PROTOCOL SUBMISSION FORM **Amendment Form**	PROTOCOL NO. 07C0059-I	PRINCIPAL INVESTIGATOR (NIH Employee Name, Inst/Br, Telephone and e-mail): William Dahut NCI MOB 301.435.8183 dahutw@mail.nih.gov

PROTOCOL TITLE: A Phase II Study of AZD2171 in Metastatic Androgen Independent Prostate Cancer

ABBREVIATED TITLE: AZD2171 in Prostate Cancer Reference Number: 309589

Amendment Version Date: 03/17/2010 Amendment Letter: I

The Following revisions were incorporated into this protocol and approved by:

☒ Expedited Review (risk/ benefit ratio not changed)
☐ Full Board Review (meeting date)

Amendment includes changes required by:

☐ N/A
☐ NCI IRB
☒ CTEP
☐ Other Sponsor
☐ FDA
☐ Other

If Other, list:

Amendment required Scientific Review?

☐ Yes ☒ No

ADMINISTRATIVE CHANGES

☐ Protocol Title/ Abbreviated Title
☐ New Principal Investigator
☐ NIH Personnel Change
☐ Non-NIH Personnel Change
☐ Converting to multi-institutional trial

DEC clearance required? ☐ Yes ☒ No

Date submitted to IC DEC: N/A Date cleared by IC DEC: N/A

PROTOCOL CONTENT CHANGES

☐ Precis
☐ Study Objectives
☐ Background and Rationale
☐ Eligibility Assessment and Enrollment
☐ Implementation of Study Design
☐ Supportive Care
☐ Accrual Ceiling Changed to: N/A
☐ Data Collection/Evaluation
☐ Human Subject Protections
☒ Data Reporting
☐ IND/IDE/Commercial Products Information
☐ Pharmaceutical Information
☐ Appendices

Does the amendment impact the risk/benefit assessment?

☐ Yes ☒ No

INFORMED CONSENT DOCUMENTATION

☒ Text Revisions to Consent(s)
☐ Investigator Contact Information on Consent(s)
☐ No Changes to Consent Form

SIGNATURE

William Dahut - applied signature on 05/14/2010 4:18 PM EDT
New and Old Principal Investigators - electronic signature and date

APPROVALS

Giuseppe Giaccone - applied signature on 05/05/2010 3:54 PM EDT
Branch Chief - electronic signature and date

Not Applicable
Branch Scientific Review Committee Chair - electronic signature and date

Kevin Camphausen - applied signature on 05/19/2010 11:32 AM EDT
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Wanda Salzer - applied signature on 05/19/2010 3:21 PM EDT
Chair, IRB Review - electronic signature and date

Ramya Ra 5/24/10 AM I

IRB Meeting Date:

NCI Protocol #: CTEP LOI 7395

Local Protocol #: 07C0059 Amendment I

TITLE: A Phase II Study of AZD2171 in metastatic androgen independent prostate cancer

Abbreviated Title: Phase II AZD2171in Prostate Cancer

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NCI Supplied Agent: AZD2171 (NSC 732208) IND # 72740

Protocol Version Date: March 17, 2010

Schema (All times are approximated):

Frequent blood pressure monitoring
Renal function monitoring
Troponin T or troponin I monitoring
Enzymes monitoring monthly

Cycles repeat every 28 days with AZD2171 20 mg, oral administration, once daily.

Prior to C1D1 Baseline Evaluation
Technetium-99 Bone Scintigraphy, Chest X-ray, CT scan of chest, abdomen and pelvis (within 4 wk prior to enrollment)
Laboratory Evaluation (within 16 days prior to enrollment)
Tumor Markers (within 16 days prior to enrollment)
History and Physical Exam, with vital sign (Within 1 week prior to enrollment)
PSA (baseline – within 7 days prior to enrollment)
Cardiac evaluation (baseline– obtained within 16 days prior to enrollment)

C1D1 AZD2171 tablets equal to 20 mg, oral administration, with 250 ml water, taken in empty stomach

Pharmacokinetic samples will be drawn at pre, 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 12 hr, 24 hr, and 48 hours after drug administration

C1D2 Pharmacokinetic samples will be drawn at 24 hr

Pharmacokinetic samples will be drawn at each following clinic visit

Approximately every subsequent 4 weeks,
Follow-up Evaluation
Laboratory Evaluation
Tumor Markers
History and Physical Exam

PRECIS

Background:
* AZD2171 is an oral potent inhibitor of receptor tyrosine kinases which impact vascular endothelial growth factor-A (VEGF)
* VEGF appears important in blood vessel formation and disease progression in prostate cancer
* No known effective therapy in patients with progressive androgen-independent prostate cancer after treatment with docetaxel

Objectives:
* Primary objective of this study is to determine if AZD2171 is associated with a 30% 6 month probability of progression free survival in patients with metastatic AIPC as determined by clinical and radiographic criteria
* Secondary objective of this study will be demonstration of biologic effect by the drug in the patient and on the tumor (when possible). Correlative studies will be conducted on serially obtained tissue biopsies and white blood cell collections.
* Laboratory correlates will include elucidation of activation of components of the VEGFR2 and angiogenesis pathways and evaluation of endothelial cell adhesion molecules (released by damaged cells) using ELISA, pharmacogenetic analysis of KDR variants and single nucleotide polymorphisms, and pharmacokinetic characterization of AZD2171 activity.

Eligibility:
* Metastatic progressive androgen-independent prostate cancer.
* Prior treatment with docetaxel.
* May not have QTc > 470 msec
or >1+ proteinuria on 2 consecutive dipsticks no less than 1 week apart

Design:
* Phase II trial with a two stage design. 12 patients enrolled in first cohort, if 2 or more are progression free @ 6 months than enroll up to 35 evaluable patients. The ceiling will be set at 37 to allow for inevaluable patients.
* Starting dose 20 mg QD for all patients
* Once two stage design is complete then prednisone 10 mg once per day will be given in combination with AZD2171. The total number of patients will be 23 for this portion of the protocol.

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1. OBJECTIVES

1.1. Primary

The primary objective of this study is to determine if AZD2171 is associated with a 30% 6 month probability of progression free survival in patients with metastatic AIPC as determined by clinical and radiographic criteria.

1.2. Secondary

1.2.1 Measurement of overall response rate and overall survival. Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee.

1.2.2 Document survival from the point of PSA progression in the absence of radiologic or clinical progression.

1.2.3 Demonstration of biologic effect by AZD2171 in the patient and on the tumor (when possible) via correlative studies will be conducted on serially obtained tissue biopsies, and dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI). Laboratory correlates will include determining serum and tissue concentrations of Vascular Endothelial Growth Factor Receptor (VEGFR) as well as tissue microvessel density count.

1.2.4 Measurement of the pharmacokinetics of AZD2171 in human patients with prostate cancer.

1.2.5 Description of the prostate specific antigen (PSA) response rate to therapy with AZD2171

2. BACKGROUND

2.1 Androgen-independent Prostate Cancer

Prostate adenocarcinoma is the most common malignancy in American men and the second leading cause of cancer related deaths (Rini 2002; Jemal 2003). According to the SEER database, 42% of patients have either metastatic disease or will eventually progress following local therapy. Whereas androgen ablation therapy is an effective initial modality in patients with metastatic disease, androgen independence and progression of disease eventually occurs in all. (Goktas 1999; Klotz 2000). The utilization of second line hormonal agents is generally associated with low response rates, and has no documented survival benefit. Data from previous trials of NCI patients with similar eligibility requirements demonstrated a 2.1 month median progression free survival when using thalidomide (n=63) (Figg 2001). Median progression free survival on ketoconazole alone is expected to be 4 months based on previous trials (Oh 2002; Figg 2005).

Chemotherapies have been extensively evaluated in patients with metastatic androgen independent prostate cancer (AIPC) since the 1970s. The initial studies showed low response rates and high toxicities. Recently, however, with the development of new agents targeting prostate cancer both on the cellular and molecular level, promising results have been emerging. The agents, including docetaxel, mitoxantrone, estramustine, vinblastine and etoposide, either as a single agent or as a combination therapy, have produced significant PSA responses in 30-80% of patients with median progression free survival of 3-5 months (Beedassy 1999). Recently, two regimens containing docetaxel and either prednisone or estramustine have shown to have a significant increase in overall survival when compared to standard mitoxantrone/prednisone (Petrylak 2004; Tannock 2004). There is no standard therapy for patients who have progressed following docetaxel therapy. Plasma VEGF levels are significantly higher in patients with AIPC than in those with localized disease (Duque 1999); in patients with AIPC, elevated pretreatment plasma VEGF inversely correlates with survival (George 2001). A recent study found an increasing plasma VEGF level gradient when healthy patients were compared to those with localized and metastatic disease (Shariat 2004). New therapeutic modalities are needed in patients with advanced AIPC. Siegal demonstrated that microvessel density was higher in prostate cancer tissue than the adjacent hypoplastic or benign tissue (Siegal 1995). Angiogenesis also has been shown to play an important role in prostate cancer progression (Sokoloff 1999, Choy 2001). Antiangiogenic therapy directed at the VEGF signaling axis may therefore be helpful in advanced AIPC.

2.2 AZD2171

AZD2171 (NSC 732208), an orally available small molecule, is a potent inhibitor of receptor tyrosine kinases (RTKs) which influence a key angiogenic factor, vascular endothelial growth factor-A (VEGF). VEGF is implicated in tumor blood vessel formation and in disease progression in a wide range of solid tumor malignancies. Expression of this factor is increased by diverse stimuli which include proto-oncogene activation and hypoxia, with the hypoxic state frequently occurring in solid tumors because of inadequate perfusion. In addition to its angiogenic role, VEGF also profoundly increases the permeability of the vasculature and thereby potentially contributes to tumor progression – a leaky tumor endothelium enhances nutrient and catabolite exchange and represents less of a barrier to tumor cell migration during metastasis. With the goal of suppressing neovascularization and thus inhibiting tumor growth and metastasis, numerous antiangiogenic agents have been developed. In contrast to many of these intravenously-administered antiangiogenic agents, a recently emerging class of novel orally-administered VEGF TK inhibitors including AZD2171 has been developed (Hennequin 1999; Wedge 2000, 2002).

Two high-affinity receptors for VEGF with associated TK activity have been identified on human vascular endothelium, KDR (kinase insert domain-containing receptor = VEGFR2) and Flt-1 (fms-like tyrosine kinase 1 = VEGFR1). Although the relative contributions of KDR and Flt-1 signaling in mediating tumor progression have not been elucidated, a number of studies suggest that KDR performs a predominant role. AZD2171 is a potent inhibitor of both KDR (IC_{50} <0.002 microM) and Flt-1 (IC_{50} = 0.005 microM) and shows activity versus c-kit, platelet-derived growth factor receptor beta (PDGFRβ), and Flt-4 at nanomolar concentrations, but is selective against other serine/threonine kinases studied. It has been shown that AZD2171 potently and selectively inhibits VEGF-stimulated human umbilical cord vascular endothelial cell (HUVEC) proliferation with an IC_{50} of 4 nM (Ogilvie 2004). These authors have also demonstrated the agent's profound inhibitory effect on vessel area, length, and branching at subnanomolar concentrations using a modified fibroblast/endothelial cell co-culture system. AZD2171's effects on hemodynamic parameters have been studied in an athymic rat xenograft model of human colorectal carcinoma (SW620) using perfusion-permeability dynamic contrast-enhanced magnetic resonance imaging (*pp*-DCE-MRI) (Bradley 2004). This method clearly demonstrated that in this model, AZD2171 significantly reduced vascular permeability by 80% ($P<0.005$) and vascular volume by 68% ($P<0.05$).

Nonclinical Efficacy

The effect of AZD2171 was studied in athymic *nu/nu* mice bearing established subcutaneous human tumor xenografts of diverse histologies [SW620 (colon), PC-3 (prostate), Calu-6 (lung), SKOV-3 (ovarian), and MDA-MB-231 (breast)] (Wedge 2005). Animals were administered AZD2171 orally (PO) at doses from 0.75 to 6 mg/kg/day (2.25-18 mg/m^2/day) in a constant volume of 0.1 mL/10 g body weight for 24-28 days. AZD2171 produced a statistically significant inhibition of tumor growth in all human tumor types examined when dosed at 1.5 mg/kg/day (4.5 mg/m^2/day) or higher (Wedge 2005).

Angiogenesis and VEGF signaling play central roles in endochondral ossification. AZD2171 cased a dose-dependent increase in the hypertrophic chondrocyte zone of the epiphyseal growth plates in growing rats when dosed for 28 days. The effect was reversed upon withholding AZD2171. These results are consistent with the drug's ability to inhibit VEGF signaling and angiogenesis in this model (Wedge 2005).

