CLINICAL PROTOCOL

Protocol Title: A Phase II Study of PD-0332991 in Adult Patients with Advanced Hepatocellular Carcinoma

Study Medication: PD-0332991

IRB Number: 11D.14

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Protocol Number:

Protocol Title:	A Phase II Study of PD-0332991 Treatment of Patients with Advanced Hepatocellular Carcinoma
Study Objectives:	**Primary Objective:**

	To assess the time to disease progression (TTP) in patients with advanced hepatocellular carcinoma treated with PD-0332991 **Secondary Objectives:** To assess the safety and tolerability of PD-0332991 in patients with advanced hepatocellular carcinoma To assess overall survival (OS) in patients with advanced hepatocellular carcinoma treated with PD-0332991 To assess the response rate (RR) in patients with advanced hepatocellular carcinoma treated with PD-0332991
Study Population:	Patients with inoperable, therapy-refractory advanced HCC
Study Design:	Single-institution study
Investigational Product:	PD-0332991
Dosage Form:	Capsule
Route of Administration:	Oral
Dosage and Treatment Schedule:	125 mg oral capsules daily for 21 days, followed by week rest, with cycle consisting of 28 days, in repeated cycles
Endpoints:	Time to disease progression (TTP) defined as time from entry on study to progression of disease. Safety and Tolerability Overall survival (OS) Response rate (RR)
Duration of Treatment:	Until progression of disease
Duration of Subject Participation in Study:	Progression of disease, subject withdrawal or death
Duration of Follow-up:	Subjects will be followed after disease progression with visits at 28 days, and 56 days post treatment discontinuation and every 3 months until death, subject is lost to or declines follow up. Safety data will be collected until AEs are resolved after the last dose of treatment is given.

Number of Subjects Required:	19 evaluable
Maximum Total Acrual:	25

1.0 Background

1.1 Current Treatment of Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most frequent cause of cancer-related mortality (El-Serag et al. 2007). While the majority of HCC cases occur in developing countries due to the high prevalence of hepatitis B (HBV) and hepatitis C (HCV) infection, the incidence of HCC has significantly increased in the United States over the last three decades and is predicted to remain a major health risk for future generations (El-Serag 2004). To date, surgical resection and liver transplantation are considered the main curative treatment options for HCC (El-Serag et al. 2006). However, the majority (~75%) of patients present with advanced tumor stage and poor liver function, rendering the patient ineligible for surgical interventions (Siegel et al. 2008). Furthermore, until very recently, there have been no standard systemic therapies for advanced HCC, as classical cytotoxic drugs (administered singularly or in combination) have not led to reproducible response rates or survival benefit (Llovet and Bruix 2003).

Recently, the advent of promising "targeted" therapies has introduced new possibilities for the treatment of otherwise chemo-resistant tumors. Specifically, the multikinase inhibitor sorafenib displayed a significant increase in progression-free and overall survival of patients with advanced or metastatic HCC in two randomized phase III trials (Llovet et al. 2008, Cheng et al. 2009). However, even with such favorable and landmark results, the response rate to sorafenib was remarkably low, and the overall benefits were reported to be relatively modest with a response rate of only 2% in both pivotal phase III trials. Thus, while the treatment of advanced HCC with targeted therapy has generated encouraging results, there is still a critical need for more key molecular targets and targeting compounds for truly successful therapeutic intervention.

1.2 Mechanism of Action, Pre-clinical and Clinical Data for PD-0332991

PD-0332991 is an orally available, pyridopyrimidine-derived, selective inhibitor of cyclin dependent kinase 4/6 (CDK4/6) (Fry et al. 2004, Toogood et al. 2005). Functionally, PD-0332991 is a potent and highly selective inhibitor of CDK4/6-cyclin D1 kinase activity, which ultimately results in the inhibition of retinoblastoma (Rb) protein phosphorylation and cell cycle arrest. In vitro and in xenograft models, PD-0332991 was observed to inhibit a panel of Rb-positive, solid tumor cell lines (Fry et al. 2004). A phase I clinical trial with PD-0332991 in patients with Rb-positive advanced solid tumors demonstrated a mean therapeutic dose (MTD) of 125 mg/d for 3 out of 4 weeks and a principal, dose-limiting toxicity of myelosuppression (O'Dwyer et al. 2007). Furthermore, in the context of metastatic teratoma, PD-0332991 as a single agent provided durable progression-free survival in excess of 18 months (Vaughn et al. 2009). A phase II trial of PD-0332991 in the treatment of mantle cell lymphoma (MCL) is currently ongoing, as well as combination studies with letrozole for breast cancer and with bortezomib and dexamethasone for multiple myeloma.

In preclinical studies, PD-0332991 has extensive cytostatic activity. In hepatoma cell lines this effect is dependent on the RB protein, and PD-0332991 was observed to be significantly more effective than the only currently approved therapeutic agent, sorafanib. Furthermore, in animal models, PD-0332991 was effective at inhibiting the proliferation of

hepatocytes in liver, indicating that effective doses can be achieved in vivo (Rivadeneira et al. 2010). Finally, ongoing studies suggest that PD-0332991 is a potent inhibitor of tumor proliferation in the context of xenograft models. Combined, these findings suggest that PD-0332991 could be effective in the treatment of therapy refractory HCC.

1.3 Rationale for Treatment of Advanced HCC with PD-0332991

The majority of patients with HCC present with advanced disease, and there are currently very limited options available that yield reproducible response rates or significant overall survival benefits. (Llovet, 2003) While targeted therapies such as sorafenib point the way to new, promising treatment options, there is an unmet need for trials using these agents in advanced HCC. Pre-clinical data with PD-0332991 demonstrates potent target-specificity and significant inhibition of tumor cell growth in vitro and in xenografts (Fry et al. 2004, Rivadeneira et al. 2010). Furthermore, early clinical studies demonstrate acceptable toxicities of PD-0332991, a critical factor in the treatment of patients with advanced HCC that is often associated with compromised liver function (Bruix and Sherman 2005). Thus, PD-0332991 represents an ideal candidate for the treatment of patients with advanced HCC.

