements:
   - Adequate adrenal function (absence of symptoms or electrolyte imbalances that indicate adrenal insufficiency).
   - WBC count ≥ 3,000/µl
   - Absolute Neutrophil Count (ANC) ≥ 1,500/µl
   - Hemoglobin ≥ 8.0 g/dL independent of transfusion
   - Platelet count ≥ 75,000/µL
   - Serum albumin ≥ 3.0 g/dL
   - Serum creatinine < 1.5 x ULN or a calculated creatinine clearance > 60 mL/min
   - Serum potassium ≥ 3.5 mmol/L
12) No evidence of chronic or acute DIC (Disseminated Intravascular Coagulation) or bleeding tendency and no angina at rest.
13) Patient must be willing and able to comply with protocol requirements. All patients must sign an informed consent indicating that they are aware of the investigational nature of this study. Patients must also have signed an authorization for the release of their protected health information.

4.2 Exclusion Criteria

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

1. Histologic variants other than adenocarcinoma in the primary tumor
2. Abnormal liver functions consisting of any of the following:
   a) Serum bilirubin ≥ 1.5 x ULN

   b) AST and ALT > 2.5 x ULN
3. Therapy with other hormonal therapy, including any dose of Ketoconazole, finasteride (Proscar), dutasteride (Avodart) any herbal product known to decrease PSA levels (eg, Saw Palmetto and PC-SPES) within 4 weeks of study drug.
4. Requirement for corticosteroids greater than the equivalent of 7.5 mg of prednisone daily.
5. Therapy with samarium or strontium within 8 weeks prior to first dose of study drug.
6. Active infection or concomitant illness that is not controlled with medical management.
7. Prior radiation therapy completed < 4 weeks or single fraction of palliative radiotherapy within 14 days prior to first dose of study drug.
8. Any “currently active” second malignancy, other than non-melanoma skin cancer. Patients are not considered to have a "currently active” malignancy, if they have completed therapy and are considered by their physician to be at least less than 30% risk of relapse over next 3 months.
9. Active psychiatric illnesses/social situations that would limit compliance with protocol requirements.
10. Active or uncontrolled autoimmune disease that may require corticosteroid therapy during study
11. Severely compromised immunological state, including being positive for the human immunodeficiency virus (HIV)
12. Acute or chronic hepatitis B or C
13. Chemotherapy and other investigational therapies (targeted or immunotherapy) will require a 4-week washout period before treatment initiation
14. Initiation of bisphosphonate therapy within 4 weeks prior to first dose of study drug. Patients on stable doses of bisphosphonates that show subsequent tumor progression may continue on this medication; however, patients are not allowed to initiate bisphosphonate therapy during the study.
15. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
    a. History or presence of serious uncontrolled ventricular arrhythmias or presence of atrial fibrillation
    b. Clinically significant resting bradycardia (< 50 beats per minute)
    c. LVEF assessed by 2-D echocardiogram (ECHO) < 50% or lower limit of normal (whichever is higher) or multiple gated acquisition scan (MUGA) < 45% or lower limit of normal (whichever is higher)

d. Any of the following within 6 months prior to study entry: myocardial infartction (MI), severe/unstable angina, Coronary Artery Bypass Graft (CABG), Congestive Heart Failure (CHF), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), Pulmonary Embolism (PE).
e. Uncontrolled hypertension defined by an SBP>150 and/or a DBP>100 mm Hg with or without anti-hypertensive medication.
f. Previous pericarditis; clinically significant pleural effusion in the previous 12 months or current ascites requiring 2 or more interventions per month.

16. History of pituitary or adrenal dysfunction
17. History of gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with the absorption of the study drug.
18. Prior therapy with TKI258
19. Any acute toxicities due to prior chemotherapy and/or radiotherapy that have not resolved to a NCI CTCAE (version 3.0) grade of ≤ 1. Chemotherapy induced alopecia and grade 2 neuropathy is allowed.
20. Condition or situation which, in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study.
21. Men whose partner is a woman of child-bearing potential, (i.e. biologically able to conceive), and who is not employing two forms of highly effective contraception. Highly effective contraception (e.g. male condom with spermicide, diaphragm with spermicide, intra-uterine device) must be used by both sexes during the study and must be continued for 8 weeks after the end of study treatment. Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study. Women of child-bearing potential is defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (e.g., who has had menses any time in the preceding 12 consecutive months).

5.0 STUDY TREATMENT(S)

5.1 TKI258 dose and schedule

Patients will receive a single daily oral dose of of TKI258 for 5 consecutive days, followed by a 2-days rest period. Following an initial 4-week cycle at a starting dose of 400 mg 5 days- on and 2 days off, TKI258 may be escalated to 500 mg/day 5 days-on/2 days off if no significant Grade3/4 AEs or laboratory abnormalities are observed. The dose of TKI258 is NOT individually adjusted by weight or body surface area. TKI258 should be ingested with sufficient amount of water at least 1 hour prior to a meal (breakfast) or at least 2 hours following a meal (breakfast). Alternatively, TKI258 may be taken with a. low-fat meal of ≤ 500 calories with ≤ 20 grams fat.

Treatment cycle

A cycle is arbitrary defined as 28 days (4 weeks) for the purposes of scheduling procedures and evaluations.

A complete treatment cycle is defined as 28 days or 4 weeks.