The murine renal cell carcinoma (RENCA) model, which rapidly (generally within 10 days) metastasizes to the lung and abdominal lymph nodes, has also been used for AZD2171 efficacy studies (Drevs 2004). In experiments incorporating a vehicle control, AZD2171 (at a dose of 6.3 mg/kg/day PO) reduced primary tumor growth, metastasis, and microvessel density more potently than any other previously-studied VEGF RTK inhibitor reported in the literature.

Using a transgenic mouse model in which multiple mammary tumors spontaneously develop after two pregnancies, investigators studied the temporal effects of AZD2171 administration (Klinowska 2004). When dosed with AZD2171 (0.75 to 6 mg/kg/day PO) at the time early lesions start to develop, the number of tumor foci was not affected, but their growth was inhibited. When tumors were well established before AZD2171 was given (at doses of 3 and 6 mg/kg/day), dose-dependent growth inhibition occurred as well as tumor regression.

In another model, athymic *nu/nu* mice bearing human MCF-7 breast cancer xenografts were exposed to AZD2171. In this model, drug administration resulted in significant inhibition of tumor growth. This

inhibition was at least partially dependent on VEGF expression, as the drug effect was transient in tumors expressing VEGF (Miller 2006).

Nonclinical Pharmacology and Toxicology

Nonclinical pharmacology and toxicology company-sponsored AZD2171 studies have been conducted in rats, dogs, and cynomolgus monkeys. In rats and dogs, oral bioavailability is high, but absorption is relatively slow, with peak plasma concentration (C_{max}) of the agent seen 4-6 hours after PO dosing. Plasma concentrations and exposure are generally linear over the dose ranges studied in rats. AZD2171 is excreted in the feces (>70% of the dose) of rats, dogs, and cynomolgus monkey after both PO and intravenous administration. Fecal excretion was the predominant route of elimination (>70% of the dose) in both rat, dog and cynomolgus monkey after both oral and intravenous administration. Elimination was rapid in rats and monkeys with over 75% of the dose being recovered in the first 48 hours; in dogs excretion was slightly slower but again substantially complete by 7 days.

Over the dose ranges examined in the rat, plasma concentrations and exposure generally increased in proportion to dose; however, in monkeys, plasma AZD2171 concentration-time profiles obtained following a single oral dose indicated that systemic exposure increased in a greater than dose-proportional manner over the dose range 0.05 to 2.5 mg/kg.

Protein binding of AZD2171 (90 to 95%) was relatively high across all species examined and was independent of concentration (range: 0.03 to 10 mcg/mL) and gender. AZD2171 was approximately 95% bound to human plasma proteins, with human serum albumin and α_1-acid glycoprotein accounting for most of this binding.

VEGF has three major biological activities in endothelial cells of rats and primates of the age groups used in the nonclinical studies. It is an important angiogenic factor, a potent physiological mediator of vascular tone (specifically of vasodilation), and a potent modulator of capillary permeability inducing endothelial cell fenestrations. VEGF receptor inhibition was therefore considered to be the cause of many of the pathophysiological changes encountered.

Vascular (myocarditis, choroid plexus) and renal (glomerulosclerosis and tubular degeneration) pathologies have been seen in rat, dog, and primate dosed with AZD2171 which are considered to be consistent with lesions induced by hypertension, although a direct effect by AZD2171 on these tissues cannot be excluded. Pathological findings were also seen in the adrenal glands (degenerative cortical changes), pancreas (acinar epithelial cell necrosis), thyroid (follicular epithelial cell atrophy), liver (hepatocyte necrosis), and biliary system (cholangitis and bile duct proliferation and bile duct cholangitis) of the rat. In addition in the primate, changes were seen in the gallbladder (mucosal hypertrophy) and bile duct (hyperplasia/hypertrophy).

AZD2171 did not induce rat hepatic microsomal P450 activity but caused a 40 to 60% reduction in CYP1A activity at the 2.5 mg/kg dose level. Inhibition studies *in vitro* using human hepatic microsomal protein gave IC_{50} values for AZD2171 against CYP2D6, CYP3A4 testosterone, and CYP3A4 midazolam of 32.9, 16.2, and 21.4 mcg/mL, respectively. For CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1, the IC_{50} values were outside the concentration range of AZD2171 examined. As the clinically relevant plasma concentration of AZD2171 has not yet been determined, any possible effect on compound clearance and drug interaction is currently unknown.

Clinical Studies

The safety, tolerability, efficacy, and pharmacokinetics (PK) of AZD2171 are currently being evaluated in three phase 1 monotherapy studies in patients with solid tumors and metastatic liver disease (Study 2171IL/0001), in relapsed or refractory acute myeloid leukemia (Study 2171IL/0002), and in elderly patients with metastatic prostate adenocarcinoma (Study 2171IL/0003). In addition, an ongoing company-sponsored phase 1 study is currently assessing the safety and tolerability of AZD2171 in combination with gefitinib (IRESSA™) in patients with advanced cancer (Study 2171IL0004).

In Study 2171IL/0001, patients have received AZD2171 at doses ranging from 0.5 to 60 mg. Patient cohorts receive a single dose of AZD2171 followed by a 7-day washout period then start a 28-day cycle of daily doses of the agent at the same dose level they received initially. The company reports that preliminary safety data from this study show that AZD2171 appears to be well tolerated at doses up to

and including 45 mg/day. The 60 mg dose of AZD2171 appears to be less well tolerated and is associated with increased adverse events, dose interruptions, and increases in serum thyroid stimulating hormone (TSH). The most frequently reported adverse events (AEs) in Study 2171IL/0001 were fatigue (13/36 [36%]), nausea (13/36 [36%]), diarrhea (10/36 [28%]), and vomiting (10/36 [28%]). Three serious adverse events (SAEs) including an abnormal liver function test, hypertension, and hypoglycemia were considered to be related to AZD2171. The company reported that the patients reporting the incidences of hypertension and hypoglycemia recovered, while the patient with an abnormal liver function test improved while on trial. Increases in mean arterial blood pressure (MAP) were observed for at least one time point in several patients across all of the AZD2171 doses studied. No clinically relevant changes in electrocardiogram parameters, heart rate, or laboratory parameters have been observed. The company reports that while only limited and preliminary safety data are currently available from the other three studies, those data also suggest that AZD2171 is well tolerated.

Preliminary AZD2171 PK data from two ongoing phase 1 clinical studies (Study 2171IL/0001 and 2171IL/0003) have established that following a single dose, AZD2171 is orally available with C_{max} ranging from 1 to 8 hours post dosing. Concentrations declined in an apparent bi-exponential manner thereafter with a $t_{½lz}$ ranging from 12.5 to 35.4 hours. Steady-state plasma concentrations were predicted by the single dose PK with the grand arithmetic mean temporal change parameter value being 1.07. This observation supports the concept that there are no time-dependent PK changes. Dose proportionate increases in C_{max}, $C_{max,ss}$, AUC, and AUC_{ss} provide no evidence to reject linear PK for single and multiple AZD2171 doses ranging from 0.5 to 60 mg. The PK profile of AZD2171 supports once-daily oral dosing.

The metabolism of AZD2171 is not fully clear. It appears to be metabolized slowly and to a limited extent in microsomes. However, radiolabeled AZD2171 was metabolized by hepatocytes by a number of species to several metabolites. Isozymes involved have not been fully identified. AZD2171 has shown no inhibition of CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1. One experiment showed a 40-60% reduction in CYP1A1 activity in animals.

Initial assessments from the ongoing phase 1 study in patients with solid tumors and metastatic liver disease (Study 2171IL/0001) have produced encouraging indications of potential biological efficacy in the patient population studied. Reductions in blood flow in hepatic metastases have been detected by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), and initial biomarker assessments (VEGF and VEGF-R2) have been encouraging. In addition, the company reports that one ovarian cancer patient had a minor-partial response in lung and liver metastases, while a colorectal cancer patient had a minor response.

A phase I study of AZD2171 in 24 patients with hormone-refractory prostate cancer was recently reported (Ryan 2006). Doses $\leq$ 10 mg caused only mild, CTCAE Grade 1 and 2 adverse events (AEs) were fatigue, anorexia, and nausea. In cohorts receiving 20 and 30 mg, grade 3 AEs considered to be possibly drug-related were hypertension (n = 2), fatigue, muscular weakness, myalgia, and transient ischemic attack (n = 1 each). PK data supported once-daily dosing, with a mean effective half-life of about 20 hours. One patient in the 20 mg cohort had a PSA decline of 30% from baseline; PSA fell > 50% from baseline in a second patient in the same cohort with resolution of adenopathy for > 6 months without further antitumor therapy. The authors conclude that AZD2171 is well-tolerated in doses $\leq$ 20 mg/day in this patient population, and that PSA changes and off-study objective response suggests further investigation of treatment of this patient population with AZD2171 is warranted (Ryan 2006).

Based on evidence from animal data with AZD2171 (vascular and renal pathology) and results in the ongoing phase 1 clinical studies, it is possible that the agent will produce hypertension in man. Because hypertension seen in animals has been abrogated by nifedipine, the change is thought to be mechanistically related to inhibition of VEGF signaling, although a direct toxicologic effect on the blood vessels and kidneys cannot be ruled out. The potential for hypertensive changes following AZD2171 administration is additionally supported by evidence from use of other antiangiogenic agents in the clinic. For these reasons, patients should be monitored frequently for changes in blood pressure and renal function (blood urea nitrogen, creatinine, and urinary protein). The potential for myocardial injury indicates that patient levels of troponin T or troponin I should also be measured.

Certain physiologic processes other than endothelial cell growth are dependent on VEGF signaling, so inhibition of that growth factor may have implications for use of AZD2171 in selected patient populations.

Pediatric studies with AZD2171 should be undertaken with caution because the agent increases the zone of hypertrophy in the epiphyseal growth plates thus preventing ossification during long bone growth. AZD2171 interferes with normal reproductive processes and completely prevents fetal development in rats at a dose of 2.5 mg/kg/day. For this reason, women of childbearing potential should have a negative pregnancy test before treatment with AZD2171 is initiated. In rat studies, AZD2171 significantly inhibited endochondral ossification and corpora lutea formation (Wedge 2004).

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome: RPLS or clinical syndromes related to vasogenic edema of the white matter have been rarely reported in association with AZD2171 therapy (<3%). Clinical presentations are variable and may include altered mental status, seizure and cortical visual deficit. Hypertension is a common risk factor and was present in most (though not all) patients on cediranib who developed RPLS. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2 and FLAIR images and hypointensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes' less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be in the differential diagnosis in patients presenting with unexplained mental status change, visual distrubance, seizure or other CNS findings. RPLS is potentially reversible, but timel correction of the underlying causes, including control of blood pressure and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

Clinical Experience with Prednisone

As of June 2008, there have been 28 patients treated on this protocol. There have been several signs that the drug has tumor activity. To date, the event free survival at 6 months has been 38% which has exceeded our initial goal of 30% with tumor shrinkage in several patients. Although the current results have been exciting, the limiting factor for the AZD-2171 appears to be constitutional side effects (fatigue, weight loss, anorexia) which have occurred as at least a Grade 2 toxicity in 19 of 28 patients. There have been a total of 10 dose reductions of which 40% have been for fatigue, weakness or weight loss. These side effects are similar to that seen in other AZD-2171 protocols in other solid tumors (verbal communication at AZD-2171 Investigator meeting and with Dr Percy Ivy, CTEP). In addition, Ryan et al. found similar dose limiting toxicities in the Phase 1 trial in prostate cancer that established the current dose. The prostate dose of 20 mg/day is lower than is used in many other trials, thus maintaining this relatively low dose may be important.
In prostate cancer, prednisone has been used as a complimentary treatment to therapies such as docetaxel and mitoxantrone. In addition, a trial combining prednisone with docetaxel and AZD-2171 in metastatic prostate cancer is currently ongoing. In discussions with Dr. Ivy and other investigators it appears that low dose corticosteroids can potentially decrease the constitutional symptoms associated with this agent (although the mechanism remains cryptogenic). In our current trial, we have anecdotal evidence that prednisone can lead to the improvement of symptoms. There have been 4 patients that have been treated to date with prednisone for clinical symptoms. The four patients are briefly described below:

Patient 1
70 y/o male with CRPC with metastatic disease in bone and soft tissue who began to have worsening symptoms of fatigue during cycle 1 about 2-3 weeks after initiating therapy. The patient was on prednisone prior to this for his docetaxel and prednisone (10 mg) chemotherapeutic regimen. He was tapered over approximately 2-3 weeks. His fatigue gradually worsened till he was not able to continue with some of his ADL's. He was then started on prednisone 10 mg per day. AZD-2171 was not held. After the prednisone his activity level and fatigue began to improve within 24 hours.