2.0 Study Objectives and Endpoints

2.1 Study Objectives:

2.11 Primary Objective

To assess the time to disease progression (TTP) in patients with advanced hepatocellular carcinoma treated with PD-0332991.

2.12 Secondary Objectives

1. To assess the safety and tolerability of PD-0332991 in patients with advanced hepatocellular carcinoma.

2. To assess overall survival (OS) in patients with advanced hepatocellular carcinoma treated with PD-0332991.

3. To assess the response rate (RR) in patients with advanced hepatocellular carcinoma treated with PD-0332991.

2.2 Study Endpoints:

1. Time to disease progression (TTP) defined as time from enrollment on study to documented progression of disease.

2. Safety and Tolerability including adverse events, and significant laboratory abnormalities

3. Overall survival (OS) defined as the time from entry on trial to the time of death, from any cause.

4. Objective Response Rate defined as the proportion of subjects with either a confirmed CR or a confirmed PR as determined using modified RECIST (Version 1.1) criteria

3.0 Study Design

This is an open-label non-randomized single-institution study for subjects with inoperable, recurrent/refractory advanced hepatocellular carcinoma (HCC). Subjects must have failed or be intolerant of standard first line therapy, sorafinib (Nexavar®). Eligible subjects will receive 125 mg PD-0332991 capsules orally once daily, administered days 1-21 of a 28-day cycle, in repeated cycles.

Subjects will be permitted to receive protocol directed therapy until disease progression by modified RECIST (Version 1.1) (Response Evaluation Criteria in Solid Tumors) guidelines or clinical progression, unacceptable toxicity, withdrawal of consent or death. Tumor response assessment will be performed by the Investigator and will consist of evaluation by CT or MRI using modified RECIST (Version 1.1) guidelines every 8 weeks. Subjects who discontinue therapy for disease progression or other reasons will be followed for safety on Day 28 (± 3 days), Day 56 (± 3 days) and every 3 months thereafter or until death, from the last administration of protocol –directed therapy.

Subjects will be continuously assessed for evidence of acute and cumulative toxicity. Vital signs, Physical examinations, performance status, laboratory safety tests will be obtained and assessed prior to drug administration and at regular intervals throughout the study. Toxicity will be evaluated every 2 weeks during the first 3 cycles and thereafter monthly (once per cycle) by the Investigator according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (which can be viewed on-line at the following NCI web site: http://ctep.cancer.gov/reporting/ctc.html).

4.0 Patient Recruitment, Eligibility, and Exclusion

Subjects will be recruited from the outpatient oncology and multidisciplinary liver clinics of Thomas Jefferson University.

4.1 Eligibility Inclusion Criteria

1. Male or female, age ≥18 years with HCC refractory to currently available therapies.

2. Documented HCC by pathologic criteria.

   Recommendations for diagnosis of HCC have been issued in a guideline from the American Association for the Study of Liver Diseases, which can be accessed through the AASLD web site at http://www.aasld.org/practiceguidelines/Pages/default.aspx.

3. Subject must be able to give written informed consent and be able to follow protocol requirements

4. Life expectancy greater than 3 months

5. Be Child's-Pugh class A or B

6. ECOG Performance status of ≤ 2

7. If female of childbearing potential must have negative pregnancy test at screening and may not be breast-feeding

8. Females of child-bearing potential (< one year post-menopausal with documented FSH greater than 30 IU/L or surgically not sterile), must agree to practice an effective method of avoiding pregnancy (including oral or implanted contraceptives, intrauterine device, condom, diaphragm with spermicidal, cervical cap, abstinence or sterile sex partner) from the time informed consent is signed through follow-up. Males must agree to take appropriate precautions to avoid fathering a child from screening through follow-up.
9. No other active malignancy requiring treatment in the last 3 years other than adequately treated non-melanomatous skin cancer, adequately treated cervical carcnoma in-situ, superficial adequately treated bladder cancer or prostatic intraepithelial neoplasia without evidence of prostate cancer.
10. Adequate bone marrow, liver and renal function as assessed by the following:

    - Hemoglobin ≥ 8 g/dL
    - WBC ≥ 4,000/uL
    - Absolute neutrophil count ≥ 1,500/uL
    - Platelets ≥ 75,000/uL
    - Total bilirubin ≤ 1.5 times ULN
    - ALT and AST ≤ 5 times ULN
    - Creatinine ≤ 1.5 times ULN
    - Albumin ≥ 2.5 mg/dL

11. Subjects who have received previous radiotherapy, loco-regional, or systemic therapy are eligible. A minimum interval of 4 weeks since the last anti-cancer treatment of any kind is required.

12. Subjects with brain metastases or a history of previously treated brain metastasis are eligible but must:

    - Have been treated by surgery or stereotactic radiosurgery (SRS) at least 4 weeks prior to enrollment

- AND have a baseline MRI or CT that shows no evidence of active intercranial disease
- AND be off steroids for at least 1 week prior to study enrollment

4.2 Exclusion Criteria

1. Any concurrent active malignancy requiring treatment (other than basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, superficial bladder tumors, or other malignancies curatively treated > 3 years prior to study entry)

2. History of severe cardiovascular disease within the last 12 months: symptomatic congestive heart failure, myocardial infarction, coronary artery disease (CAD), life threatening arrhythmias, uncontrolled hypertension

3. Renal failure requiring hemo- or peritoneal dialysis

4. Unstable systemic diseases or active uncontrolled infection

5. Known history of HIV infection

6. Clinically significant gastrointestinal bleeding within 30 days prior to study entry

7. Major surgery, open biopsy or significant traumatic injury within 4 weeks prior to study entry

8. Child's-Pugh Class C

9. Any malabsorption problem that, in the investigator's opinion, would prevent adequate absorption of the study drug

10. Presence of any other medical complications that in the investigator's opinion, suggests a survival of < 3 months

11. Substance abuse, or medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results

12. Patient inability to swallow oral medications

13. Any condition that is unstable or which could jeopardize the safety of the patient and his/her compliance in the study

14. Pregnant or breast-feeding patients

15. Being of reproductive potential and unable or unwilling to practice an effective contraceptive method

16. Lack of positive staining for RB-function on tumor biopsy.

5.0 Treatment Procedures

Before subjects are entered into the study and any study-specific procedures are performed, he/she must personally sign and date consent form and an informed consent discussion must be conducted. All appropriate committees and the Jefferson Institutional Review Board (IRB), prior to enrollment of any subjects on this study, must approve the study protocol, informed consent form and all study-related materials. The patient will be asked to fast for 1 hour before and 2 hours after dosing.