- TKI258 if given on days 1-5, 8-12, 15-19, 22-26 (5 days on/2 days off) of each cycle.
- The first administration of TKI258 defines Day 1 of the cycle. The last day of a complete cycle is Day 28.

5.2 Permitted study drug adjustments

5.2.1. Dosing schedule.

The decision whether to continue with study drug should be based on individual circumstances and the physician's judgment that continuation is in the patient's best interest. If the study treatment is interrupted, because of its toxicity or a lack a compliance to the treatment schedule by the patient, the following guidelines should apply.

- If TKI258 is taken on a "rest days", then the patient will resume the original 5 days on/2 days off schedule starting with the next day of dosing as follows: if the patient takes an additional dose on Day 6, then the patient will rest on Day 7 and start the 5 days on/2 days off dosing on Day 1; if patient takes a dose on Day 7, then the patient will skip Day 1 of the 5 days on/2 days off and start dosing the following day (Day 2). If patient takes a dose on Day 6 and 7, then the patient will skip Day 1 and 2 of the 5 days on/2 days off and start dosing the following day (Day 3).
- If the patient missed TKI258 dose on Day 1, 2, 3 or 4, he should restart TKI258 the next dosing day and rest on Days 6 and 7
- If the patient missed TKI258 dose on Day 5, 6, 7, he should rest on Days 6 and 7 and restart TKI258 on Day 1 of the next week.

Regardless of the reason for the delay in study treatment, patient must discontinue study treatment when the interval between 2 administrations of treatment exceeds 21 days.

These changes must be recorded on the Dosage Administration Record of the electronic Case Report Form (eCRF).

5.2.2 Dosing modifications.

For patients who are unable to tolerate the protocol-specified dosing schedule of TKI258, dose reduction is permitted to a minimum of 300 mg Table 5-1:

Table 5-1 Dose reduction steps for TKI258

Dose reduction*			
	Dose level - 0	Dose level - 1	Dose level - 2
TKI258	500 mg	400 mg	300 mg**
*Dose reduction should be based on the worst toxicity demonstrated at the last dose. **Dose reduction below 300 mg is not allowed.			

Tables 5-1 and 5-2 provide guidelines for reducing the dose of TKI258 or delaying the treatment when toxicity related to TKI258 occurs. Dose reduction should be based on the worst toxicity demonstrated at the last TKI258 administration. Dose modifications or delays may occur in the setting of lower grade toxicity than defined below if the investigator believes that it is in the interest of the subject's safety. A patient who requires a delay of treatment of >21 days must discontinue the study treatment. All dose modifications should be based on the worst preceding toxicity. Patients are only allowed dose reductions to a minimum of 300 mg.

Toxicity intensity [a]	Dose modification
Hematologic	
Neutropenia	
Grade 1 (ANC < LLN - 1500/mm^3) Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm^3) Grade 4 (ANC < 500/mm^3)	Delay study treatment until resolved to ≤ grade 2, then: If resolved by ≤ 7 days after suspending TKI258, maintain dose level If resolved by > 7 days after suspending TKI258, ↓ 1 dose level
Thrombocytopenia (Platelets)	
Grade 1 (PLT < LLN - 75,000/mm^3) Grade 2 (PLT < 75,000 - 50,000/mm^3)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Delay study treatment until resolved to ≤ grade 1, then: If resolved by ≤ 7 days after suspending TKI258, maintain dose level If resolved by > 7 days after suspending TKI258, ↓ 1 dose level
Grade 4 (PLT < 25,000/mm^3)	Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level
Febrile neutropenia fever of unknown origin without clinically or microbiologically documented infection (ANC <1.0 x 109/L, fever ≥ 38.5°C)	Delay study treatment until resolved, then ↓ 1 dose level
Renal	
Serum creatinine	
Serum creatinine < 1.5 x ULN	Maintain dose level
Serum creatinine 1.5 - 3 x ULN	Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 3 (> 3.0 - 6.0 x ULN) Grade 4 (> 6.0 x ULN)	Discontinue study treatment.

Table 5-2 TKI258 related toxicity management guidelines

Toxcity Intensity	Dose Modification
Hepatic	
Bilirubin	
Total bilirubin < 1.5 x ULN	Maintain dose level
Total bilirubin 1.5 - 3 x ULN	Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 3 (> 3.0 - 10.0 x ULN) Grade 4 (> 10.0 x ULN)	Discontinue study treatment 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. Discontinuation of study treatment is required if concurrent elevations of total bilirubin > 2.0 X upper limit of normal (ULN) and ALT or AST > 3.0 X ULN are observed. In order to characterize hepatic toxicity more precisely, fractionation of bilirubin and alkaline phosphatases will be required for elevated values > 2.0 X ULN and ≥ CTCAE grade 2, respectively.
AST or ALT	
Grade 1 (> ULN - 2.5 x ULN) Grade 2 (> 2.5 - 5.0 x ULN)	Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN)	Delay study treatment until resolved to ≤ grade 1 (or ≤ grade 2 if liver infiltration with tumor present), then If resolved by ≤ 7 days after suspending TKI258, maintain dose level If resolved by > 7 days after suspending TKI258, ↓ 1 dose level Discontinuation of study treatment is required if concurrent elevations of total bilirubin > 2.0 X upper limit of normal (ULN) and ALT or AST > 3.0 X ULN are observed. In order to characterize hepatic toxicity more precisely, fractionation of bilirubin and alkaline phosphatases will be required for elevated values > 2.0 X ULN and ≥ CTCAE grade 2, respectively.
Grade 4 (> 20.0 x ULN)	Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level