Patient 2
73 y/o male with CRPC with metastatic disease in bone and soft tissue who began to have worsening symptoms of fatigue and weight loss during cycle 16 who was doing well prior to that. The patient indicated that he had loss of appetite. He stated that his activities had begun to decrease and most recently he was unable to continue with work. It was decided to hold AZD-2171 and begin the patient on prednisone 10 mg per day for 7 days. The patient by the third day was eating much better, restarted to work and continued his yard work. The patient was restarted on AZD-2171 at a reduced dose and did well during the rest of his therapy.

Patient 3
59 y/o male with CRPC with metastatic disease to bone and soft tissue who experienced worsening

fatigue after cycle 1 which resulted in delay of cycle 2. The patient also was given 7 days of prednisone 10 mg per day. The patient reported that after 3 days he had improvement in his symptoms but developed symptoms of UTI. The prednisone was discontinued after 5 dyas of therapy and the patient was given antibiotics. The patient restarted AZD-2171. He continued on therapy to be taken off therapy due to clinical deterioration from a ureteral obstruction.

Patient 4
72 y/o male with CRPC with metastatic disease to bone and soft tissue who experienced worsening fatigue after cycle 2 and decreased in appetite that began to interfere with his quality of life. The patient was given prednisone 10 mg for 7 weeks concurrently with his AZD-2171. The patient did indicate that during his 7 days that he did have some improvement in his symptoms. The patient eventually due to symptoms withdrew himself from the study.

As mentioned three of the patients appeared to have benefit from the prednisone and one patient appeared to have adrenocorticol insufficiency although a cortisol level was not drawn. Our experiences with these patients have led us to further explore the potential to use prednisone in combination with AZD. The drug has biologic activity and appears to be limited mainly due to side effects which have been observed in other trials using the same agent.

2.3 Rationale

In 1971, Dr. Folkman proposed that angiogenesis is important for tumor progression (Folkman 1971). He has gone on to hypothesize that angiogenesis plays an important role in determining the possibility of metastasis and patient prognosis (Folkman 1995). His group has put forward the idea of an "angiogenic switch" that is required to "turn on" angiogenesis in the tumor. Basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) and tumor necrosis factorα (TNF-α) are among the most important angiogenic proteins found in tumors (Folkman 1995). Malignant cells can alter endogenous angiogenic pathways and retard antiangiogenic factors, thus providing an imbalance in blood vessel formation (Nicholson 2004). VEGF has been shown to be upregulated in new blood vessel formation, although the exact mechanism by which this occurs remains a mystery (Nicholson 2004). $VEGF_{121}$, $VEGF_{165}$, and $VEGF_{189}$ are the three most commonly found isoforms of VEGF that are secreted. $VEGF_{121}$ is found most often in circulation, whereas $VEGF_{165}$ is found in malignant cells and the extracellular matrix and $VEGF_{189}$ is located within the extracellular matrix exclusively (Nicholson 2004). Mutations in the tumor suppressors *p53*, a ubiquitous tumor suppressor gene, and PTEN, which is found in a minority of prostate cancer patients, have been correlated to VEGF over-expression (Nicholson 2004).

In order to elucidate its effects on cell proliferation, VEGF must bind to a receptor. There have been at least three VEGF receptors (VEGF R) reported to date; VEGF R1 (Flt-1), VEGF R2 (Flk-1/KDR) and VEGF R3 (Flt-4) (Chevalier 2002). It has been reported that all three VEGF isoforms, in addition to VEGF R1 and R2 have been detected in Dunning tumors, when grown in Copenhagen and Copenhagen x Fisher rats (Haggstrom 2000). VEGF expression was highest in the AT-3 subline of the Dunning tumor, which is the most metastatic subline (Haggstrom 2000). There was a statistically relevant correlation between VEGF concentration and microvessel density (MVD) ($p<0.05$) (Toi 1995; Haggstrom 2000; Seo 2000; Straume 2001). Balbay and coworkers reported increased VEGF expression in a highly metastatic variant of LNCaP cells, when compared to normal LNCaPs or slightly metastatic LNCaPs (Balbay 1999). They also reported that the LNCaP-LN3 cells had a statistically higher MVD and Flt-1 expression than the less metastatic forms of LNCaP (Balbay 1999). Hahn and colleagues reported on the expression of Flt-1 in various human prostatic tissues (Hahn 2000). This group reported that Flt-1 was expressed by endothelial cells from benign, premalignant and malignant prostate tissues, which was confirmed by Kollermann and Helpap (Kollermann 2001). Hahn showed that there was a progressive loss of Flt-1 expression as the tissue decreased in differentiation, from normal to malignant, within the same patient biopsy samples (Hahn 2000). The reasons for decreasing Flt-1 expression as the cells dedifferentiate are not fully understood, but a theory could be that as the malignant transformation occurs, Flt-1-mediated signaling is progressively turned off.

Data has been presented that suggests angiogenesis is a crucial step in the progression of prostate cancer from early to advanced disease (Sokoloff 1999; Choy 2001). Microvessel density is an indicator of biological aggressiveness and metastatic potential in many primary tumors (Weidner 1993). Interruption of this process would halt the progression of cancers that are dependent upon angiogenesis

for advancing pathology by eliminating their potential for growth. Inhibition of angiogenesis is expected to augment the effects of other therapies such as chemotherapy or radiation by limiting the tumor to a dormant state of low metastatic potential (McNamara 1998). Prostate cancer progression from primary neoplasia to advanced disease requires the acquisition of microcirculation to support the developing neoplastic mass (Izawa 2001). Hypoxia induces angiogenesis and HIF-1α. HIF-1α activates genes regulating cell growth, vascular remodeling, and cell survival (Siegal 1995; Bergers 2003). Immunohistochemical analysis of specimen from high-grade prostate intraepithelial neoplasia shows HIF-1α upregulation compared with normal epithelium, stromal cells, and benign prostatic hyperplasia (BPH) tissue samples (Zhong 2004). HIF-1α has been shown to induce VEGF up-regulation in LNCaP cells (Mabjeesh 2003) and hypoxia induces VEGF in human prostate cancer (Cvetkovic 2001). VEGF has been associated with progression to a malignant phenotype in prostate cancer (Soker 2001). The dependence of prostate tumors on androgens for induction of tumor growth and metastasis is unique to this cancer (Choy 2001). Androgens have been implicated in the induction of VEGF expression, supporting the hypothesis that androgen ablation affects prostate tumors at least in part through inhibition of angiogenesis (Choy 2001).

A growing body of literature implicates VEGF as a tumor promoter, and VEGF R3 over expression is related to lymphangitic spread of prostate cancer (Li 2004; Lissbrant 2004; Zeng 2004). Biopsy samples from 640 patients, including normal prostate, benign prostatic hyperplasia (BPH) and prostate cancer, were analyzed by microarray (Li 2004). VEGF R3 was expressed in all three tissue types, but expressed to a greater extent in prostate cancer. VEGF R3 expression was also correlated to pre-operative PSA, Gleason score and the possibility of lymph node metastasis (Li 2004). Patients with lower VEGF R3 expression had a better 5-year overall survival (77.3% vs 69.6%, p=0.037). Li's paper suggests that increased VEGF R3 expression results in higher incidence of aggressive disease and a poorer overall survival (Li 2004). Zeng and colleagues confirmed that expression of VEGF R3 is associated with advanced disease, lymph node metastasis, extracapsular extension, and surgical margin status (Zeng 2004). Lissbrant showed that, while inhibiting VEGF receptors resulted in a decreased epithelial cell proliferation when testosterone was reintroduced into castrated mice, the tumor was still able to respond to testosterone(Lissbrant 2004).

Vascular endothelial growth factor and its receptors appear as a likely therapeutic target in the treatment of cancer. The Food and Drug Administration (FDA) recently approved the first anti-VEGF compound, bevacizumab. Bevacizumab is a humanized monoclonal antibody that binds VEGF and prevents it from attaching to the VEGF receptor (Zondor 2004). Bevacizumab binds all isoforms of VEGF and blocks tumor growth in xenografts (Zondor 2004). Currently, at least three small molecule agents are in various stages of development, which act by antagonizing the VEGF receptor. CEP-7055, a pan-VEGFR inhibitor, has shown activity in a variety of preclinical tumor models (Ruggeri 2003). CEP-7055 showed a dose-dependent reduction in neovascularization, when tested in the rat aorta assay and the HUVEC assay. In LNCaP cells tested in nude mice, there was a decrease in the metastatic potential as well as significant antitumor activity (Ruggeri 2003). ZD6474, a KDR tyrosine kinase inhibitor, has been shown to decrease tumor vascular permeability on dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) (Checkley 2003).

AZD2171 has been shown to inhibit VEGF signaling by inhibiting KDR and Flt-1 kinase activity (Hennequin 2004; Ogilvie 2004; Wedge 2004). This compound, when tested in athymic mice with various tumor xenografts, showed a dose-dependent inhibition of tumor growth in each model (Ogilvie 2004). When tested in murine renal cell carcinoma model (RENCA), primary tumor volume was reduced by 58% and primary tumor vessel density by 70%, after 10 days of therapy (Drevs 2004). Preliminary pharmacokinetic and safety analysis shows AZD2171 can be safely administered once-daily (Medinger 2004). AZD2171 was well tolerated up to 10mg daily, with a terminal half-life of 20 hours, following linear pharmacokinetics (Medinger 2004).

Parallel observations with respect to molecular determinants of angiogenesis in prostate and other cancers suggest that antiangiogenic therapeutic strategies are relevant to prostate cancer. Antiangiogenic agents have demonstrated efficacy in the treatment of prostate cancer in various clinical trials (Macpherson 2002). Based on the knowledge that prostate cancer proliferation and progression is directly related to VEGF expression, and that MVD and VEGFR expression denotes more advanced disease, as well as the fact that AZD2171 has been shown to antagonize the VEGF R1 and VEGF R2 receptors, it is with great interest that we wish to study this drug in patients with androgen-independent prostate cancer.

The Genitourinary Clinical Research Section has had a long history of success in developing antiangiogenic compounds for use in treating advanced stage adenocarcinoma of the prostate. Beginning with 92-C-0265, combining aminoglutithimide with suramin, and high-dose ketoconazole in combination with alendronate, through a phase II trial evaluating thalidomide alone and in combination with docetaxel, hundreds of patients have benefited from the unique trials designed by our group. More recently, we have begun studying small-molecule inhibitors including sorafenib, which may provide additional benefit to this patient population. It has become increasingly clear that PSA decline rates of 50% alone may not be adequate to asses activity with many of these agents. In an exploratory fashion, we have incorporated time to progression as the primary endpoint in trials of small molecules. Although time to progression can be problematic in single-arm phase II trials, the objective nature of PSA eliminates a significant portion of investigator bias.

In a study presented at this year's ASCO, a randomized phase II trial studied patients with taxane-resistent androgen-independent prostate cancer treated with prednisone and irofulven, a novel DNA binding agent and a semisynthetic derivative of the natural product illudin S, in the presence or absence of capecitabine. When compared with a control arm treated with mitoxantrone and prednisone, both experimental arms demonstrated a median time to progression (TTP) of 2.1 months, compared with a 1.1 month TTP in the control arm. (Hart 2006)

In a large unpublished study provided to CTEP by the Memorial Sloan Kettering Cancer Center, 10% of patients experienced a progression free survival of 6 months. (Ivy 2006)

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histopathological confirmation of prostate cancer by the Laboratory of Pathology of the NCI, Pathology Department of the National Naval Medical Center or Pathology Department of Walter Reed Army Medical Center prior to entering this study. Patients whose pathology specimens are no longer available may be enrolled in the trial if the patient has a clinical course consistent with prostate cancer and available documentation from an outside pathology laboratory of the diagnosis. In cases where original tissue blocks or archival biopsy material is available, all efforts should be made to have the material forwarded to the research team for use in correlative studies.

3.1.2 Patients must have metastatic progressive androgen-independent prostate cancer. There must be radiographic evidence of disease that has continued to progress despite hormonal agents. Progression requires that a measurable lesion is expanding, new lesions have appeared, and/or that PSA is continuing to rise on successive measurements. Patients on flutamide must have disease progression at least 4 weeks after withdrawal. Patients on bicalutamide or nilutamide must have progression at least 6 weeks after withdrawal.

3.1.3 Patients must have received prior therapy with docetaxel for androgen-independent prostate cancer. Any number of prior treatments are acceptable.

3.1.4 Age $\geq$18 years

3.1.5 Life expectancy of greater than 3 months.

3.1.6 ECOG performance status $\leq$ 2 (Karnofsky $\geq$ 60%; see Appendix A).

3.1.7 Patients must have normal organ and marrow function as defined below:

Absolute neutrophil count	$\geq$1,500/mcL
Platelets	$\geq$100,000/mcL
Hemoglobin$\geq$ 8 g/dL	
Total bilirubin	≤ 1.5 x institutional upper normal institutional limits (unless with clinical Gilbert's syndrome)
AST(SGOT)/ALT(SGPT)	≤ 2.5 × institutional upper limit of normal

Creatinine ≤ 1.5 x institutional upper normal institutional limits

OR

Creatinine clearance ≥ 40 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal. as calculated by the Cockcroft Gault formula.