Treatment Schedule

Treatment will be divided into 28-day cycles. One cycle of treatment will consist of 21 days (3 weeks) of daily oral administration of 125 mg PD-0332991 followed by 7 days without treatment for a total of 28 days (4 weeks) per cycle. Subjects may continue to receive PD-332991 for additional cycles until disease progression, intolerability, death, failure to return for follow up, and/or withdraw of consent. Patients will be evaluated at each visit and treatment continued at the discretion the Investigator

5.1 Visit 1 – Pre-study Evaluation

Prior to performing study related procedures, subjects will read, understand and sign informed consent. Investigator and medical staff involved will discuss PD-0332991 treatment with potential candidate for the study and obtain informed consent. Pre-study evaluations (other than biopsy) are to be obtained within 28 days prior to start of treatment. These will include:

1. MUGA scan or Echocardiogram if clinically indicated
2. Pulmonary Function Test if clinically indicated
3. CT scan of chest, abdomen, and pelvis
4. MRI of the liver
5. Biopsy if required to confirm diagnosis of HCC and assess RB-pathway status via immunohistochemistry (IHC). PD-0332991 is a highly selective inhibitor of CDK4/6 that is dependent on a functional RB-pathway to exert its anti-proliferative effects. It is inactive against RB-negative tumors. The complete RB-pathway consists of several families of proteins: CDKN(INK4A), D-type cyclins, cyclin-dependent protein kinases (CDK4, CDK6), RB-family proteins, and E2F transcription factors. In addition to RB protein status, overexpression of CDKN (p16INK4A) protein is associated with lack of sensitivity to PD-0332991. In vitro efficacy tests have suggested that Ki67 may be used as a biomarker of cell proliferation and indirectly correlate with sensitivity to PD-0332991. For the current study, IHC of liver biopsy tissue will be used to assess protein expression of RB, p16INK4A and Ki67, which will then be used to determine whether a patient is eligible for trial participation (i.e. likely to show sensitivity to PD-0332991).

The following pre-study evaluations are to be obtained within 14 days prior to start of treatment:

1. Complete history, physical exam including height and weight
2. Performance status, Child-Pugh status

3. Blood cell counts (CBC with differential, platelets) and comprehensive metabolic panel (albumin, alkaline phosphatase, total protein, BUN, creatinine, AST (SGOT), ALT (SGPT), total bilirubin, calcium, sodium, potassium, chloride, bicarbonate), lactate dehydrogenase (LDH), pregnancy test, and TSH, PT/PTT, INR
4. Concomitant medication review

5.2 Visit 2 – Study Initiation (Start of cycle 1)

After the eligibility is confirmed, subject will be enrolled into the study. The following assessments should be completed before the study drug is dispensed on the first day of treatment:

1. Clinical assessment – including complete physical examination to history, weight, vital signs, signs/symptoms, and performance status
2. CBC, comprehensive metabolic panel, coagulation studies
3. Serum AFP
4. Concomitant medication review

5.3 Visit 3 – Toxicity Assessment

Initial safety and tolerability of the study drug will be assessed after 2 weeks on PD-0332991. The evaluation will include:

1. Clinical assessment – including interval history, physical examination, weight, vital signs, signs/symptoms, and performance status.
2. Toxicity assessment. Adverse events will be graded using the National Cancer Institute (NCI) Common Toxicity Terminology Criteria for Adverse Events v 4.0 (CTCAE v 4.0).
3. Concomitant medication review
4. Blood cell counts (CBC with differential, platelets) and comprehensive chemistries (albumin, alkaline phosphatase, total protein, BUN, creatinine, AST (SGOT), ALT (SGPT), total bilirubin, calcium, sodium, potassium, chloride, bicarbonate), lactate dehydrogenase (LDH).

If subject experiences a Grade 3 or greater toxicity deemed related to study drug, PD-0332991 will be temporarily discontinued. After the resolution of toxicity to Grade 2 or less, PD-0332991 will be restarted at the initial dose. The study treatment will be continued until disease progression or unacceptable side effects (Grade 3 or greater). Subjects with unacceptable side effects (Grade 3 or greater) for a second time on PD-0332991 will be removed from the study. The only exception to this are: Grade 3 anorexia, nausea vomiting, stomatitis/mucositis or diarrhea that will lead to investigational product withdrawal only if not manageable despite maximum supportive care.

5.4 Subsequent visits on study – Response and Toxicity Assessment

Safety and tolerability of the study drug will be assessed every 2 weeks after the initiation of PD-0332991 for the first 3 cycles of treatment, and every 4 weeks thereafter. Procedures will be as described for Visit 3. Additionally, Serum AFP will be monitored every 4 weeks and imaging will occur every 8 weeks after initiation of therapy to determine response of the disease to treatment. Subjects will undergo tumor response assessment per modification of RECIST (Version 1.1) guidelines. Radiological assessments must include CT of the chest, abdomen and pelvis and MRI of the liver. Magnetic Resonance Imaging is the preferred study for imaging the liver and must include T1, T2/flair and diffusion weighted imaging. Studies will be obtained at

baseline and according to schedule of observations until disease progression, death, withdrawal of consent, end of study or start of a new treatment. Unscheduled imaging may be conducted at the discretion of the Investigator.

Adverse events are defined in section 9.0. The investigator is responsible for reviewing all laboratory and clinical data, determining clinical significance and assessment of adverse events. It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require subject's removal from treatment or from the study. The subject may also withdraw voluntarily from treatment due to what he/she perceives as an intolerable adverse event. If this arises the subject will be observed with extra visits until symptoms cease or the condition becomes stable. Adverse events will be graded using the National Cancer Institute (NCI) Common Toxicity Terminology Criteria for Adverse Events v 4.0 (CTCAE v 4.0).