Cardiac	
Hypertension	Treatment-emergent hypertension should be treated as per standard cardiology practice. Recommended agents for the management of blood pressure elevations on TKI258 include angiotensin-converting enzyme inhibitors and calcium channel blockers.
Grade 1	Maintain dose level
Grade 2 / 3	Delay the study treatment and initiate/intensify antihypertensive therapy. TKI258 may be restarted in conjunction with standard anti-hypertensive medication if BP is controlled (i.e BP ≤ 150/100 mmHg). If BP is controlled ≤ 7 days after suspending TKI258, maintain dose level If BP is controlled > 7 days after suspending TKI258, ↓ 1 dose level
Grade 4	Delay the study treatment and initiate/intensify antihypertensive therapy. ↓ 1 dose level TKI258 may be restarted in conjunction with anti-hypertensive medication if BP is controlled (i.e BP ≤ 150/100 mmHg).
Cardiac – Other	
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 3/4 (despite maximal anti-diarrheal medication)	Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level
Neurotoxicity	

≥ 1 CTCAE grade level increase	Grade 0 → Grade 1: maintain dose level Grade 0 or 1 → Grade 2 : delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level
≥ CTCAE grade 3	Discontinue study treatment
Hypertriglyceridemia and/or hypercholesterolemia	
Grades 1, 2 or asymptomatic grade 3	Maintain dose level. Initiation or adjustment of an existing triglyceride-and/or cholesterol-lowering agent will be at the discretion of the investigator.
Grade 3 with symptoms or grade 4	Delay study treatment and initiate/ optimize triglyceride-and/or cholesterol-lowering therapy. If the toxicity returns to ≤ grade 3 without symptoms by ≤ 14 days, treatment with TKI258 may resume at the same dose level. **At the re-occurrence** of grade 3 with symptoms or grade 4 toxicity. If within 14 days the patient returns to ≤ grade 3 without symptoms, dosing with TKI258 may resume at the next lower dose level If toxicity does not returns to ≤ grade 3 without symptoms within 14 days, discontinue study treatment.
Amylase and/or lipase elevations	
Grade 1 or 2	Maintain dose level
Asymptomatic grade 3 or 4	Delay TKI258 and evaluate at least twice weekly until ≤ grade 2 then restart at current dose level. If levels have not returned to ≤ grade 2 within 3 weeks then no further TKI258 may be given and the patient should discontinue permanently from the study. A CT scan or other imaging study to assess the pancreas, liver and gallbladder must be performed within 1 week of the first occurrence of any grade 3 elevation of amylase and/or lipase.
Symptomatic grade 3 or 4	TKI258 must be stopped immediately and proper medical intervention taken. Evaluate at least twice weekly until resolution to ≤ grade 1. Clinical manifestations should be monitored as needed until resolution or stabilization of the disease condition. No further TKI258 may be administered.
Pancreatitis	
Grade 1	Maintain dose level
Grade 2, 3 or 4	Discontinue study treatment.
Other adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Delay dose until resolved to ≤ grade 1, then ↓ 1 dose level

Grade 4	Discontinue TKI258 Suspend dose for ≥ CTCAE grade 3 vomiting or nausea only if it could not be controlled despite the use of standard anti-emetics.
All dose modifications should be based on the worst preceding toxicity. Isolated values of ≥ grade 3 alkaline phosphatase values will NOT require dose interruption. ≥ Grade 3 anemia judged to be a hemolytic process secondary to study drug will require discontinuation of study treatment. ≥ Grade 3 lymphopenia considered clinically significant will require dose interruption until resolved to ≤ grade 1, then ↓ dose level. Patients are allowed two dose reductions. If a patient requires a dose interruption of > 21 days, then the patient must be discontinued from the study. Patients who discontinue the study for a study related adverse event or abnormal laboratory value must be followed at least once a week for 28 days and subsequently at 28 day intervals until resolution or stabilization of the event, whichever comes first. [a.] Common Terminology Criteria for Adverse Events (CTCAE Version 3.0) otherwise specified values.	

5.3 Restrictions

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

Oral contraceptives are generally metabolized by CYP3A4/2C9, and act also 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 two highly effective contraceptive methods during the study participation.

Permitted treatments during the study include, but are not limited to the following:

- 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, prasugrel, dipyridamole, fondaparinix) should be allowed except prasugrel, due to its potential drug-drug interaction with either sorafenib or TKI258. Prasugrel is primarily metabolized by the CYP3A4 and CYP2B6 and to a lesser extent by the CYP2C9 and CYP2C19. Co-administration of prasugrel with sorafenib could increase the systemic exposure of parsugrel, since sorafenib could inhibit CYP2B6. In addition, in vitro study demonstrated that TKI258 is an inducer of CYP2C9 and CYP2C19, co-administration of TKI258 with parsugrel is likely to reduce the exposure of parsugrel. For oral anticoagulants, the upper limit of INR is < 1.5.

The following concomitant treatments are not allowed during the study:

- Concurrent use of isoniazid, labetolol, trovafloxacin, 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, 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.