3.1.8 Patients must have recovered from any acute toxicity related to prior therapy, including surgery. Toxicity should be ≤ grade 1 or returned to baseline.

3.1.9 All patients who have not undergone bilateral surgical castration must continue suppression of testosterone production by appropriate usage of GnRH agonists or antagonists.

3.1.10 Patients must not have other invasive malignancies (within the past three years with the exception of non-melanoma skin cancers or non-invasive bladder cancer).

3.1.11 AZD2171 has been shown to terminate fetal development in the rat, as expected for a process dependent on VEGF signaling. Enrolled patients must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, the duration of study participation and 3 months after the end of the treatment.

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.1.13 Patients must have a blood pressure of <140/90 at the time of enrollment. Details of antihypertensive treatment, if required, will be left up to the primary care physician.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy, radiotherapy, or major surgery within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study.

3.2.2 Patients may not be receiving any agents not approved by the FDA within the past four weeks.

3.2.3 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 Mean QTc >470 msec (with Bazett's correction) in screening electrocardiogram or history of familial long QT syndrome.

3.2.5 Greater than +1 proteinuria on two consecutive dipsticks taken no less than 1 week apart.

3.2.6 Uncontrolled intercurrent illness including, but not limited to hypertension, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with AZD2171.

3.3 Inclusion of Women and Minorities

Men of all races and ethnic groups are eligible for this trial. Women are excluded by the nature of the disease.

3.4 Baseline evaluation

3.4.1 Imaging studies (baseline – obtained within one month prior to enrollment): Technetium-99 Bone Scintigraphy, Chest X-ray, CT scan of chest, abdomen and pelvis.

3.4.2 Laboratory evaluation (baseline – obtained within 16 days prior to enrollment)

3.4.2.1 Hematological profile: CBC with differential and platelet count, PT, aPTT, fibrinogen.

3.4.2.2 Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, total bilirubin, calcium, phosphorus, albumin, magnesium, uric acid, C-reactive protein, albumin, amylase, lipase, testosterone level, TSH, and troponin.

3.4.2.3 Tumor marker profile: PSA (baseline – within 7 days prior to enrollment), acid phosphatase (if PSA <4ng/mL, for research purposes only).

3.4.2.4 History and physical exam with vital signs.

3.4.3 Cardiac evaluation (baseline – obtained within 16 days prior to enrollment)

3.4.3.1 Electrocardiogram

3.4.3.2 Laboratory evaluation – troponin

3.4.3.3 Echocardiogram

3.5 REGISTRATION PROCEDURES

3.5.1 Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://camp.nci.nih.gov/ccr/welcome.htm) must be completed and faxed to 301-480-0757. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail. Please note, it is very important for all registrars to acquire encrypted e-mail from NIH Help Desk, since the verification of registration includes patient's information. A recorder is available during non-working hours.

3.5.2 Off-Study Procedure: Authorized staff must notify Central Registration Office (CRO) when a patient is taken off-study. An off-study form from the web site (http://camp.nci.nih.gov/ccr/welcome.htm) main page must be completed and faxed to 301-480-0757.

4. TREATMENT PLAN

4.1 AZD2171-Prednisone Administration

At the outset of the study, the patient may be admitted to the inpatient service for a period of approximately 24 hours to complete research studies including biopsies and PK measurements. Otherwise, treatment will be administered on an outpatient basis. Reported adverse events (AEs) and potential risks are described in Section 6. Appropriate dose modifications for AZD2171 are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

AZD2171 is supplied in a matched series of beige film-coated tablets containing 10 mg or 15 mg of AZD2171 free base. Patients are to swallow tablets to equal 20 mg without crushing with approximately 250ml (8 oz.) of water, once daily. AZD2171 tablets should be taken on an empty stomach, 1 hour before or 2 hours after meals. AZD2171 will be given as self-administered oral doses of 20 mg once daily continuously throughout the 28 day cycle.

Patients will be provided with a pill diary (Appendix B), instructed in its use, and asked to bring it with them to each appointment. A new copy of the Pill Diary will be given to patients whose dose is reduced due to adverse events. Pill counts will also be maintained be study personnel.

The combination of treatment of AZD with prednisone may help to alleviate some of the constitutional symptoms and allow us to maintain therapeutic dosing. All patients will receive Prednisone 10 mg orally daily and AZD2171 20 mg orally daily. Both drugs should be taken together in the morning. In addition, we will also check cortisol levels in patients who are not on steroids at the time of enrollment.

4.2 General Concomitant Medication and Supportive Care Guidelines

4.2.1 Frequent blood pressure monitoring is important in patients receiving AZD2171. Experience to date

suggests that increases in blood pressure may occur following dosing with AZD2171 for a number of weeks and that these increases may occur relatively quickly. Patients will be provided with a blood pressure monitoring device and a log in which to record their twice-daily blood pressure readings (Appendix C). If two successive systolic readings are ≥140 mmHg OR two successive diastolic readings are ≥90 mmHg OR any combination of elevated systolic and diastolic blood pressure are observed, patients will be instructed to contact their physician as soon as possible. Patients should seek medical advice if their BP exceeds 180 mmHg (systolic) or 105 mmHg (diastolic) at any time and should also be encouraged to contact their physician if they are concerned about any symptoms that may be associated with high blood pressure (*e.g.*, headache). Section 5.1 includes specific guidelines on the management and, if appropriate, dose modifications for treatment-emergent hypertension.

4.2.2 Renal function (creatinine and urinary protein) should be frequently monitored as suggested by the pathologic changes noted in animal studies and evidence from studies of other antiangiogenic agents. Patients will have a monthly chemistry panel and urinalysis.

Management of Proteinuria

Proteinuria Value	Monitoring	Dose modification
>1+ (dipstick or equivalent routine laboratory analysis)	Perform the following tests: • 24-hour urine collection for total protein and creatinine • microscopic examination of fresh urine • urine protein electrophoresis (at first occurrence of >1+ proteinuria only)	See below.
Based on results of the 24-hour urine collection:		
≤ 1g protein (24-hour collection)	Continue dipstick or equivalent routine laboratory analysis	Continue planned dose.
> 1g but ≤ 2g protein (24-hour collection)	Perform 24-hour urine collection (total protein, creatinine) prior to day 1 of each subsequent cycle of therapy (q4wk) until total protein is <500mg/24 hours.	Decrease one dose level; continue treatment.
> 2g protein (24-hour collection)	Perform 24-hour urine collection (total protein, creatinine) weekly unitl proteinuria is <2g/24 hours.	Hold AZD2171. When protein is < 2g/24 hours, resume treatment at one lower dose level.
	Perform 24-hour urine collection (total protein, creatinine) prior to day 1 of each subsequent cycle of therapy (q4wk).	Continue until patient is off study.

4.2.3 Because of the potential for myocardial injury with AZD2171, patients will undergo electrocardigram testing and measurement of serum of troponin levels at each clinic visit.

4.2.4 Because there is a potential for interaction of AZD2171 with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected P450 isoenzymes; these agents/drugs should be documented along with any associated AEs that occur.

4.2.5 No premedications will be used with the initiation of therapy

4.2.6 Concurrent use of bisphosphonates will be allowed for patients with known bone metastases

4.2.7 Patients who require hematopoietic growth factor support (e.g. epogen, darbepoetin), NSAIDs and other maintenance medications prior to study entry will be allowed to continue their supportive therapies.

4.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Radiographic disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Patients who meet the criteria for PSA progression (See Section 10.5) may continue on study unless they meet the above criteria.

4.4 Follow-up Criteria

All study subjects will be followed for overall survival only once active treatment has been completed (as indicated above).
Follow-up will be annual telephone contact to assess survival status. Every attempt will be made to contact patient/subject including: contacting referring physician, contacting emergency contact patient identified on admission, checking SSDI (Social Security Death Index)
All attempts will be noted in the medical record.

4.5 Off-Study Criteria

- Discretion of the principle investigator
- Patient Choice
- Patient Death

5. DOSING DELAYS/DOSE MODIFICATIONS

Toxicities will be described using CTCAE v3.0. The following adjustments will only apply if the toxicities reported are attributed by the investigators to be related to AZD2171 therapy.

AZD2171 should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. Cediranib should be discontinued upon diagnosis of RPLS. After Consultation with the principal investigator and the NCI, consideration of restarting the study may be evaluated in light of any clinical benefit.

For Grade 1 toxicity, treatment with AZD2171 need not be interrupted. For symptoms that last more than 7 days and have been found to be intolerable to the patient, the dose of AZD2171 may be reduced to 15mg/day.

For Grade 2 toxicity

For nausea, vomiting, and diarrhea, maintain dosing with symptomatic treatment. The dose of AZD2171 may be repeated if emesis occurs within 30 minutes of taking the tablets or all the tablets are seen in the emesis.

For persistant nausea, vomiting or diarrhea despite symptomatic treatment that remains unacceptable (intolerable) to the patient, reduce dose to 15 mg/day, as indicated in the table below.

For other grade 2 toxicities, the dose does not need to be reduced unless side effects become intolerable to the patient.

Patients with intolerable or limiting toxicity while taking 10 mg/day will be removed from study

For Grade 3 nonhematologic toxicity, or Grade 4 hematologic toxicity

Hold AZD2171 and reevaluate the patient at least weekly until toxicity improves to ≤ Grade 1 or pre-treatment baseline. Reduce dose of AZD2171 by one dose level, as indicated in the table below except for grade 3 hypertension (follow chart found below). Treatment will be discontinued in patients who experience toxicity ≥ grade 3 or 4 that does not resolved to ≤ grade 1 or baseline within 3 weeks. Hypophosphotemia, hypokalemia, and hypomagnesimia that can be corrected within 48 hours to grade 2 or less will not require a dose reduction.

Patients with intolerable or limiting toxicity while taking 10 mg/day will be removed from study

For Grade 4 non-hematologic toxicity

Patients who had clinical grade 4 non-hematologic toxicity (except pulmonary embolism without significant hypoxia and hemodynamic instability) will be taken off study permanently.

Dose level	AZD2171 Dose
-2	10 mg qd
-1	15 mg qd
1	20 mg qd

As this trial allows patients to receive treatment indefinitely, patients may have the doses of any or all drugs (AZD-2171 and prednisone) temporarily withheld (maximum of 21days at which time the patient will be taken off study), and potentially resume treatment as long as they do not fulfill the off-study criteria outlined in section 4.5.

5.1 Management of Hypertension

Increases in blood pressure and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation. Hypertension following AZD2171 treatment has been seen in animal studies as well as clinical trials. Blood pressure will be measured by a health professional at the time of enrollment, and at each clinic visit. In addition, patients will be asked to monitor their blood pressure at home on a twice daily basis, consisting of a a morning resting blood pressure and an evening blood pressure, and to log blood pressure values in a blood pressure diary (Appendix C). Patients will be asked to call their research nurse with any abnormal values (CTCAE v3.0 Grade 1 or above) or if they experience new headache or dizziness.Specific guidance for management of this AE is provided below.

BP monitors for patients enrolled in the study may be ordered from

Andrea R. Dickerson, MS
AstraZeneca Pharamceuticals
1800 Concord Pike / C2B-701
Wilmington, DE 19850-5437
Andrea.dickerson@astrazeneca.com
Phone: (302) 885-9873

Grade (CTCAE v3.0)	Antihypertensive Therapy	Blood Pressure Monitoring	AZD2171 Dose
1	None	Consider increased monitoring	No change
2	Initiate monotherapy (suggest dihydropyridine calcium-channel blocker)	Increase frequency and monitor (by health professional) every 2 days until stabilized.	No change
3	Add agent(s): Ca++ channel blocker (if not already used), K+ channel opener, beta-blocker, thiazide diuretic)	Increase frequency and monitor (by health professional) every 2 days until stabilized; continue q2d monitoring to stabilization after dosing restarted.	Hold dose until symptoms resolve and diastolic BP ≤100 mm Hg. Restart at same dose (investigator discretion).
	If diastolic BP not controlled to ≤100 mm Hg on therapy when dose restarted …		Hold dose until symptoms resolve and diastolic BP ≤100 mm Hg. Restart at next lower dose level.
4	Manage symptoms per local practice.	Continue frequent BP monitoring until stabilization.	Discontinue AZD2171*

* If patient is considered to be benefiting from AZD2171 treatment, dosing may continue at the next lower dose level provided the responsible study sponsor (DCTD, NCI) physician concurs after discussion of the case.