5.5 Follow-up Visits

After disease progression or drug intolerance, subjects will be scheduled for follow-up assessment approximately 30 days after the last administration of protocol specific therapy.
At this visit subjects will undergo clinical assessment including: interval history, limited physical examination, weight, vital signs, signs/symptoms, and performance status. AEs and concomitant meds will be obtained. Bloodwork including: CBC, comprehensive metabolic panel, AFP will be collected and recorded. Subjects will be followed every 3 months in clinic to collect information on their general health status and their liver cancer. This visit must include at a minimum interval history, physical exam, concomitant medications and toxicity assessment. If possible other treatments, outcomes and survival should be obtained.

5.6 Withdrawal of Subjects

The following criteria will be used to withdraw subjects from the study:

1. Evidence of progressive disease, as defined by RECIST (Version 1.1) criteria.
2. If as judged by the investigator the subject would be best served by a change in therapy or that it is in the patient's best interest to come off study.
3. Unacceptable toxicity.
4. Subject withdrawal of consent.
5. Noncompliance with study medication or protocol-required evaluations and visits as determined by the investigator.
6. If there is a major protocol violation, or if requested by a regulatory agency.
7. Death of a subject.
8. If subject receives less than 50% of the protocol-required dose of PD-0332991 for 2 consecutive cycles, for any reason.

At the investigator's discretion, a subject may be continued on study drug for additional treatment cycles if he or she is deriving clinical benefit from PD-0332991 and interval imaging results demonstrate mild progression e.g. 25% increase in the sum of the longest diameter of target lesions rather than less than or equal to 20% used to define stable disease. If at the next interval imaging the subject shows further progression rather than disease stabilization, he/she

must be withdrawn from the study. The Principal Investigator must approve of the continuation on study.

5.7 Follow-up after Withdrawal from the Study

Subjects will be followed after withdrawal from the study and scheduled for follow-up visits. Safety data after the last dose of treatment is given until toxicity has resolved. Survival information will be collected via phone or visit on a quarterly basis for each subject if subject not able to come for regular visits.

6.0 Evaluation of Response

6.1 Definition of Progressive Disease

Progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee. 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.

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).

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.

Target Lesions

All measurable lesions up to a maximum of five lesions per organ and ten 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 at time of disease recurrence.

Non-Target Lesions

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at time of disease recurrence. 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.

6.2 Response Assessment

Response is assessed on the basis of clinical, radiological, and pathological criteria. Standard imaging via MRI and/or CT scan will be used for evaluation of nodal disease based on RECIST criteria. 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.

The subject's response will be assessed based on the response of the target lesions, the response of non-target lesions and the presence or absence of new lesions through out the course of the study.
Response Criteria for Target Lesions:

Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD)	At least 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 recorded since the treatment started

Response Criteria for 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 lesions and or maintenance of tumor marker above normal limits.
Progressive Disease (PD)	Appearance of one or more new lesions and or unequivocal progression of existing non target lesions

Subjects with global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression will be classified as having symptomatic deterioration. Every effort will be made to document objective progression.

7.0 Endpoints:

7.1 Primary Endpoint

Time to Progression (TTP)

Progression-free survival (PFS) is the time elapsed between treatment initiation and tumor progression or death from any cause, with censoring of patients lost to follow up. Time to

Progression (TTP) is defined by the FDA as the time from subject randomization until tumor progression is documented. Time to treatment failure (TTF) is a composite endpoint defined as the time from randomization until the patient stops trial treatment for any reason including progression, adverse events, insufficient therapeutic response, death, failure to return, and refused treatment/did not cooperate/withdrew consent. PFS assumes that patient deaths are randomly related to tumor progression. Compared to TTP, PFS is the preferred regulatory endpoint however in situations where deaths may be unrelated to cancer such as in patients with HCC and cirrhosis, TTP is an acceptable endpoint. In this study, TTP will be defined as the date of enrollment on trial to the first observation of disease progression, as classified by modified RECIST (Version 1.1) or clinical progression. The date of last dose of treatment or death will be used as the date of this event in the case that recurrent disease was not assessable. An interim analysis for futility will be conducted after the first 10 events have occurred. The probability of a significant final result given the observed data at the time of the interim analysis (i.e., the conditional power) will be estimated (Lachin 2005). The study will be stopped for futility if the conditional power is less than 60%. That is, the study will be stopped if there is a preponderance of evidence that completion will not yield a significant result.

7.2 Secondary Endpoints

Safety and Tolerability

Safety analysis will be conducted on all patients that received at least one dose of PD-0332991 during the study period or follow-up. An adverse event is any unfavorable and unintended sign, symptom, syndrome or illness that develops during the period of observation in the clinical study, including a new illness or condition, worsening of a concomitant illnesses or condition, effect of the study medication or combination of 2 or more factors. Causal relationships are not addressed in this nomenclature. Adverse events will be collected from the time the subject signs the informed consent form throughout the period of follow-up.

Overall Survival

Overall survival (OS) is measured form the entry onto a trial until death of any cause. Date and cause of death will be recorded. The cause of death will be categorized as either cancer-related or cancer-unrelated.

Overall Response Rate

The best overall response is the best response recorded from the start of treatment until disease progression or recurrence. The objective response rate (ORR) is the proportion of subjects with either a confirmed CR or a confirmed PR as determined using modified RECIST (Version 1.1) criteria, as evaluated by the Investigator. A confirmed CR or PR requires repeat assessments no less than 28 days after the response criteria are first met. Subjects who have not met this criteria for response will be considered non-responders. As the clinical relevance of stable disease (SD) may be important in HCC, subjects with the response of SD will be recorded and documented. Disease control rate defined as CR + PR +SD will be calculated for all subjects treated with PD-0332991.

8.0 Drug Information

8.1 General
PD-0332991 (molecular weight: 573.67 g/mol) is a highly selective, reversible inhibitor of cyclin-dependent kinases (Cdk) 4 and 6 that is being studied for use in the treatment of cancer. Inhibition of Cdk4/6 blocks DNA synthesis by prohibiting the progression of the cell cycle from G1 to S-phase. Thus, PD-0332991 functions as a cytostatic agent.