5.3.2 Concomitant therapy with the following is **prohibited**:

- Chemotherapy
- Multifraction radiation therapy
- Immunotherapy
- Radiopharmaceuticals such as strontium (^{89}Sr) or samarium (^{153}Sm)

Patients who require the use of any of these therapies will be discontinued from study-treatment, entered into long-term follow-up for overall survival assessments. Patients who discontinue from the study will be followed for safety outcomes for **30 days** following the patient's last dose or until the patient receives another anticancer therapy, whichever occurs first.

5.3.3 Concomitant therapy with the following is **restricted:**

- 5 α-reductase inhibitor
- Ketoconazole, diethylstilbestrol, PC-SPES, and other preparations such as saw palmetto thought to have endocrine effects on prostate cancer
- Potent inhibitors/inducers of the following CYP450 enzymes including quinidine (a CYP2D6 inhibitor), fluvoxamine (CYP1A inhibitor), omeprazole (a CYP1A inducer), ketoconazole, itraconazole, erythromycin and glibenclamide (CYP3A4 inhibitors), as well as phenobarbital, phenytoin, carbamazepine and rifampicin (all CYP3A4 inducers), should be

used with caution. A comprehensive list of medications that inhibit, induce, and/or are metabolized by the various CYP 450 enzyme isoforms can be found at http://medicine.iupui.edu/flockhart. See also, Appendix H.

The decision to administer a restricted therapy should be made based on the consideration of the safety of study participant. Such therapies will be used with careful monitoring.

5.4 Treatment Compliance

The investigator must keep an accurate accounting of the number of investigational capsules received from Novartis, dispensed to the patients, the number of units returned to the investigator by the patient, and the number of units returned to Novartis during and at the completion of the study. The study drug must be dispensed only by an appropriately qualified person to patients in the study. The drug is to be used in accordance with the protocol by patients who are under the direct supervision of an investigator.

5.5 Packaging and Labeling

TKI258 100 mg is supplied as a hard gelatin capsule/tablet. The capsules will be provided in either blisters or bottles. TKI258 medication labels will comply with the legal requirements of each country and be printed in the local language. The inactive ingredients for the dovitinib capsules are pregelatanized starch, colloidal silicon dioxide, microcrystalline cellulose, and magnesium stearate.

5.6 Storage and Accountability

The study drug must be stored in a secure area, limited access area. The storage conditions are described on the medication label. It will be administered only to patients entered into the clinical study, at no cost to the patient, in accordance with the conditions specified in this protocol. The capsules/tablets should be stored according to the label in a secured, limited access area until required.

5.7 Investigational Product Retention at Study Site

The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (patient by patient accounting), and accounts of any study treatment accidentally or deliberately destroyed. At the end of the study, reconciliation must be made between the amount of study treatment supplied, dispensed, and subsequently destroyed or returned to Novartis or its representative.

6.0 STUDY PROCEDURES

6.1 Informed Consent

The study will be discussed with the patient, and any patient wishing to participate must give informed consent and Authorization for Use and Release of Health and Research Study Information prior to any study-related procedures or change in treatment.

A signed, Institutional Review Board (IRB) approved, informed consent must be obtained from patients before any study specific procedures or registration for study treatment can occur.

6.2 Medical History

Medical history, such as previous treatments, procedures, and conditions will be collected during the screening period.

6.3 Physical Examination

Physical examination includes weight, HEENT (head, eyes, ears, nose, and throat), chest, cardiac, abdominal, extremities, neurologic, and lymph node examinations.

6.4 Vital Signs

Vital signs include blood pressure, heart rate, respiratory rate, and oral body temperature.

6.5 Adverse Events Assessments

6.5.1 Performing Adverse Events Assessments

All study patients who have received any dose of TKI258 will be evaluable for safety. Adverse events including laboratory adverse events deemed clinically significant by the investigator will be graded and summarized according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0.

6.5.2 Definition of an Adverse Event

An adverse event (AE) is any reaction, side effect, or other untoward medical occurrence, regardless of relationship to study drug that occurs any time from the beginning of the first study dose administration until the final study visit or early termination visit. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

6.5.3 Timing

Any AE or SAE experienced by the patient from Day 1 to 30 days post last dose should be followed-up to determine if any new or ongoing drug-related AE or any SAE regardless of relationship to study drug exists. Follow-up could be conducted by site via telephone attempts.

6.5.4 Severity

Adverse-event severity is a clinical determination of the intensity of an AE. The severity assessment for a clinical AE should be completed using the NCI CTCAE (version 3.0).

6.5.5 Relationship

A determination should be made by the investigator regarding the relationship (if any) between an AE and the study drug. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE may have been caused by the study drug.

6.5.6 Expectedness

Management of Symptoms Related to Castration
Treatment with androgens, estrogens, and progestin to control hot flushes is not allowed. Antidepressants are permitted for the management of hot flashes. Selective serotinin reuptake inhibitors (SSRIs) are also permitted.