CTCAE v3.0 hypertension grade definitions

Grade 1: asymptomatic, transient (<24 hours) increase by >20 mm Hg (diastolic) or to >150/100 if previously WNL; intervention not indicated
Grade 2: recurrent or persistent (>24 hours) or symptomatic increase by >20 mm Hg
Grade 3: requiring more than one drug or more intensive therapy than previously
Grade 4: life-threatening (e.g., hypertensive crisis)

Notes:

- While patients are receiving treatment with AZD2171, the early initiation of antihypertensive treatment for grade 1 or 2 hypertension to minimize more severe or persistent hypertension is not considered a grade 3 adverse event.
- Decisions to hold or decrease the AZD2171 dose during treatment must be based on BP readings taken in the clinic by a medical professional.

Table 1. Dihydropyridine calcium-channel blockers (DHP CCB)

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Nifedipine XL	30 mg po qd	60 mg po qd	90 mg po qd	CYP 3A4 substrate
Amlodipine	2.5 mg po qd	5 mg po qd	10 mg po qd	CYP 3A4 substrate
Felodipine	2.5 mg po qd		10 mg po qd	CYP 3A4 substrate + inhibitor

Table 2: Selective β blockers (BB)

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Metoprolol	25 mg po bid	50 mg po bid	100 mg po bid	CYP 2D6 substrate
Atenolol	25 mg po qd	50 mg po qd	100 mg po qd	**No**
Acebutolol	100 mg po bid	200mg-300 mg po bid	400 mg po bid	Yes(CYP450 unknown)
Bisoprolol	2.5 mg po qd	5-10 mg po bid	20 mg po qd	Yes(CYP450 unknown)

Table 3. Angiotensin Converting Enzyme Inhibitors (ACEIs)

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Captopril	12.5 po tid	25 mg po tid	50 mg po tid	CYP 2D6 substrate
Enalapril	5 mg po qd	10-20 mg po qd	40 mg po qd	CYP 3A4 substrate
Ramipril	2.5 mg po qd	5 mg po qd	10 mg po qd	Yes (CYP450 unknown)
Lisinopril	5 mg po qd	10-20 mg po qd	40 mg po qd	**No**
Fosinopril	10 mg po qd	20 mg po qd	40 mg po qd	Yes (CYP450 unknown)
Rarely used:				
Perindopril	4mg po qd	none	8mg po qd	Yes but not CYP450
Quinapril	10mg po qd	20 mg po qd	40 mg po /qd	No

Table 4. Angiotensin II Receptors Blockers (ARBs)

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Losartan	25mg po qd	50 mg po qd	100 mg po qd	CYP 3A4 substrate
Candesartan	4mg po qd	8-16 mg po qd	32mg po qd	CYP 2C9 substrate
Irbesartan	75mg po qd	150 mg po qd	300 mg po qd	CYP 2C9 substrate
Telmisartan	40 mg po qd	none	80 mg po qd	**Yes but not CYP450**
Valsartan	80 mg po qd	none	160mg po qd	**Yes but not CYP450**

Table 5. α and β blocker

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Labetolol	100 mg po bid	200 mg po bid	400 mg po bid	CYP 2D6 substrate and inhibitor

Agents in bold characters above are suggested as optimal choices to avoid or minimize potential drug-interactions with AZD2171 through CYP450.

5.2 Management of LVEF

There have been reports of VEGF inhibitors leading to decreases in ejection fraction. In support of this, recent trials have shown asymptomatic decreases in ejection fraction with different VEGF inhibitors. Specifically, a reduced LVEF (left ventricular ejection fraction) has been observed with sunitinib in up to 5–11% of patients, and 5% of patients treated with bevacizumab (Motzer 2006, Karp 2004, Motzer RJ, Rini 2006). Recent data from breast cancer trials using AZD-2171 and doxorubicin at the NCI have identified two patients' who experienced

asymptomatic ejection fraction decreases that were reversible upon withdrawal of AZD-2171. Since it is difficult to differentiate whether this is a toxicity that is associated with VEGF inhibitor monotherapy or concurrent regimens including VEGF inhibitors, further investigation is needed. These questions that arise because of the safety of AZD-2171, in regards to cardiac function have prompted us to obtain echocardiograms for patients concurrently with CT scans and bone scans. As there are currently no guidelines on evaluation and management of ejection fraction in the setting of AZD-2171 use, similar criteria to that previously used for trastuzumab, which is known to decrease ejection fraction, and the NCI breast cancer trials will be employed (Tan-Chiu 2005).

Continuation Guidelines for AZD based on Echocardiogram**

	Asymptomatic Decrease in LVEF from baseline		
Relationship of LVEF to the LLN	Decrease of < 10 percentage points	Decrease of 10 to 15 percentage points	Decrease of ≥ 15 percentage points
Within radiology facility's normal limits	Continue AZD-2171	Continue AZD-2171	Hold AZD-2171 and repeat Echo in 4 weeks and reevaluate
1 to 5 percentage points below the LLN	Continue AZD-2171	Hold AZD-2171 and repeat Echo in 4 weeks and reevaluate	Hold AZD-2171 and repeat Echo in 4 weeks and reevaluate
≥ 6 percentage points below the LLN	Continue AZD-2171	Hold AZD-2171 and repeat Echo in 4 weeks and reevaluate	Hold AZD-2171 and repeat Echo in 4 weeks and reevaluate

**Please note that reevaluation should be conducted as per the table above.

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. Adverse events occurring during the study will be graded according to the NCI Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0).

Definition of an Adverse Event (AE)

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug. AEs that are considered treatment related, expected, continuing, but not resolvable by 30 days after treatment completion (e.g., alopecia) will not be followed after the 30-day period.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the abnormality should be recorded as the AE.

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 3.0. A copy of the CTCAE version 3.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

6.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) was developed to provide a single, complete list of reported and/or potential adverse events associated with an agent using a uniform presentation of adverse events by body system. In addition to the comprehensive list, the subset of those events that are "expected" [i.e., the Agent Specific Adverse Event List (ASAEL)] is presented in a separate column and identified with ***bold*** and ***italicized*** text. This subset is used to guide expedited reporting requirements. The CAEPR for AZD2171 is shown on the next page.

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Cediranib (AZD2171, NSC 732208)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. *Frequency is provided based on 681 patients.* Below is the CAEPR for cediranib (AZD2171).

Version 2.9, February 19, 2010[1]

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 4.0 Term) [n= 681]			**EXPECTED AEs FOR ADEERS REPORTING Agent Specific Adverse Event List (ASAEL)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	***Expected***
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	
ENDOCRINE DISORDERS			
	Hyperthyroidism		
	Hypothyroidism		***Hypothyroidism***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain***
	Anal mucositis		***Anal mucositis***
	Constipation		***Constipation***
Diarrhea			***Diarrhea***
	Dry mouth		***Dry mouth***
	Dysphagia		***Dysphagia***
	Mucositis oral		***Mucositis oral***

	Nausea		***Nausea***
	Rectal mucositis		***Rectal mucositis***
	Small intestinal mucositis		***Small intestinal mucositis***
	Vomiting		***Vomiting***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Investigations - Other (increased blood erythropoietin)		
	Investigations - Other (increased thyroid stimulating hormone)		***Investigations - Other (increased thyroid stimulating hormone)***
	Neutrophil count decreased		
	Platelet count decreased		
	Weight loss		***Weight loss***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia***
	Dehydration		***Dehydration***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness***
	Headache		***Headache***
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
	Proteinuria		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough***
	Dyspnea		***Dyspnea***
	Laryngeal mucositis		***Laryngeal mucositis***
	Pharyngeal mucositis		***Pharyngeal mucositis***
	Tracheal mucositis		***Tracheal mucositis***
	Voice alteration		***Voice alteration***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome***
VASCULAR DISORDERS			
Hypertension			***Hypertension***
		Vascular disorders - Other (arterial thrombosis)	

This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Also reported on cediranib (AZD2171) trials but with the relationship to cediranib (AZD2171) still undetermined:
BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Leukocytosis

CARDIAC DISORDERS - Acute coronary syndrome; Chest pain - cardiac; Myocardial infarction
EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo
ENDOCRINE DISORDERS - Endocrine disorders - Other (thyrotoxicosis)
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colitis; Dyspepsia; Enterocolitis; Esophagitis; Flatulence; Gastric perforation; Ileus; Oral pain; Rectal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Fever; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatic hemorrhage; Hepatic pain
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Gum infection; Lung infection; Sepsis; Skin infection; Soft tissue infection; Urinary tract infection
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin T increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (decreased thyroxine); Lymphocyte count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Muscle weakness lower limb; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dysgeusia; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Confusion; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Nail loss; Pruritus; Purpura; Rash maculo-papular
VASCULAR DISORDERS - Hematoma; Hypotension; Thromboembolic event

Note: Cediranib (AZD2171) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.
Precautions: Hypertension is an expected adverse event with agents that inhibit VEGF signaling. In cediranib (AZD2171) studies, increases in blood pressure have been observed and cases of hypertension have been reported, including CTC grade 4 hypertension and end-organ damage related to hypertension. Clinical experience with cediranib (AZD2171) has shown that hypertension occurs at doses of 20 mg and higher. Cediranib (AZD2171) studies include monitoring of blood pressure and renal function, and a hypertension monitoring and management protocol has been developed which will be appended to all future study protocols.

6.2 Expedited Adverse Event Reporting to Sponsor

6.2.1 Expedited AE reporting for this study is via AdEERS (Adverse Event Expedited Reporting System) accessed via the secure CTEP web site https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/adeers.html).

6.2.2 AEs that require notification to the Investigational Drug Branch (IDB) within 24 hours should be made via the AdEERS web site: https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup.

6.2.3 All AEs reported via AdEERS **must** be copied to the Study Coordinator wdfigg@helix.nih.gov using the copy feature of AdEERS. The Study Coordinator will submit AE reports to the Principal Investigator for timely review.

6.2.4 Expedited Reporting Guidelines – AdEERS Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unex-pected	Expected	with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	Unex-pected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

AdEERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

December 15, 2004

Note: All deaths on study must be reported using expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of designation as expected or unexpected and attribution with the exception of events listed in Section 7.3.5 (Protocol-Specific Expedited Adverse Event Reporting Exclusions).Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number on all reports.
- Events that are clearly consequences of the "main" event may be noted in the Description of Event in the AdEERS report, and do not require separate AdEERS reports.

The possibility of the contribution of comorbid conditions to the event should be considered when reporting AEs.

6.3 NCI-IRB Expedited Adverse Event Reporting Requirements:

The PI will report:

- All serious adverse events (SAEs) that are **not** in the consent form, but are possibly, probably or definitely related to the research. A SAE is defined as an untoward medical occurrence that

  resulted in a death;

was life-threatening;
required or prolonged hospitalization;
caused persistent or significant disability/incapacity;
resulted in congenital anomalies or birth defects; or
required intervention to prevent permanent impairment or death.

- All other deaths.
- All grade 3 and 4 (CTCAE) events that are not in the consent and that are possibly, probably or definitely related to the research.

Reports must be received by the NCI-IRB within 7 calendar days of the investigator's notification of the event.
A copy of the current NCI IRB Adverse Event Form can be downloaded from the following URL: http://home.ccr.cancer.gov/irb/adverse.html

NCI IRB Contact Information:

- E-mail- nciirbadmin@mail.nih.gov
- Mail- Building 82/Room 115, 9030 Old Georgetown Road, Bethesda, MD, 20892
- FAX- 301-480-0106

6.4 NCI-IRB Requirements for PI Reporting of Expected and Unexpected Adverse Events at Continuing Review

The NCI-IRB requires a summary report of adverse events that have occurred on the protocol since the previous continuing review. The method of presentation should provide the NCI-IRB with the information necessary to clearly identify risks to participants and to make a risk:benefit determination. The summary report is based on the following guidance:

Any unexpected severity and/or unexpected frequency of expected events needs to be reported and interpreted in relation to the risk:benefit of study participants in the narrative.

1. Grade 1 events are not required.
2. Grade 2 unexpected events related to the research that are not in the consent is required.
3. Grade 3 and 4 events related to the research are required.
4. All Serious Events regardless of attribution are required.
4. All Grade 5 events are required regardless of attribution.

Based on protocol associated risks to participants, the NCI-IRB retains the authority to establish more frequent Continuing Review periods than the customary annual review period.

6.5 Routine Adverse Event Reporting

Those AEs that do not require expedited reporting **must** be reported in routine (CDUS) study data submissions. **AEs reported through AdEERS must also be reported in routine study data submissions.**

6.6 Secondary AML/MDS

Investigators are required to report cases of secondary AML/MDS occurring on or following treatment on NCI-sponsored chemotherapy protocols using the NCI/CTEP Secondary AML/MDS Report Form. This form can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/index.html). Second malignancies and non-AML/MDS secondary malignancies (*e.g.*, endometrial cancer in a breast cancer patient receiving tamoxifen) should NOT be reported via AdEERS but should be submitted as part of the study results via routine CDUS reporting.