PD-0332991 is delivered as on oral capsule that is packaged and stored at 15-25^{o}C.

8.2 Clinical Pharmacology

Pharmacokinetics and Metabolism of PD-0332991
As of March 1, 2008, three studies evaluating the safety, efficacy, pharmacodynamics and PK of PD-0332991 have started. Preliminary PK parameters are available from 73 subjects following a single-dose (Day 1) and 51 subjects at steady-state (Day 8) following administration of daily doses ranging from 25 to 225 mg of PD-0332991. Peak serum concentrations varied from 10-104 ng/mL (Day 1) and 16-186 ng/mL (Day 8) with escalating PD-0332991 dose, and time to peak concentration was 4-7 hours (Day 1) and 3-7 hours (Day 8). Mean estimates of the pharmacokinetic parameters after oral administration of 200 mg of PD-0332991 at steady-state (Day 14 of Cycle 1) were 155 ng/mL peak serum concentration at 4 hours after dosing and effective plasma $t_{1/2}$~32 hours.

Absorption and Elimination of PD-0332991
A pilot food effect assessment was conducted in 12 subjects following administration of either125 mg or 200 mg doses of PD-0332991. For the fed state, subjects completed an 800-1000 calorie meal (at least 50% of which was from fat). The fasted condition was a 10-hour overnight fast. In general, no change in rate of absorption (median T_{max}=7, range 4-24 hours) was observed between the fed and fasted state. Higher exposures and peak concentrations were observed in the fed state compared to the fasted state, but these were not considered to be clinically significant as the mean % increase in exposure was less than 25%. Thus, PD-0332991 can be administered without regard to food.

Renal excretion of PD-0332991 was determined to be a minor route of elimination in humans (1.4% of unchanged drug in the urine; clearance rate = 6373 mL/hr).

8.3 Dispensing PD-0332991
PD-0332991 will be dispensed via the Jefferson Medical Oncology outpatient offices.

8.4 Rationale for Dose and Regimen
A single agent Phase I study in advanced cancer (N=74) determined the recommended Phase II dose for the Schedule 3/1 (3 weeks on and 1 week off, cycling) and Schedule 2/1 (2 weeks on and 1 week off, cycling) to be 125 mg/d and 200 mg/d, respectively. Two additional studies using the Schedule 3/1 are ongoing at Pfizer. For this study, Schedule 3/1 will be utilized unless adverse events require dose modifications as described below (**Table 8.1**).

Table 8.1 Dose Modification Levels for PD0332991

Dose Level	Daily oral dose	Number of tablets	
	per day x 21d, 1 w off	100 mg	25 mg
Standard Dose	125 mg	1	1
Dose Reduced – 1	100 mg	1	0
Dose Reduced – 2	75 mg	0	3

Table 8.1 outlines the recommended dose reductions for bone marrow toxicity due to PD-0332991.

Study eligible subjects potentially may have baseline myelosuppression due to their underlying liver disease or hypersplenism that is equivalent, according CTCAE v 4 scale to Grade 1 leucopenia, neutropenia and thrombocytopenia and Grade 2 anemia. For example, subjects are eligible to be enrolled on this study with:

Hemoglobin ≥ 8.0 g/dl (CTCAE v 4 Grade 2)
WBC ≥ 4,000/uL (CTCAE v 4 Grade 1)
Absolute neutrophil count ≥ 1,500/uL (CTCAE v 4 Grade 1)
Platelets ≥ 75,000/uL ((CTCAE v 4 Grade 1)

See **Table 8.2** for definitions and **4.1 Eligibility Inclusion Criteria.**

Table 8.2 Standard CTCAE v 4 scale

Adverse Event	0	1	2	3	4
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dl	8 - < 10 g/dl	6.5 - < 8 g/dl	< 6.5 g/dl or life threatening
WBC	WNL	< LLN - 3.0 x 10^9/L	≥ 2.0 - < 3.0 x 10^9/L	≥ 1.0 - < 2.0 x 10^9/L	< 1.0 x 10^9/L
ANC	WNL	< LLN – 1.5 x 10^9/L	≥ 1.0 - < 1.5 x 10^9/L	≥ 0.5 - < 1.0 x 10^9/L	< 0.5 x 10^9/L
Platelets	WNL	< LLN - 75 x 10^9/L	≥ 50.0 - < 75.0 x 10^9/L	≥ 25 - < 50.0 x 10^9/L	< 25 x 10^9/L

PD-0332991 is a highly specific selective small molecule inhibitor of CDK 4 and 6 and induces G0-G1 cell cycle arrest. Because it is a reversible inhibitor, PD-0332991 needs to be present continuously to inhibit CDK4 and CDK6, as withdrawal allows for reactivation of inhibited enzymes and stimulation of cell growth. In all Phase I studies of this agent as well as subsequent Phase II studies; the dose limiting toxicity (DLT) was dose-dependent neutropenia, consistent with cell cycle inhibition (11). In general, the myelosuppression observed is reversible, not cumulative, and uncomplicated. In this study, we have commonly observed up to a 50% reduction in WBC count, however there have been no instances of febrile neutropenia. Only one subject has had sepsis and this was in the setting of a normal WBC count following manipulation of the biliary system. He was treated successfully with broad-spectrum antibiotics.

Due to these factors, to preserve drug efficacy in subjects with advanced HCC on PD-0332991, dose reduction is not allowed "prophylactically" for a decreased WBC count or low ANC. A

subject may be dose reduced after having a significant untoward event caused by drug-related myelo-suppression, including: A. febrile neutropenia or B. sepsis associated with neutropenia. For all other events, the procedure for bone marrow (mechanism-based) toxicity is as follows: 1. Hold study drug and have subject return in one (1) week for CBC. If count is CTCAE grade 2 or less, treat on time without dose modification. If count remains at grade 3 or 4 at one-week check, continue to hold PD-0332991. Administer pegfilgrastim (Neulasta) 6 mg subcutaneously. Obtain repeat CBC weekly and resume PD-0332991 without dose change when WBC count is CTCAE grade 2 or less. If leucopenia or neutropenia recur at this dose level, then dose reduction by one DL is allowed. If the WBC or ANC do not increase to Grade 2, preventing resumption of drug for an entire cycle (28 days), then PD-0332991 may be restarted at the -1 dose level. If pegfilgrastim successfully prevents the lowering of the WBC count associated with study drug it should be administered with subsequent cycles at standard dose of 6 mg subcut on day 1 once per cycle to prevent drug interruption.