Management of Persistent and Refractory Toxicity
Utilizing the NCI CTCAE (version 3.0), events which are moderate and interfere with function that are not consistent with a patient's medical history, and are refractory to medical treatment, should be investigated carefully to ensure that no other etiology is present. Study drug will be held for any toxicity events deemed definitely, probably, or possibly drug-related (such as diarrhea, hypertension, vomiting, diarrhea, and dizziness) and that are greater than grade 2. Drug will be held until severity is reduced to Grade 1 or less and then resumed daily dosing with a dose reduction of 1 capsule as outlined in section 5.2. Up to 2 dose reductions, ie, 5→4 capsules, 4→3 capsules, are allowed as outlined in section 5.2. Patients with toxicities that fail to resolve to ≤Grade 1 within 21 days will be taken off study.

Management of All Other Toxicities
Other toxicities may occur. Supportive care should be prescribed as needed. They may also be prescribed prophylactically to prevent toxicity from developing or recurring. The examples include anti-emetics for nausea/vomiting, analgesics for pain, antipyretics for fever and antidiarrheals for diarrhea. Because long-term

androgen deprivation may lead to metabolic diseases, such as glucose intolerance, hypercholesterolemia, osteoporosis, and anemia, appropriate medication may be prescribed.

Abnormal laboratory values will be only be captured as adverse events if deemed "clinically significant" by the investigator.

6.5.7 Clinical Laboratory Adverse Events

The results of all laboratory tests required by the protocol will be recorded in the patient's medical record. All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator or until a diagnosis that explains them is made.

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, and/or
3. Test result leads to a change in study dosing or discontinuation 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 SAE, and/or
5. Test result is considered to be an adverse event by the investigator or sponsor.

*Merely repeating an abnormal test, in the absence of any of the above conditions, does not meet Condition 2 above for reporting as an adverse event.

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.

6.7 Serious Adverse Event (SAE) Reporting

A serious adverse event is – any adverse drug experience occurring at any dose that 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 disability/incapacity – a substantial disruption of a person's 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 drug abuse (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, Office of Research Education and Regulatory Management (ORERM).

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must by reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to ORERM, regardless of attribution.

- All life-threatening or fatal events, expected or unexpected, and regardless of attribution 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 ORERM.

- The MDACC "Internal SAE Report Form for Prompt Reporting" will be used for reporting to ORERM.

- Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory test 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 ORERM. 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 ORERM) 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.

Investigator Communication with Supporting Companies:

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Integrated Medical Safety.
All events reported to the FDA by the investigator are to be filed utilizing the MDACC Serious Adverse Events form.

All events must be reported, by FAX (*877-778- 9739*) along with Novartis SAE Report FAX Cover sheet, to Novartis Pharmaceuticals Integrated Medical Safety Department within 24 hours of learning of it's occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

6.8 Concomitant Medication Assessments

Supportive care medications are permitted with their use following institutional guidelines. For patients who did not undergo orchiectomy, concurrent treatment with LHRH analogue is mandatory and must be recorded.

The concurrent administration of other anticancer therapy, including cytotoxic, hormonal (except LHRH agonists), or immunotherapy is prohibited during study

treatment phase. Use of other investigational drug therapy for any reason is prohibited.

6.9 Removal of Patients from the Study or Study Drug

6.9.1 The investigator must withdraw a patient from study treatment or the study for any of the following reasons:

- Progressive disease. As clinical benefit may be independent of PSA-modulation, progressive disease will not be defined by PSA criteria alone. Rather progressive disease will be defined as any skeletal related event (6.9.2) or tumor progression as defined by RECIST criteria (Appendix I) accompanied by PSA progression or investigator defined clinical progression:
- A serious or intolerable AE occurs as described in 6.7.
- The sponsor or investigator terminates the study.
- The patient requests to be discontinued from the study.

6.9.2 Definition of skeletal-related events (SREs) consisting of the following discrete clinical events or unequivocal radiological changes related to underlying disease progression:

- Progression by radionuclide bone scan with 2 or more new lesions. If progression is noted at the first assessment (ie, Week 12), then a confirmation by a second scan is required 6 or more weeks later that shows a minimum of 2 or more additional new lesions.
- Pathologic bone fracture in the region of cancer involvement that occur spontaneously or as the result of trivial trauma. Each pathologic fracture (vertebral and non-vertebral is to be documented by appropriate diagnostic imaging.
- Radiation therapy to bone - radiation administered to bone to palliate painful lesions or prevent or treat pathologic fractures or spinal cord compression.
- Administration of a radioisotope, such as strontium 89, will be included as radiation to bone.
- Cancer-related surgery to bone - procedures that are performed to set or stabilize pathologic fractures or areas of spinal cord compression, and surgical procedures that are performed to prevent a pathologic fracture or spinal cord compression.
- Spinal cord or nerve root compression - these will be confirmed by MRI. If spinal cord compression occurs in conjunction with vertebral compression, each will be counted seapartely.

6.9.3. Tumor progression as defined by RECIST criteria (see Appendix I).

Bone lesions will not be considered measurable for purposes of RECIST evaluation of disease.

6.10 Other Study Procedures

Supportive care medications are permitted with their use following institutional guidelines. As mentioned in the eligibility criteria, patients must have ongoing gonadal androgen deprivation therapy with LHRH analogues or orchiectomy. Patients, who have not had an orchiectomy, must be maintained on effective LHRH analogue therapy for the duration of the trial.

The concurrent administration of other anticancer therapy, including cytotoxic, hormonal (except LHRH agonists), or immunotherapy is prohibited during study treatment phase. Use of other investigational drug therapy for any reason is prohibited.