7. PHARMACEUTICAL INFORMATION

AZD2171 (NSC 732208) IND # 72740

Chemical Name: 4-[(4-Fluoro-2-methyl-1*H*-indol-5-yl)oxy]-6-methoxy-7-(3-pyrrolidin-1-

	ylpropoxy) quinazoline maleate
Other Names:	AZD2171 maleate, Recentin™
CAS Registry Number:	288383-20-0 (for the free base)
Molecular Formula:	$C_{25}H_{27}FN_4O_3 \cdot C_4H_4O_4$
Molecular Weight:	566.59 as maleate salt (450.52 as free base)
Approximate Solubility:	The aqueous solubility of AZD2171 has been measured as 0.0006 mg/mL for the free base (distilled water, pH 8.1 at 25°C) and 1.9 mg/mL for the maleate salt (distilled water, pH 4.4 at 25°C).
Mode of Action:	AZD2171 is a highly potent inhibitor of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase activity, which may inhibit vascular endothelial growth factor-A (VEGF) driven angiogenesis and, as a consequence, constrain solid tumor growth.
How Supplied:	Until September, 2007, NCI will distribute AZD2171 as 9 mm round, beige film-coated tablets containing 10 mg or 15 mg of AZD2171 free base in bottles of 100. In addition to the active ingredient, tablets contain mannitol, dibasic calcium phosphate anhydrous, sodium starch glycollate, and magnesium stearate with a film coat coating hypromellose 606, polyethylene glycol 400, red iron oxide, yellow iron oxide, black iron oxide, and titanium dioxide. Sites can use these tablets to their expiration dates. In September 2007, NCI will distribute AZD2171 as round, beige film-coated tablets containing 10 mg and 15 mg of AZD2171 free base. The 10 mg and 15 mg tablets are 6 mm and 7 mm in diameter, respectively. Each bottle contains 35 tablets. In addition to the active ingredient, the tablets contain mannitol, dibasic calcium phosphate anhydrous, sodium starch glycollate, microcrystalline cellulose, and magnesium stearate with a film coat coating hypromellose 606, polyethylene glycol 400, red iron oxide, yellow iron oxide, black iron oxide, and titanium dioxide.
Storage:	Store intact bottles at controlled room temperature [20°C-25°C, (68-77°F)] and protect from light.
Stability:	Stability studies are ongoing.
Route of Administration: Oral.	AZD2171 tablets should be taken either 1 hour before or 2 hours after meals.

Adverse Events and Potential Risks

A list of the AEs and potential risks associated with AZD2171 can be found in Section 5.

Availability

AZD2171 is an investigational agent (IND 72740) supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

AZD2171 is provided to the NCI under a Clinical Trials Agreement (CTA) between _Astra Zeneca International and the DCTD, NCI (see Section 11.3).

Agent Ordering

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN Rm. 7149, Bethesda, MD 20892.

Agent Accountability

The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form. See the CTEP web site for Policy and Guidelines for Accountability and Storage of Investigational Drugs (http://ctep.cancer.gov/requisition/storage.html), as well as the CCR Standard Operating Procedure: *Conducting and Documenting Drug Accountability for Oral Investigational Agents that are Self Administered by Patients* (http://ccrintra.cancer.gov/clin_ops/policies/SOPCLIN1.pdf).

Prednisone

a) Chemical formula: 17a, 32-Dihydroxy-1,4-pregnadiene- 3,11,20-trione
   - Chemical Formula: $C_{21}H_{26}O_5$ Molecular weight of 358.4

b) Classification: Glucocoticorticoids

c) Mechanism of Action: Multiple mechanisms leading to anti-inflammatory and immune suppression outcomes

d) How supplied: Prednisone is supplied as a tablet or suspension. We will use commercially available 5 mg tablets for this study.

e) Storage: Prednisone should be stored in original containers at room temperature, out of direct sunlight.

f) Stability: Prednisone tablets are stable for three years from date of manufacture

g) Route of administration: Oral

h) Toxicities: Anemia, eosinopenia, leukocytosis, lymphopenia, thrombocytopenia, leukocytosis, hypertensive crisis, hypertension, psychosis, schizophrenic psychosis, extrapyramidal effects, pseudotumor cerebri, hyperglycemia, hyperuricemia, hypercalcemia, adrenal suppression, Cushing's syndrome, porphyria, lipid abnormalities, hypokalemia, peptic ulcers, pancreatitis, abdominal pain, nephrotoxicity, proteinuria, cataracts, papilledema, acne, osteonecrosis, osteoporosis, myopathy, and superinfections.

i) Availability: Prednisone will be obtained from commercial stock purchased by the NIH CC Pharmacy Department.

8. CORRELATIVE/SPECIAL STUDIES

Given the nature of this pharmacologic intervention, characterization of the actual biological manipulation will be critical in understanding the biological effects seen following drug administration. Blood and tissue samples will be analyzed to achieve this goal.

The collection of correlative studies is designed to characterize a baseline molecular profile as well as a treatment-induced molecular profile. VEGFR mutational analysis will allow for retrospective analysis of responsiveness in the presence or absence of mutations. Pharmacokinetic analysis will provide insight into dosing efficacy as it relates to both biological activity and clinical response.

Correlative laboratory studies for this trial will be conducted in the Clinical Pharmacology Research Core and the Molecular Pharmacology Section, both under the direction of Dr. William D. Figg. All patients will have leukocyte collections by standard buffy coat preperation to evaluate for tumor and gene expression alterations related to drug therapy.

Proposed correlative studies follow. Other studies may be performed as further data is developed both within the study and from other investigators.

8.1 Tissue Studies

8.1.1 Soluble KDR

The Molecular Pharmacology Section will utilize an ELISA assay to determine VEGF R concentration, as previously described (Belgore 2001; Neulen 2001; Robak 2003; Wierzbowska 2003). Patients will have serum drawn for VEGF R concentration analysis prior to cycle one, and subsequently prior to each cycle there after. Vascular endothelial growth factor receptor concentrations will be correlated to response and disease progression.

8.1.2 Adhesion Molecules

Endothelial cell-specific adhesion molecules (VCAM-1, E-selectin, ICAM-1) are released by damaged endothelial cells; ELISA analysis of these markers will assess the level of cell dysfunction.

8.1.3 Biopsies

If tissue is obtained from biospies, the expression of of KDR & phospho-KDR will be assessed via immunohistochemical staining. Although KDR is expressed on endothelial cells, there are reports that it can also be expressed on epithelial tissues (tumor tissues) REF. The assay will provide information as to whether drug targets the endothelium or the tumor itself.

Biopsies are optional and will be limited to those that are easily accessible and involve minimal risk. The procurement of tissue samples will be discussed with patients at enrollement in the protocol. Biopsies will be obtained prior to initiating AZD2171 (0 months), and after cycles 2 and 6, and every six months thereafter. Participation in the phase II study is in no way contingent on consent to biopsy.

8.1.4 Pharmacogenetic Analyses

Rationale

Knowledge of variation in kdr/flk-1 (the target of AZD2171) as well as other genes in this pathway will assist in the interpretation of biomarker data. The proteins encoded by these other genes are either biomarkers themselves (VEGF-A) or they regulate the expression of biomarkers (Hif1 alpha ,microvessel density). Additionally, other genes regulated by this pathway include candidates for genetic factors predisposing to the development of hypertension in response to anti-angiogenic therapy.

Two common (>10% allele frequency) variants of the kdr/flk-1 gene were discovered and validated by an AstraZeneca polymorphism screen and have subsequently been reported in public domain data bases. Both of the polymorphic amino acid residues (Val/Ile 297; Gln/His 472) are located in the external domain of the receptor. Single nucleotide polymorphisms have also been described in the promoter region of the kdr/flk-1 gene and may correlate with expression levels of the receptor. While somatic mutations in the kdr/flk-1 gene have been described in colorectal tumors (Bardelli 2003), there are no data on the functional consequences of these mutations and there are no reports of mutations in the kdr/flk-1 gene in other tumor types.

Although no decrease in circulating VEGF was detected in a study with bevacizumab in rectal cancer (Willett 2004), VEGF-A levels may be modulated by AZD2171. There is a wide inter-individual variation in VEGF-A levels, and an understanding of the factors influencing basal levels of VEGF-A may aid the interpretation of results. Polymorphisms in the VEGF-A gene have been shown to affect expression levels of the protein both *in vitro* and *in vivo* (Watson

2000; Renner 2000; Stevens 2003).

Analysis of the HIF1α gene should be included in studies where microvessel density (MVD) is being analyzed as a biomarker. HIF1α is a key regulator of cellular response to hypoxia and is thought to play an important role in tumor progression and metastasis through activation of genes that are involved in the regulation of angiogenesis, energy metabolism and other functions (reviewed by Semenza 2002). Tanimoto *et al.* (2003) have demonstrated a correlation between two polymorphic variants of HIF1α and MVD in head and neck cancer.

The development of hypertension has been reported in ~11% of patients treated with bevacizumab plus chemotherapy compared to 2% in patients treated with chemotherapy alone (Hurwitz 2004), indicating that a proportion of patients on antiangiogenic therapy may be susceptible to the development of hypertension. If hypertension is observed in patients treated with AZD2171, analysis of candidate genes such as endothelial nitric oxide synthase gene (eNOS) could be undertaken. Variants of eNOS have been associated with essential hypertension and renal disease (reviewed by Wattanaitayakul 2001) and may correlate with the development of hypertension in patients treated with antiangiogenic therapy. Nitric oxide release is mediated via the activation of kdr/flk-1 through downstream signaling mechanisms, and components of these pathways could provide additional candidates (Duval 2003).

All study participants will be invited to provide a blood sample for retrospective genotyping. Participation in pharmacogenetic studies will be optional for all patients entering the study and will involve a separate consent procedure. A patient's acceptance of pharmacogenetic analyses will not be a requirement of their participation in this study.

8.1.5 Blood Sample Collection for Tumor Biomarker Studies

NCI, Dr. William D Figg's laboratory is the designated laboratory, (POC, Mr. Gareth Peters, 10/5A09, 102-11964, 301-402-3622).

Collection

- Samples for tumor biomarkers will be drawn at baseline, 24 hours after starting daily oral dosing, and at each clinic visit prior to the start of the next cycle.
- Collect blood in two 10 mL polypropylene tubes containing the anticoagulant Heparin
  - SARSTEDT Monovette® EDTA KE (9 mL), Part # 02.1333.001 **or**
  - Becton-Dickinson Vacutainer™ K2E (10 mL), Part # 367525 **or**
  - Greiner Bio-One Vacuette® K3E EDTA K3 (9 mL), Part 455036
- Blood tubes must be gently inverted several times after collection to ensure thorough mixing of EDTA with the sample to prevent clotting.
- **Glass tubes MUST NOT be used** as they may break during transport and freeze-thaw cycles.
-
- After collection, blood samples must be refrigerated (+ 4°C) or frozen (see chart below) at the site of collection and transported to the central reference laboratory or designated DNA processing laboratory **as soon as possible**.

Option	Storage Temperature at Treatment Site	Maximum Duration of Storage at Treatment Site	Transport Temperature	Delivery Time
1	+ 4°C (fridge)	24 hours	0 - 4°C (ice blocks)	24 hours
2	+ 4°C (fridge)	24 hours	Less than -20°C (dry ice)	24-72 hours
3	-20°C	Up to 1 month	Less than -20°C	24-72

	(freezer) or -70°C		(dry ice)	hours

- If blood samples are to be frozen for storage at -20°C or less, **non-frost free freezers** must be used to prevent repeated freeze-thaw of blood which may reduce yield and quality of the DNA obtained.

Samples must not be thawed and then re-frozen at any point.

Labeling, Storage, and Tracking

- All labels used must be freezer-proof.
- Barcode labels will be used in this study.
- Label each collection tube with the following information:
  - unique sample I.D.
  - study I.D. (CTEP protocol number, local protocol number, etc.)
  - date of sample collection
- All data associated with samples is entered into the Clinical Pharmacology Program's "Patient Sample Database Management System" (PSDMS) - Labrador. This is a secure program that can only be accessed by authorized users in Dr. Figg's lab. PSDMS creates a unique barcode ID for every sample and sample box which cannot be traced back to patients without PSDMS access
- The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. There are patient demographics that can be obtained to correlate with the samples through the PSDMS system. For each sample, there are associated processing notes (i.e., delay in sample processing, storage conditions on the ward, etc.). Bar-coded samples are stored in bar-coded boxes in a locked freezer at either -20 or -85°C according to stability requirements. These freezers are located onsite in Dr. Figg's lab and offsite at NCI Frederick Central Repository Services (Fisher Bioservices) in Frederick, MD. Samples will be stored until requested by the researcher assigned to the protocol (however, those requests must come from a member of Dr. Figg's laboratory with PSDMS access/clearance). All requests are monitored and tracked in the PSDMS system. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol – that protocol is stored in the PSDMS system) and that any unused samples must be returned to Dr. Figg's laboratory.