If a subject is not able to tolerate the 75 mg dose, then treatment should be discontinued. If a dose reduction has been performed, the subject may be re-escalated by the treating physician provided toxicities have resolved to Grade 2.

Table 8.3 outlines the procedures for dose modifications for bone marrow toxicity related to PD0332991.

Due to baseline coagulopathy and tendency to have bleeding events due to underlying liver disease, dose modifications should not be based on hemoglobin values. If a subject experiences bone marrow toxicity of both WBCs and platelets the recommended dose adjustment should be based on WBC count. It is recommended that standard of care be followed for administration of RBCs and platelets and for vitamin K in patients with ESLD.

Table 8.3 Dose modifications/delays for bone marrow toxicity related to PD0332991

Grade of Event CTCAE v 4.03	**Dose Interruption**	**Dose Modification for Remainder of Cycle.**	**Dose Modification for Subsequent Cycles**
0-2	Treat on time	No change	No change
3-4	• Delay until ≤ Grade 2 • Administer 6 mg pegfilgrastim (Neulasta) subcut if WBC/ANC does not recover to ≤ Grade 2 after 1 week dose interruption	• First episode: No change • Second episode within cycle after co-administration with pegfilgrastim: Reduce 1 dose level	• Continue at dose level from previous cycle • If serious drug-related myelosuppression occurs including: A. febrile neutropenia or B. sepsis with neutropenia, in previous cycle institute permanent dose reduction at -1 dose level • If bone marrow toxicity recurs at ≥ Grade 3 with leucocyte growth factor administration then

			institute permanent dose reduction at -1 dose level • If unable to resume PD-0332991 due to BM toxicity for an entire cycle, institute permanent dose reduction at -1 dose level • If bone marrow toxicity remains at ≤ Grade 2 for remainder of a previous cycle after administration of pegfilgrastim, then administer with subsequent cycles, 6 mg subcut on day 1 once per cycle

Note: if a subject does not have insurance coverage for pegfilgrastim it is permissible to substitute filgrastim (Neupogen) 5 mcg/kg, rounded up to nearest vial size, subcut daily x 3 days.

The Sponsor-Investigator, Dr. Susan J. Littman, must approve dose adjustments.

9.0 Safety Measurements

9.1 Definitions of Adverse Event

Adverse Event (AE) is any untoward medical occurrence in a patient or trial subject administered a drug or biologic (medicinal) product or using a medical device; the event does not necessarily have a causal relationship with that treatment or usage.

AEs include the following:

- All suspected adverse medication reactions
- All reactions from medication, overdose, abuse, withdrawal, sensitivity, or toxicity
- Apparently unrelated illnesses, including the worsening of a preexisting illness (see Preexisting Conditions below).
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as two separate adverse events. The outcome of the accident (e.g., hip fracture secondary to the fall) should be recorded under Comments.
- Abnormalities in physiological testing or physical examination (findings that require clinical intervention or further investigation beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (e.g., elevated liver enzymes in a patient with jaundice) should be described under Comments on the report of the clinical event rather than listed as a separate adverse event.

9.2 Preexisting Conditions
In this trial, a preexisting condition (i.e., a disorder present before the adverse event reporting period started and noted on the pretreatment medical history/physical examination form) should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period. Recurrence or progression of tumor will not be regarded as an adverse event.

9.3 Procedures
Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy noted under comments.

9.4 Adverse Event Reporting Period
The adverse event reporting period for this trial begins when the patient receives the first dose of investigational medication and ends 28 days after the patient receives the last dose of his/her study medication regimen for all non-serious adverse events. All serious adverse events will be followed through safety follow-up visits until resolution or return to baseline condition.

All adverse events that occur in trial subjects during the adverse event reporting period specified in the protocol must be reported, whether or not the event is considered treatment-related.

IN ADDITION, any known untoward event that occurs subsequent to the adverse event reporting period that the investigator assesses as possibly related to the investigational medication/product should also be reported as an adverse event.

9.5 Seriousness (Gravity) of Adverse Event
Each adverse event is to be classified by the investigator as SERIOUS (including life-threatening) or NONSERIOUS. This classification of the gravity of the event determines the reporting procedures to be followed.

An adverse event that meets one or more of the following criteria/outcomes is classified as **serious**:

- Death
- Life-threatening (i.e., immediate risk of death)
- Inpatient hospitalization, emergency room visit for a period > 24 hours or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other significant medical hazard. An important medical event that may not result in death, threaten life or require hospitalization may be considered a SAE when, based on appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such

medical events include allergic bronchospasm, requiring intensive treatment in an emergency room or at home, or convulsions that do not result in inpatient hospitalization.

A **nonserious** event is one that does not meet the criteria described for a serious or life-threatening event. Hospitalization for either elective surgery related to a pre-existing condition (without increase in severity or frequency) or routine clinical procedures that are not the result of an adverse event need not be considered as an AE and therefore are not a SAE. A routine clinical procedure is a procedure occurring during the study period that does not interfere with the study product administration or any of the ongoing protocol specific procedures. If anything untoward is reported during an elective procedure, that occurrence must be reported as an AE or SAE, according to the usual criteria.

9.6 Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial subject. In addition, as part of the physical exam and clinical assessment, each trial subject will be questioned about adverse events and symptoms at each clinic visit, following initiation of treatment. The question asked will be "Since your last clinic visit, have you had any health problems?"