7.0 STUDY ACTIVITIES (Appendix J)

On-study tests/visits that must occur within a defined time frame shall have a standing window of allowance that is equal to +/- 2 days for any laboratory testing**.**

7.1 Screening Period (Days –30 to Day 1)

The following activities/procedures will be conducted during the screening period which may occur within 30 days prior to registration the following baseline evaluations shall be performed:

- Complete medical history must be available in the patient's medical record
- Chest X-ray
- CT or MRI scans of the pelvis and abdomen.
- Bone Scan
- Baseline (pre-treatment) bone marrow biopsy and aspiration within 30 days prior to registration. The specimens will be evaluated by pathology. A portion of bone marrow will be banked for bone marker testing. Patients who have undergone a bone marrow aspirate and biopsy outside the context of this clinical trial are eligible for the trial and may elect not to repeat these baseline studies if the samples were collected within 12 weeks prior to initiation of TKI258 therapy. If a portion of the tissue collected from a previous bone marrow aspirate and biopsy was banked for future use under Lab02-152, Lab03-0320, or another GU clinical trial, the tissue will be requested for this timepoint.
- Electrocardiogram (ECG)
- Echocardiogram or MUGA scan

7.2 Screening Period (Days –14 to Day 1)

The following activities/procedures will be conducted during the screening period which may occur within 14 days prior to registration the following baseline evaluations shall be performed:

- Interim medical history including demographics
- Oncology history
- Physical examination
- Vital signs including blood pressure, heart rate, respiratory rate, oral body temperature, weight and height.
- List of concurrent medications and baseline adverse events
- Assessment of ECOG Performance Status
- Laboratory testing:
  - CBC with differential/platelets
  - Serum chemistry must include: BUN , creatinine, total bilirubin, albumin, SGOT [AST], SGPT [ALT], GGT, LDH, amylase, lipase, alkaline phosphatase, fasting glucose, calcium, sodium, magnesium, phosphorus, and potassium
  - PSA assessment.
  - Serum testosterone and DHT levels.
  - Bone Specific Alkaline Phosphatase
  - Blood for Biomarker Studies
  - N-telopeptides in urine

Correlative Studies: Assessment of serum and bone marrow aspirate androgen levels, plus additional serum/plasma banking.

7.3 Treatment Period (Day 1 to Termination of Treatment)

7.3.1 Day 1

Patients who are eligible after screening will be registered and start study treatment after the Screening visit. For all patients, a minimum of 3 sequential ECGs, separated by at least 5-10 minutes, must be performed on cycle 1 day 1 prior to the first administration of TKI258. This is necessary to get an accurate baseline QTc calculation. ECGs will also be performed during the course of treatment (see section 7.4 below)

7.3.2 Day 1 Treatment

At initiation (Day 1) and for the duration of the study, patients will be instructed to take five 100mg capsules by mouth once daily (total of 500 mg of TKI 258 per day). TKI258 should be ingested with sufficient amount of water at least 1 hour prior to a meal (breakfast) or at least 2 hours following a meal (breakfast).

7.4 Evaluation during Treatment

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 for any laboratory testing. If

screening lab tests take place less than 7 days prior to C1D1, laboratory testing will not be repeated.

7.4.1 Beginning on Cycle 1 Day 1 and continuing every 4 weeks thereafter, patients will undergo the following additional testing:

- History and physical exam
- Vital Signs (BP, pulse)
- Weight
- PS (ECOG)
- Assessment of concurrent medications
- Assessment of AEs
- PSA test
- Blood for Biomarker studies (Day 1 of Cycles 2 and 3 only)
- Serum chemistry must include: BUN , creatinine, total bilirubin, albumin, SGOT [AST], SGPT [ALT], GGT, LDH, amylase, lipase, alkaline phosphatase, fasting glucose, calcium, sodium, magnesium, phosphorus, and potassium

7.4.2 On Cycle 1, Days 12 and 26 and Cycle 2 Day 12 patients will undergo the following tests:

- CBC with differential/platelets
- Serum chemistry must include: BUN , creatinine, total bilirubin, albumin, SGOT [AST], SGPT [ALT], GGT, LDH, amylase, lipase, alkaline phosphatase, fasting glucose, calcium, sodium, magnesium, phosphorus, and potassium
- There will be a blood draw for a TKI258 trough concentration (Cycle 2 Day 12 Only) to evaluate the potential relationship of safety and efficacy in regards to steady state drug concentrations.

Note that the Day 26 of Cycle 1 visit could end up being scheduled on the same day as the Day 1 of Cycle 2 visit described above.

7.4.3 Beginning on Cycle 1 Day 1 and every 4 weeks for the first 8 weeks, and every 8 weeks thereafter, patients will undergo the following additional testing:

- Urine N-telopeptide
- Bone Alkaline Phosphatase

7.4.4 ECGs, cardiac enzymes, and MUGA/ECHO during therapy will be assessed as shown below in Table 7.1:

Table 7.1

Assessment	Cycle and Day	Time Point
12-lead ECG	Screening	Anytime
	Cycle 1, Day 1	3 sequential ECGs, separated by at least 5 to 10 minute intervals pre-dose
	Cycle 1, Day 1	1 ECG six hours post-dose
	Cycle 1, Day 26	1 ECG pre-dose
	Cycle 2, Day 26	1 ECG pre-dose
	Cycle 3, Day 26	1 ECG pre-dose
	Cycle 4+, Day 1	Anytime at the end of the previous cycle
	EOT	Anytime
Cardiac enzymes (troponin I or B, CPK, and CPK-MB)	Screening	Anytime to coincide with ECHO/MUGA
	Every 12 weeks while receiving therapy	To coincide with ECHO/MUGA
	EOT	Anytime to coincide with ECHO/MUGA
ECHO/MUGA	Screening	Anytime to coincide with cardiac enzymes
	Every 12 weeks while receiving therapy	To coincide with cardiac enzymes
	EOT	Anytime to coincide with cardiac enzymes.