Protocol Completion/Sample Destruction

- Once primary research objectives for the protocol are achieved, intramural researchers can request access to remaining samples providing they have an IRB approved protocol and patient consent.
- Samples, and associated data, will be stored permanently unless the patient withdraws consent. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to Dr. Figg's laboratory.
- The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Dr. Figg's laboratory will report any freezer problems, lost samples or other problems associated with samples to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

8.2 Imaging Studies

8.2.1 Dynamic Contrast Enhanced – Magnetic Resonance Imaging (DCE-MRI)

Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) has been used extensively with novel antiangiogenic agents in Phase 1/2 to monitor their effect on tumor

vasculature through parameters reflecting both tumor perfusion and permeability. **This protocol is limited to DCE-MRI using T1 weighted studies with low molecular weight gadolinium (Gd) chelates.** Other MRI techniques (which are not covered by this protocol) include the following: DCE-MRI using T2* weighted images; contrast-enhanced MR with high molecular weight contrast agents; and non-contrast enhanced MRI techniques such as diffusion-weighted MRI, T2* weighted MRI or BOLD.

DCE-MRI studies will be interpreted by Dr. Peter Choyke, MD, Chief, NCI Molecular Imaging Department, 301.435.4046, 10/1B40. Other members of the clinical imaging program may contact Dr. Choyke for information purposes regarding the imaging protocol and data capture methodology.

8.2.1.1 DCE-MRI End Points

- The primary end points of these DCE-MRI studies are the Initial Area Under the Gd Curve measured over 60 seconds (IAUC60) and the Transport Constant (K^{trans}).
- IAUC (initial area under the gadolinium concentration time curve) does not require a model but does not have a simple relationship to physiology. It is a relatively robust and simple technique. Each institution participating in this DCE-MRI study should measure the initial area under the curve (IAUC, mMGd/sec) over the first 60 seconds from a region of interest (ROI) analysis averaged over the whole tumor volume (3D techniques) or over the tumor area (2D techniques) to provide a basic measurement for collation of DCE-MRI data across studies.
- Transport Constant (K^{trans}) should ideally be provided by each institution participating in this DCE-MRI study from a region of interest (ROI) analysis averaged over the whole tumor volume (3D techniques) or over the tumor area (2D techniques).
- Both K^{trans} and IAUC60 require calculation of instantaneous tumor Gd concentration based on the change in relaxivity due to contrast uptake ΔR1. The basic requirements for these calculations are:
  - An estimate of contrast agent relaxivity in tumor vasculature and tissue
  - Measurement of tumor T1 immediately prior to contrast uptake
  - An accurate T1 measurement method verified for all spatial locations, coils and scanners used
  - Cardiac output (or arterial input function) for K^{trans} (population based estimates may be appropriate)
  - Reproducible injection (ideally power injector)
- All data including ROI definition and analysis should be recorded and traceable to support external review.
- Additional end points may be generated at a study / protocol level in addition to these primary end points. The production of the primary DCE-MRI end points for comparison between studies does not preclude other end points within studies such as parametric maps of IAUC/K^{trans}, blood volume (Vb), extravascular space (Ve), Kep (a function of K^{trans} and Ve), etc.

8.2.1.2 Tumor Type and Location

- Current guidance for AZD2171 studies is that lesions within the **lung** are excluded from DCE-MRI studies due to “breathing” artifacts which make image data difficult to analyze reliably.
- Recommendations for lesion selection:
  - Exclude lung lesions.
  - If possible, exclude lesions in close proximity to the heart or major vascular structures.
  - If possible, choose lesions towards the center of the image volume.
  - If possible, choose lesions towards the center of the image plane.
  - Lesions should be at least 1.5 cm and preferably > 2 cm in longest in plane diameter.
  - Lesions preferably should be < 7 cm in the z plane [the entire lesion(s) should be within the volume scanned].
  - Lesions should be well defined on standard CT or MR imaging.

8.2.1.3 Schedule of CT/Bone scan and DCE-MRI Assessments

- Preliminary results in AZD2171 phase 1 studies indicate that reduction in DCE-MRI parameters reflecting tumor "blood flow" (IAUC60) and permeability (K^{trans}) can be seen after a single dose of the agent as well as after daily dosing over 28 and 56 days. Then DCE-MRI will be scheduled every 4 months after cycle 4.
- CT Bone scans, Echo should be obtained at 0, 2, and 4 months after enrollment, then every 3 months thereafter. If CTs show no evidence of soft tissue disease, subsequent CTs may be omitted. Echo guidelines should be followed as per Section 5.2.
- DCE-MRI scans should be obtained:
  - prior to treatment (preferably within 7 days of treatment start)
  - 24-36 hours after starting daily oral dosing
  - 28 +/- 2 days after starting daily oral dosing
  - 56 +/- 2 days after starting daily oral dosing, depending on the study design
  - further follow-up scans, depending on the study design

8.2.1.4 Data to be Collected

The following information on a per patient basis should be supplied to the NCI with the final study manuscript.

- Study identifier (NCI protocol number)
- Subject identifier (patient I.D.)
- AZD2171 dosing information
  - Date of first dose of AZD2171
  - Date of last dose of AZD2171
  - Dose of AZD2171
  - Any relevant dosing information, e.g., drug holidays
- Tumor type
- For each DCE-MRI scan
  - Location of lesion studied, e.g., liver metastases
  - Date of DCE-MRI scan
  - Tumor IAUC60
  - Tumor K^{trans}
- For each RECIST response assessment
  - Date of each RECIST assessment
  - Response assessment (if progression is recorded, then it should be specified whether the progression is in the lesion assessed by DCE-MRI)

8.3 Assessment of the pharmacokinetic parameters of AZD2171

Samples should be sent to NCI, Dr. William D Figg's laboratory, (POC, Mr. Gareth Peters, 10/5A09, 102-11964, 301-402-3622).

Each PK sample requires that at least 4ml blood be collected in Lavender-top tube containing EDTA. After collection, each tube should be completely and gently inverted ten times, placed on ice and subsequently refrigerated until picked up the point of contact noted above. Pickup should ocurr within 30 minutes of collection to ensure prompt processing as described below. During the first cycle, blood samples will be obtained serially from prior to ingestion until 48 hours post-dose at the following time points: immediately pre-dose, and 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 12 hr, 24 hr, and 48 hours after ingestion, and then a trough sample at each clinic visit. Patients will be asked to refrain from taking their dose prior to trough levels being obtained. Patients will not take drug on day 2, and will resume taking drug on day 3 after the 48 hour PK timepoint. Patients may have PKs done on either an inpatient or outpatient basis.The Clinical Pharmacology Research Core of Dr. William D. Figg will coordinate rapid acquisition and evaluation of patient samples. The maximum concentration, time to maximum concentration, the area under the curve extrapolated to infinity, and the apparent terminal half-life will be calculated. Pharmacodynamic study will address any correlation in AZD2171 concentration with disease response and/or toxicities.

Each PK sample requires that at least 4ml blood be collected in Lavender-top tube containing EDTA. After collection, each tube should be completely and gently inverted ten times, then centrifuged within 30 minutes for 10 minutes at 1500 x g. The supernatant/plasma (2ml) will be transferred into a 4ml Corning cryovial and frozen upright at -20^{o}C until samples can be sent to Quest Diagnostics for further analysis. Samples should be shipped on dry ice. If samples are sent to Quest the same day of collection, cryovials should be sent to Quest Diagnostics on dry ice for analysis. Each sample should be labeled

with labels provided by Quest, and shipped to the following address:

Quest Diagnostics Clinical Trials
Attn: Specimen Processing
7600 Tyrone Avenue
Van Nuys, CA 91405 USA

Quest contacts for PK samples are as follows:

US and Canada Toll-Free:	800-877-7004
Direct Line:	818-830-2200
Fax – General Inquiries:	818-891-7780
Fax – Reorder Supplies:	818-895-6803

For study-specific questions, press “1” and extension below:

Ben Delect	x2237	ben.b.delact@questdiagnostics.com
George Negron	x2272	george.x.negron@questdiagnostics.com

For general information, supplies and results, press “2” for the Client Response Center.

Client Response:	5:00 AM – 6:00 PM (Pacific Time) Monday-Friday
Center Hours:	6:00 AM – 2:30 PM (Pacific Time) Saturday, Sunday, and Holidays*
	*On Christmas and New Year’s Day, outbound critical calls only

or send inquiries to crc.us@questdiagnostics.com

Please refer to the document “ Investigator Manual for US and Canda, AstraZeneca Study ID Z6C, General Manual for AstraZeneca, AZD2171/NCI Collaboration, Version 2.0, September 21, 2006, for detailed information regarding PK sample processing.

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 16 days prior to administration of protocol therapy. Scans and x-rays must be done 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. All patients will receive AZD2171 20 mg po daily and prednisone 10mg po daily. AZD-2171. AZD-2171 dose reductions will be made in 5 mg increments; the lowest dose level is dose level -2, or 10 mg. All baseline and follow up evaluations can be done on the last week of the prior cycle.

	Pre-Study	C1D1	C2D1	C3D1	C4D1	C5D1	Off Study
AZD2171[a]		X	X	X	X	X	
Prednisone[a]		X	X	X	X	X	
Informed consent	X						
Demographics	X						
Medical history	X						
Med List	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X
Vital signs[g]	X	X	X	X	X	X	X
Height	X						
Weight	X	X	X	X	X	X	X
Performance status	X	X	X	X	X	X	X
CBC w/diff, plts, PSA	X	X	X	X	X	X	X
Serum chemistry[b]	X	X	X	X	X	X	X
Serum PAP	X						
PKs[h]	X	X	X	X	X	X	
Serum Troponin T[d]	X	X	X	X	X	X	
TSH, free T4[e]	X	X	X				
EKG	X	X	X	X	X	X	
Urine dipstick for protein[f]	X	X	X	X	X	X	
Imaging studies[c]	X		X		X		X
Biomarkers	X	X	X	X	X	X	X

a: AZD2171 and prednisone: Dose as assigned. Administered orally, daily at a fixed dose. Please keep a pill diary (Appendix B). Cycles = 28 days.
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
c: CT, Bone scan, Echo, DCE-MRI and/or ^{18}FDG-PET. See Section 8.2.1.3 for the frequency of Imaging studies.
d: Serum Troponin is to be obtained pre-study andonce a cycle thereafter.
e: TSH and free T4 is to be obtained pre-study, once a cycle for the first two cycles, then only if clinically indicated.
f: if patient has significant proteinuria, obtain a 24-hour urine for protein and creatinine clearance.
g: Blood pressure will be measured at each clinic visit. In addition, patients will be asked to measure their blood pressure twice daily at home, as follows: a resting morning blood pressure and an evening blood pressure. Any abnormal blood pressure measurements should be reported to the research nurse within 24 hours. Furthermore, the patient will be asked to record blood pressure readings in a blood pressure diary (Appendix C).
h See Section 8.3 for details as to pharmacokinetic timepoints to be drawn Pre-study. At the beginning of each cycle, a trough level will be drawn at each clinic visit prior to ingesting the first dose of drug for that cycle.

10. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be reevaluated for response after 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

10.1 Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*J Nat Cancer Inst* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

10.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

10.1.2 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

10.1.3 Target lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

10.1.4 Non-target lesions

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

10.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

10.3 Response Criteria

10.3.1 Evaluation of target lesions

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

10.3.2 Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/	

Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

10.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Sections 10.1, 10.2, and 10.3).

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

Note:

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

10.4 Confirmatory Measurement/Duration of Response

10.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see section 10.3.3).

10.4.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

10.4.3 **Duration of Stable Disease**

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

10.5 Biochemical Response Criteria –PSA measurements (PSA Consensus Criteria) (Bubley et al. 1999)

10.5.1 PSA Decline of ≥50%
A decline of PSA of at least 50% (confirmed by a second value at least 4 weeks after the first) with no other evidence of disease progression.

10.5.2. PSA Progression (all progression dates require to be confirmed by a second value after the first no sooner than 4 weeks after the initial measurement)

A 50% increase in PSA over nadir (confirmed by a second reading four weeks later) in patients whose PSA has fallen by at least 50%. PSA increase must be at least 5ng/ml.

10.5.2.1 A 25% increase in PSA over nadir (confirmed by a second reading) in patients whose PSA has not fallen by at least 50%. PSA increase must be at least 5ng/ml.

10.5.2.2 A 25% increase in PSA over baseline in patients whose PSA has not decreased. PSA increase must be at least 5ng/ml.

10.5.3 Time to PSA Progression

The time between the first day of treatment to the day of PSA progression as described in 9.5.2. the day of progression is defined as the first study day when the PSA level meets progression criteria (not the day of verification).

10.5.4 Patients will not be taken off trial for changes in PSA alone.

10.6 Progression-Free Survival

The primary objective of this study is to determine whether AZD2171, when used to treat metastatic androgen-independent prostate cancer, is associated with $\geq$ 30% of patients' progression free at 6 months by radiographic and clinical criteria. Patient monitoring studies and definitions of response are defined above. Please refer to the statistics section for further details.