9.7 Attribution of Causality of Adverse Events

The investigator will assign an attribution to each AE that occurs. Attribution will be determined according to the criteria specified in CTC 4.0, which is summarized below:

5-Definite – The AE is *clearly related* to the treatment.
4-Probable – The AE is *likely related* to the treatment.
3-Possible – The AE *may be related* to the treatment.
2-Unlikely – The AE is *doubtfully related* to the treatment.
1-Unrelated – The AE is *clearly not related* to the treatment.

9.8 Reporting of Adverse Event

Adverse events (AE) will be reported to the Thomas Jefferson University IRB and the Data Safety Monitoring Board (DMSB) via Clinical Research Management Office (CRMO) as specified in the TJU Data Safety and Monitoring Plan (Refer to Table).

All unexpected on-site adverse events and serious adverse events (SAE) will be sent to the TJU IRB and the DSMC within 48 hours of first awareness of the event. Fatal adverse events which are unexpected must be reported to the TJU IRB and the DSMB within 24 hours of first awareness of the event. Fatalities not related to the study drug must be reported within 5 days. Quarterly safety updates will be submitted to the CRMO, and the DSMC.

AEs will be reported according the table below:

Unexpected Event:

GRADE 1-3 Attribution of Possible, Probable or Definite (as defined in CTC 4.0)	**GRADE 4** Regardless of Attribution (as defined in CTC 4.0)	**GRADE 5** Death
Report to CRMO via website within 48 hours. Report to TJU IRB within 48 hours. CRMO reports to DSMC immediately following receipt.	Report to CRMO via website within 48 hours. Report to TJU IRB within 48 hours. CRMO reports to DSMC immediately following receipt.	Report to CRMO via website and TJU IRB within 24 hours.

Expected Event:

GRADE 1-3 Attribution of Possible, Probable or Definite (as defined in CTC 4.0)	**GRADE 4** Regardless of Attribution (as defined in CTC 4.0)	**GRADE 5** Death
Report to CRMO via website within 10 working days. Summary of all adverse events submitted quarterly to DSMC.	Report to CRMO via website and TJU IRB within 48 hours. CRMO reports to DSMC immediately following receipt. Summary of all adverse events submitted quarterly to DSMC.	Report to CRMO via website and TJU IRB within 5 days. Summary of all adverse events submitted quarterly to DSMC.

9.9 Safety Reporting Requirements for IND Holders

In accordance with 21 CFR 212.32, sponsor-investigators of studies conducted under an IND must comply with following safety reporting requirements:

Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report:

The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of *PD-0332991*. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be telephoned or faxed to the FDA within 7 calendar days and *Pfizer* within 24 hours of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

15 Calendar-Day Written Report:

The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in

a written IND Safety Report, of any serious, unexpected AE that is considered possibly related to the use of *PD-0332991*. An unexpected adverse event is one that is not already described in the Investigator Brochure.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, *Pfizer*, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500A Form but alternative formats are acceptable (e.g. summary letter).

FDA fax number for IND Safety Reports:

1 (800) FDA - 0178

All written IND Safety Reports submitted to the FDA by the Sponsor-Investigator must also be faxed to:

Pfizer
Fax: *1-866-997-8322*
Any issues encountered with fax transmission can be reported by calling Diane Borst (610) 519-0554

AND:

Thomas Jefferson University IRB

For questions related to safety reporting, contact Diane Borst Tel: (610) 519-0554

IND Annual Reports

In accordance with the regulation 21 CFR § 312.32, the Sponsor-Investigator shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.32 for a list of the elements required for the annual report. All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to *Pfizer*.

9.9 Recording Instructions

On the adverse event case report forms, the investigator will use the NCI Common Toxicity Criteria (CTC) version 4.0 (http:// ctep.info.nih.gov/ CTC3/default.htm) to describe the maximum intensity of the adverse event. The investigator will also be asked to assess the possible relationship between the adverse event and the investigational medication as well as any concomitant medications.

9.10 Expected Adverse Reactions for PD-0332991

The data described below represent Phase I study (N=74) of PD-0332991at escalating doses of 25-225 mg/d at either Schedule 3/1 (25-125 mg/d) or Schedule 2/1 (150-225 mg/d). The most common adverse events (regardless of causality) include fatigue (51%), neutropenia (42%),

nausea (35%), anemia (30%), diarrhea (30%), constipation (27%), vomiting (23%), dyspnea (19%), thrombocytopenia (15%), abdominal pain (14%), anorexia (14%), cough (14%), leucopenia (11%), flatulence (11%), peripheral edema (11%), back pain (11%), decreased appetite (10%), and rash (10%). Eleven dose-limiting toxicities, which consisted of neutropenia and/or thrombocytopenia, were observed. Grade 3 adverse events (regardless of causality) included dyspnea (4 subjects), hyperbilirubinemia (1 subject), jaundice (1 subject), acute renal failure (1 subject), hyperglycemia (1 subject), pleural effusion (1 subject), and peripheral sensory neuropathy (1 subject). Grade 4 adverse events (regardless of causality) included neutropenia (2 subjects), anemia (1 subject), thrombocytopenia (1 subject), increase in uric acid (1 subject), hyperglycemia (1 subject), and pulmonary embolism (1 subject).

Effects on bone marrow: Based on nonclinical studies performed to date, bone marrow was a target organ for toxicity. In these studies, hematologic and bone marrow abnormalities were reversible after dosing of PD-0332991 ceased. Neutropenia, thrombocytopenia, leucopenia, and anemia have been commonly observed in the clinical program. These events were not cumulative and were reversible, and generally did not result in treatment discontinuation. Granulocyte-colony stimulating factors should not be used prophylactically, but they may be used to treat treatment-emergent neutropenia as indicated by the current ASCO guidelines. Erythropoietin may be used for the supportive treatment of anemia. Complete blood counts with differential should be checked frequently during clinical studies, and dosing of PD-0332991 should be interrupted based on hematologic parameters specified above (Section 8.1).

Effects on the respiratory tract: Based on nonclinical studies performed to date, the respiratory tract was a target organ for toxicity. Dyspnea and cough were commonly observed in the clinical program, but were Grade 3 in severity and were attributed to the disease. There was one Grade 4 adverse event of pulmonary embolism, but this event was not considered to be treatment-related.