7.4.5 A bone marrow biopsy and aspirate will be performed between 7 and 10 weeks (preferably at week 8) after beginning treatment. The specimens will be evaluated by pathology. A small portion of the bone marrow aspirate will be used for bone marker testing (to include bone marrow androgen levels).

7.4.6 Routine restaging scans and/or other disease assessment diagnostics will be performed every 8 weeks for the first 6 months and every three months thereafter. Such studies can be also be performed at the time of clinical disease progression (at the discretion of the study investigator).

7.5 Final Study Visit:

At the end of the study and within 4 weeks of study drug termination the following will be performed

- History and physical exam
- Vital Signs (BP, pulse)
- Weight

- Eastern Cooperative Oncology Group (ECOG) Performance Status
- Assessment of concurrent medications
- Adverse event evaluation
- Laboratory testing:
- CBC with differential/platelets
- Serum chemistry must include: BUN , creatinine, total bilirubin, albumin, SGOT [AST], SGPT [ALT], GGT, LDH, amylase, lipase, alkaline phosphatase, fasting glucose, calcium, sodium, magnesium, phosphorus, and potassium
- PSA test
- N-telopeptides in urine
- Correlative Studies (serum and bone marrow androgen testing, plus additional serum/plasma banking)
- Disease Status Assessment
- Chest X-ray
- Electrocardiogram (if not done in the past 6 weeks)
- CT or MRI scans of the pelvis and abdomen (if indicated)
- Bone scan (if indicated)
- Bone marrow biopsy and aspirate: The specimens will be evaluated by pathology. A small portion of the bone marrow aspirate will be used for bone marker testing.

7.6 Long-Term Follow Up

Patients will be followed a minimum of every 3 months by clinic visit (at M.D. Anderson or a local physician), telephone or e-mail correspondence to assess delayed toxicity and survival time.

8.0 WITHDRAWAL FROM STUDY TREATMENT

The investigator may withdraw a patient from study treatment phase for any of the following reasons:

- Dosing noncompliance: Study drug administration and dosing compliance will be assessed on Week 4 visit. A count of study drug will be conducted during this visit and patient dosing compliance will be assessed. If dosing compliance is not 100% in the absence of toxicity, patient should be re-instructed regarding proper dosing procedures and continue in the study. Subsequent dosing compliance procedure will be conducted at each study visit. If a patient misses 14 or more doses within a single 28-day cycle, the patient should be discontinued from the study treatment phase. All End-of-Study treatment procedures should be followed. The patient will be followed for survival.
- Sustained Side Effects: Patients who have sustained toxicities, such as described in 6.5.6, which does not return to NCI CTCAE (version 3.0) Grade 1 or less with appropriate medical management, should be discontinued from the study treatment phase. All End-of-Study treatment procedures should be conducted. The patient will be followed for survival.
- Initiation of new anticancer treatment: Patients will be discontinued from the study treatment when investigator, in his or her judgment, determines new treatment for

prostate cancer is warranted. All End-of-Study treatment procedures should be conducted and the patient will be followed for survival.

- Administration of prohibited medications: The patient will be discontinued from the protocol treatment when prohibited drug is administered. All End of Study treatment procedures should be conducted. The patient will be followed for survival. Supportive care medications are permitted with their use following institutional guidelines. For patients who did not undergo orchiectomy, concurrent treatment with LHRH analogue is mandatory and must be recorded. The concurrent administration of other anti-cancer therapy, including cytotoxic, hormonal (except LHRH agonists), or immunotherapy is prohibited during study treatment phase. Use of other investigational drug therapy for any reason is prohibited
- Patient's withdraws consent. In this event, the reason(s) for withdrawal must be documented A patient's decision to take part in the study is voluntary and he may choose not to take part in the study or to stop taking part at anytime. If he chooses not to take part or to stop at anytime, it will not affect his future medical care or medical benefits.

9.0 QUALITY CONTROL AND ASSURANCE

During and/or after completion of the study, quality assurance officers named by Novartis or the regulatory authorities may wish to perform on-site audits. The investigators will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

Novartis representatives are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that patient confidentiality is respected.