Clinical evidence of progression even in the absence of clear radiographic or biochemical evidence of progression will be grounds for terminiation of study continutation for a given patient. Radiographic evidence of progression (progression or development of new measurable disease on CT scan or appearance of at least 2 new lesions on bone scan) without concurrent PSA rises meeting progression criteria will be considered grounds for termination of study for a given patient.

11. DATA REPORTING / REGULATORY CONSIDERATIONS

Note: Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 6.0 (Adverse Events: List and Reporting Requirements).

11.1 Data Reporting

For ease of reporting, this trial will utilize reporting guidelines as outlined by CTEP (available at http://ctep.info.nih.gov/reporting/index.html). These reporting guidelines have been formally adopted by the NCI IRB. This study will use C3D to capture data and report to CDUS and will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. *Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov/reporting/cdus.html).*

11.2 CTEP Multicenter Guidelines

This is not a multicenter trial.

11.3 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

The agent(s), supplied by CTEP, DCTD, NCI, used in this protocol is/are provided to the NCI under a Collaborative Agreement (CTA) between the Pharmaceutical Company [hereinafter referred to as "Collaborators"] and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" contained within the terms of award, apply to the use of Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient participating on the study or patient's family member, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data".):

    a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with alll applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or Principal Investigator for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation should be sent to:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   6130 Executive Boulevard, Suite 7111
   Rockville, MD 20852
   FAX 301-402-1584
   E-mail: anshers@ctep.nci.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

11.4 Data and Safety Monitoring Plan

The PI, protocol chairperson and the research nurse will meet at least monthly to review all adverse events. Unexpected adverse events and/or serious adverse events will be reported to the NCI IRB and CTEP. If trends are noted and/or risks warrant it, accrual will be interrupted and/or the protocol and/or the consent will be modified accordingly. MedWatch reporting will be used to report adverse events not previously associated with non-IND drugs to the FDA. Adverse events thought to be associated with AZD2171 will be reported via AdEERS.

12. STATISTICAL CONSIDERATIONS

The primary objective of this study is to determine whether AZD2171, when used to treat metastatic AIPC, is associated with having 30% of patients progression free at 6 months by clinical andradiographic criteria. If this is found to be the case, then this agent will be considered potentially useful when combined with other anticancer agents to be tested in later trials. Data from previous trials of NCI patients with similar eligibility requirements demonstrated a 2.1 month median progression free survival when using thalidomide (n=63). Median progression free survival on ketoconazole alone is expected to be 4 months based on previous trials. Ketoconazole is recognized as a standard therapy alterative to cytotoxic chemotherapy in the setting of failure of primary hormonal therapy with GnRH agonists and anti-androgen therapy. The Eastern Cooperative Oncology Group sponsored a phase III clinical trial comparing ketoconazole to the combination of estramustine and docetaxel. (closed recently due to poor accrual). Median progression free survival on ketoconazole alone was expected to be 4 months based on previous trials Based on these results, it would be useful to demonstrate whether AZD2171 is able to induce progression free survival in 30% of patients at the 6 month (approximately day 180 evaluation) time point.
The study will be conducted as a two-stage optimal design (Simon 1989). With alpha=0.10 and beta=0.10 as acceptable error probabilities, the trial will target 30% as the desirable proportion of patients who are still without progression by clinical and radiographic criteria by the 6^{th} monthly evaluation (p1=0.30), and will be considered inadequate if only a fraction consistent with 10% are without progression by the same evaluation time (p0=0.10). Initially 12 patients will be enrolled and followed for progression. If 0-1 of the 12 is progression free at 6 months, then no further patients will be enrolled. The enrollment will be temporarily halted after the 12^{th} patient unless we know that 2 patients have passed the 6 month point without progression. If 2 or more of the first 12 reach 6 months without progression, then enrollment will continue until a total of 35 evaluable patients have been entered. If 2-5 of 35 are able to get to 6 months without progression, this is not adequate responsiveness to treatment, while if 6 or more of 35 are progression free at 6 months, this will indicate results consistent with an

adequate progression free survival probability worthy of further investigation. Under the null hypothesis (10% progression free at 6 months), the probability of early termination after 12 patients have been evaluated at 6 months would be 66%.

Given the difficulties in interpreting progression free rates in our patients compared to historical data, the response rate will be included as a secondary clinical endpoint. In addition to evaluation of the proportion progression free at 6 months, the progression free survival will also be analyzed via a Kaplan-Meier curve. This will be done for both progression free survival evaluated by clinical, radiographic and PSA criteria, as well as secondarily based only on clinical and radiographic criteria. This latter, secondary, evaluation will be based on all patients who are able to be assessed by these criteria in either the first (retrospectively) or second stage of accrual.

12.1 Sample Size/Accrual Rate

Based on previous efforts in recruiting patients with this disease onto trials at the NCI, it is anticipated that 20-30 patients per year may be able to enroll onto this protocol. To allow for up to 2 inevaluable patients, the accrual ceiling will be set at 37. Thus, it is expected that accrual to this trial can be completed in approximately 1.5 years if all 37 patients are to be enrolled.

12.2 Stratification Factors

There are no stratification factors.

12.3 Analysis of Secondary Endpoints

PSA, pharmacokinetic, and molecular endpoints will be evaluated on the protocol in all available enrolled patients. These will all be considered exploratory analyses, and will not have their statistical results adjusted for multiple comparisons. However, all interesting findings will be carefully interpreted as hypothesis generating.

12.4 Reporting and Exclusions

12.4.1 Evaluation of toxicity.

All patients will be evaluable for toxicity from the time of their first treatment with AZD2171.

12.4.2 Evaluation of response.

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.] All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

12. 5 Statistical Analysis with prednisone

As of June 2008, protocol 07-C-0059 has enrolled 28 evaluable patients, of whom 19 have experienced at least grade 2 fatigue, anorexia, and/or weight loss (68%). Since this incidence of constitutional symptoms tends to limit the ability to provide treatment which may be associated with improvement in disease outcome, the protocol will be amended following completion of the initial enrollment of 35 patients to include prednisone in combination with AZD2171.

This amendment will permit 23 additional evaluable patients to enroll onto this trial and receive prednisone and AZD2171. Using a one-sided 0.05 alpha level Fisher’s exact test, 23 patients will provide 80% power to detect a difference between the currently identified 19/28=68% of patients with grade 2 or worse fatigue, anorexia, and/or weight loss and 30% with the same level and type of symptoms. The final comparison will be based on up to 35 evaluable patients from the first part of the trial, and thus this power calculation may remain approximately

correct based upon the findings at that time.

An event free survival curve based on the initial 28 patients indicated that the 3 month EFS probability was 57% with a lower one-sided 90% CI bound of 43%, and the 6 month EFS probability was 38%, with a lower one-sided 90% CI bound of 25%. As a stopping rule, after 10 patients have been enrolled onto the amended protocol and potentially followed for at least 6 months, a Kaplan-Meier probability estimate of EFS will be constructed. If either the 3 month or the 6 month observed probability estimates are less than the corresponding lower one-sided 90% CI bounds (43% or 25% at 3 and 6 months respectively), then no further patients will be enrolled onto this amended version of the trial. Furthermore, at the conclusion of the trial, if final Kaplan-Meier estimated results are below those same lower bounds (43% or 25% at 3 and 6 months respectively), the combination will be considered to be inferior to that of AZD alone and will not be recommended for further consideration, even if constitutional symptoms improve dramatically.

It is anticipated that approximately 1 to 1.5 years will be required to enroll 23 additional evaluable patients. In order to allow for a small number of potentially inevaluable patients, the accrual ceiling for the protocol will be revised to be 62 patients (up to 37 for the first portion and 25 for the second).

13. HUMAN SUBJECTS PROTECTIONS

13.1 Rationale for subject selection

Subjects treated on this study, will be individuals with metastatic prostate cancer, which has recurred (or persisted) after appropriate standard treatment. Individuals of any race or ethnic group will be eligible for this study. Eligibility assessment will be based solely on the patient's medical status. Recruitment of patients onto this study, will be through standard CCR mechanisms. No special recruitment efforts will be conducted.

13.2 Evaluation of benefits and risks/discomforts

The potential benefit to a patient that goes onto study, is a reduction in the bulk of their tumor and improvement in their bony lesions, which may or may not have favorable impact on symptoms and/or survival. Potential risks include the possible occurrence of any of a range of side effects, that are listed in the Consent Document (Please refer to http://ctep.cancer.gov/reporting/adeers.html to review the up-to-date expected adverse event list for AZD2171). The procedure for protecting against or minimizing risks, will be to medically evaluate patients on a regular basis as described in Section 9.

13.3 Consent process

Patients will meet with an associate or principal investigator on the trial in the Prostate Cancer Clinic, during the initial evaluation for this study. During that meeting, the investiagor will inform patients of the purpose, alternatives, treatment plan, research objectives and follow-up of this trial. The investigator will then provide a copy of the IRB-approved informed consent document that is included in this protocol. The patient will be allowed to take as much time as he wishes, in deciding whether or not he wishes to participate. If a prolonged period of time expires during the decision making process (several weeks, as an example), it may be necessary to reassess the patient for protocol eligibility. The original signed consent goes to Medical Records; copy placed in research record (NIH policy).

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on the study.

13.4 Patient Records and Quality Assurance

13.4.1 Drug Accountability

The unused AZD2171 (partial bottles, empty bottles, and full bottles) will be returned for drug accountability at each clinic visit. Protocol related data will be entered into the NCI C3D database. Research records will be maintained to include but not limited to:

- Signed, Dated Consent Form
- Completed Eligibility Checklist
- Source documents verifying eligibility criteria
- Pre-study lab, radiology, pathology reports, histopathological results
- Interim monitoring test results

- Physician notes/progress notes documenting physical evaluations, PS, history, prior therapy
- Physician/Nursing notes documenting vital signs, adverse event assessment,
- Treatment administration forms-In-patient/Out-patient
- PK Collection Forms
- Study diary/record of self administered medication schedule/compliance
- Response evaluation- results/tumor measurements
- Research PET Scan/biologic correlate sample collection/analysis
- Off study summary

See also the CCR Standard Operating Procedure: *Conducting and Documenting Drug Accountability for Oral Investigational Agents that are Self Administered by Patients* (http://ccrintra.cancer.gov/clin_ops/policies/SOPCLIN1.pdf).

13.4.2 Patients will use a diary to document daily drug intake, blood pressure, and adverse events

APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

CTEP-assigned Protocol # 7395

Local Protocol # 07-C-0059

PATIENT'S PILL DIARY

Cycle #_____

Patient Name_____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each Cycle.
2. You will take ___ pills each day. You must take the pills on an empty stomach, one hour before or two hours after meals.
3. Record the date, the number of pills you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
3. Please bring your pill bottle and this form to your physician when you go for your next appointment.

4.Total dose: ___mg per day. Number of pills each day: ___. Effective date of dosage:___

Date	Day	# pills, when taken	# pills missed	Comments	Date	Day	# pills, when taken	# pills missed	Comments
	1					17			
	2					18			
	3					19			
	4					20			
	5					21			
	6					22			
	7					23			
	8					24			
	9					25			
	10					26			
	11					27			
	12					28			
	13								
	14								
	15								
	16								

Patient's Signature: _____ Date: _____

APPENDIX C

CTEP-assigned Protocol # 7395
Local Protocol #07-C-0059_

PATIENT'S BLOOD PRESSURE DIARY

Cycle # _____

Patient Name_____

INSTRUCTIONS TO THE PATIENT:

1. Your blood pressure readings have two numbers. The first number is the pressure in your blood vessels during a heart beat (systolic), and the second number is the pressure in the vessels when the heart rests in between beats (diastolic). These numbers are usually written with a slash in between them (for example, normal blood pressure is 120/80).
2. Record the date, then record your blood pressure twice each day using a home blood pressure monitor:
   - each morning after sitting quietly for 30 minutes or reading (not while you are active: dressing, making breakfast, etc.)
   - each evening at bedtime or while you are relaxing during the evening
3. If you take your blood pressure at other times of the day, please record the numbers and time under "Other readings."
4. If your systolic pressure is greater than 150 or your diastolic blood pressure is greater than 90 twice in a row measured several hours apart, please contact your research nurse at NIH for instructions.
5. Patients should seek medical advice immediately if their BP exceeds 180 mmHg (systolic) or 105 mmHg (diastolic) at any time and should also be encouraged to contact their physician if they are concerned about any symptoms that may be associated with high blood pressure (*e.g.*, headache).
6. Please bring this form to every clinic visit or appointment.

Date	AM readings	PM readings	Other readings (include time of day)	Date	AM readings	PM readings	Other readings (include time of day)
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Patient's Signature: _____ Date:

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