10.0 PLANNED STATISTICAL METHODS

This is a phase IIA activity trial of TKI258 for treatment of castrate resistant prostate cancer with skeletal metastases. The two primary outcomes are survival time and early response as characterized by a drop in PSA as defined by working group criteria. Based on historical mean survival time 8 months, a mean survival time on average > 10 months with TKI258 would be considered promising evidence of anti-disease activity. The planned sample size is 40 patients, with an anticipated accrual rate of 3 patients per month. Based on historical experience using carefully selected candidates with evidence for iliac involvement on bone scan, we anticipate that ~60% of patients will have positive biopsies. No early stopping rule in terms of the probability of PSA response will be employed because it is not known whether blocking the stromal-epithelial interactive pathway (SE-pathway) will be related to clinical benefit. Consequently, it may be the case that PSA does not drop but survival time is prolonged due to inhibition of disease progression by TKI258. Given the short survival time of these patients and anticipated accrual rate of 3 patients per month, it also will not be

feasible to implement an early stopping rule in terms of observed survival times. Based on an historical rate of 20% grade 3 or 4 toxicity with standard therapies the method of Thall and Sung (1998) will be used to monitor toxicity. Unadjusted survival time will be estimated using the method of Kaplan and Meier (1958) and the effects of the following four potential prognostic covariates: Inhibition of FGF signaling by bone marrow biopsy at 4 weeks, modulation of the bone markers (a) urinary NTX and (b) bone specific alkaline phosphatase, and baseline signature of FGF signaling in terms of FGF R-1, FGF R-3 and FGF 9 on Prob(PSA response) will be estimated using logistic regression, and on survival time will be estimated using the Cox model or an appropriate time-to-event regression model.

Preliminaries: This is a phase IIA activity trial of TKI258 for treatment of castrate resistant prostate cancer with skeletal metastases. The two primary outcomes are survival time and early response as characterized by a drop in PSA as defined by working group criteria (25).

Historical Experience and Goals: Based on the historical experience in which the mean survival time was 8 months, under a Bayesian model we assume that the unadjusted mean survival time with TKI258 follows an uninformative inverse gamma with mean 8 and variance 1000, equivalently with scale parameter 2.064 and shape parameter 8.512, denoted mE ~ IG(2.064, 8.512). A mean survival time on average > 10 months would be considered promising evidence of anti-disease activity. Formally, assuming that the historical mean survival mH ~ IG(52, 400), TKI258 will be considered promising if, based on the data from the trial, Pr(mE > mH | data) > .95. The planned sample size is 40 patients, with an anticipated accrual rate of 3 patients per month. In addition, the relationships between several potential prognostic covariates and the above clinical outcomes will be explored, as described below.

Monitoring Rules: No early stopping rule in terms of the probability of PSA response will be employed because it is not known whether blocking the stromal-epithelial interactive pathway (SE-pathway) will be related to clinical benefit. Consequently, it may be the case that PSA does not drop but survival time is prolonged due to inhibition of disease progression by TKI258. Given the short survival time of these patients and anticipated accrual rate of 3 patients per month, it will not be feasible to implement an early stopping rule in terms of observed survival times. However, based on an historical rate of 20% grade 3 or 4 toxicity with standard therapies, it will be assumed that p = Prob(grade 3 or 4 with TKI258) follows a beta prior with parameters (.20, .80). Using the method of Thall and Suung (26), based on the observed toxicity data, accrual to the trial will be stopped early if Pr(p > .20 | data) > .95, with this rule applied after successive cohorts f size 5. This rule says to stop the trial if [# patients with a grade 3 or 4 toxicity]/[# patients evaluated] is greater than or equal to 3/5, 5/10, 7/15, 8/20, 9/25, 11/30, 12/35. The operating characteristics of this rule are summarized in the following table.

True Prob(toxicity)	Prob(Stop Early)	Achieved Sample Size 25^{th}, 50^{th}, 75^{th} percentiles

.10	.01	40 40 40
.20	.11	40 40 40
.30	.47	20 40 40
.40	.86	5 15 25

Data Analysis. If the data on the 40 patients yield a sample mean of 10 months (the targeted 25% improvement) based on total follow-up time 400 months (all 40 deaths observed) then the posterior of m would be IG(42.064, 408.512), which has mean 9.95 months and posterior 95% credible interval 7.33 – 13.4 months. Similarly, if 35 deaths are observed with 5 death times administratively censored and total follow-up 460 months at the final analysis then the posterior of m would be IG(37.064, 468.512),), which has mean 13 months and posterior 95% credible interval 9.39 – 17.95 months. Unadjusted survival time will be estimated using the method of Kaplan and Meier (27). The effects of the following four potential prognostic covariates on Prob(PSA response) will be estimated using logistic regression (28), and on survival time will be estimated using the Cox model or, if the proportional hazards assumption is not satisfied, using an appropriate time-to-event regression model chosen based on preliminary goodness-of-fit analyses of the data (29). Each of the following covariates is a binary indicator.

1. Inhibition of FGF signaling by bone marrow biopsy at 4 weeks.

2. Modulation of the bone markers (a) urinary NTX and (b) bone specific alkaline phosphatase

3. Baseline signature of FGF signaling in temrs of FGF R-1, FGF R-3 and FGF 9.

Time of disease progression if defined by PSA alone is defined as follows: Three consecutive PSA elevations above nadir or baseline are required. Each increment in PSA should be a minimum of 1 ng/ml and at least 2 weeks apart or will not count. The time of PSA progression will be taken as the time of the first of these PSA elevations that represents an increment by at least 25% above the nadir or baseline. Given that increments in PSA do not always represent treatment failure, particularly when novel agents with uncertain effects on PSA levels are being evaluated, clinical and radiological correlation is recommended at the discretion of the treating physician. In patients with PSA progression alone without clinical or radiological evidence of disease progression, continued therapy on study is at the discretion of the treating physician in consultation with the principal investigator.

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