Effects on the GI tract: GI adverse events including abdominal pain, constipation, diarrhea, flatulence, nausea and vomiting were commonly observed in the clinical program. Only those of Grade 1 severity were considered to be attributed to treatment.

9.11 Exposure in Utero

Fertility and teratology studies with PD-0332991 have not been conducted. Safety for women of childbearing capacity cannot be implied from the existing data. Thus, women should avoid becoming pregnant while on therapy, and women of childbearing potential must be apprised of the potential hazard to the fetus, which includes severe malformation (teratogenicity), failure to thrive and fetal death (embryotoxicity).

9.12 Follow-Up of Adverse Event

All adverse events should be followed until they are resolved or the subject's participation in the trial ends. In addition, all serious adverse events and those non-serious events assessed by the investigator as possibly related to the investigational medication/product should continue to be followed even after the subject's participation in the trial is over. Such events should be followed until they resolve or until the investigator assesses them as "chronic" or "stable." Resolution of such events is to be documented on the CRF.

9.13 Non-Hematological and Hematological Adverse Events

Patients will be assessed clinically for toxicity prior to each dose using the National Cancer Institute (NCI) CTCAE Version 4. If patients experience Grade 3 or greater toxicity deemed related to study drug, PD-0332991 will be temporarily discontinued. After the resolution of toxicity to Grade 1 or less, PD-0332991 will be restarted at the initial dose. The study treatment will be continued until disease progression or unacceptable side effects (Grade 3 or greater). Patients with unacceptable side effects (Grade 3 or greater) for a second time on PD-0332991 will be removed from the study. The only exception to this are: Grade 3 anorexia, nausea vomiting, stomatitis/mucositis or diarrhea that will lead to investigational product withdrawal only if not manageable despite maximum supportive care. Throughout the study investigators may prescribe any concomitant medications or treatments necessary to provide adequate supportive care other than experimental or approved anti-tumor therapies. All concomitant medications must be recorded.

10. Concomitant Medications and Non-Drug Therapies

All subjects will be asked to provide a complete list of all prescription and over the counter medications. The investigator must be informed of any new medication(s) as soon as possible for the time of screening to the completion of follow-up.

10.1 Permitted medications

All concomitant medications taken during the study will be recorded in the CRF with indication, dose, and dates of administration. Subjects should receive full supportive care during the study including transfusion with blood and blood products, antibiotics, recombinant human granulocyte colony stimulating factor or erythropoiesis-stimulating agents, bisphosphonates when appropriate. Anti-emetics may be administered prophylactically or in the event of nausea. Anti-diarrheals may be administered as needed for diarrhea.

10.2 Permitted medications- use with caution

Analgesics such as acetominophen and nonsteroidal anti-inflammatory medications should be administered with caution or not at all in subjects with impaired liver function. The use of heparin or low molecular weight heparin should be cautioned against in patients with HCC and cirrhosis, however may be indicated in specific situations. Due to dual potential for severe bleeding warfarin should not be administered.

10.3 Drug Interactions

Formal drug-drug interaction studies have not been conducted with PD-0332991. Pre-clinical data indicate that PD-0332991 is metabolized *in vivo* primarily via the cytochrome P-450 enzyme, CYP3A4. Therefore concomitant use of certain medications (substrates of CYP3A4 should be undertaken with **caution** due to potential for alterations in the pharmacological effects of these medications or an increased risk for serious or life threatening adverse events. Furthermore, there may be a risk of drug-drug interactions. These medications include but are not limited to: ergot derivatives - dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential for developing ergot toxicity including vasospasm leading to peripheral neuropathy and cerebral ischemia); neuroleptics - pimozide (potential increased risk for QT prolongation, ventricular arrhythmia and sudden death); antiarrhythmics - bepridil, flecainide,lidocaine, mexiletine, amiodarone, quinidine, propafenadone (potential increased risk for QT prolongation

and Torsades de Pointes); immune modulators - cyclosporine, tacrolimus, sirolimus (potential increased risk for nwephrotoicity and neurotoxicity; and miscellaneous drugs - quetiapine, rispiridone, clozapine and atomoxetine. Concomitant administration of agents known to induce or inhibit CYP3A isoenzymes may increase plasma drug concentrations of PD-0332991. Selection of alternative concomitant medications with no potential to inhibit CYP3A4 is recommended. Medications which may induce CYP3A4 and may decrease plasma concentrations of PD-0332991 are glucocorticoids - high dose cortisone or hydrocortisone, prednisone, methylprednisolone and dexamethasone; anticonvulsants – phenytoin, carbamezepine, phenobarbital, oxcarbazepine; HIV antivirals – efavirenz, nevirapine,; antibiotics- rifampin, rifabutin, rifapentene and miscellaneous medications - St. John's Wort, modafinil, pioglitazone, troglitazone, omeprazole, verapamil. Primidone. PROHIBITED during the study are the strong CYP3A4 inhibitors which includes but are not limited to antibiotics- erythromycin, clarithromycin, telithromycin, troleandomycin; HIV protease inhibitors- ritonavir indinavir, nelfinavir, saquinavir, amprenavir, lopinovir, delaviridine; antifungals- itraconazole, ketoconazole, voriconazole, fluconazole; antidepressants- nefazodone and grapefruit juice.

11.0 Statistical Considerations

This is Phase II open-label non-randomized single institution study with an anticipated 12-24 month accrual. The size of the study is based on biostatistical modeling of HCC and is powered to demonstrate an improved TTP. The sample size calculation is based on historical data, which demonstrates that median TTP for untreated patients with HCC is 12 weeks, and median TTP for patients treated with Sorafenib is 24 weeks (Llovet et al. 2008, Cheng et al. 2009). The proposed study will test whether PD-0332991 treatment results in at least a 24 week TTP versus the historical median of 12 weeks. For a trial with an alpha of 0.05 and power of 90%, a sample size of 19 evaluable patients is needed.

11.1 Evaluation of Efficacy

Efficacy endpoints will be estimated for all subjects. The tumor response endpoints will be performed on all subjects. The population will be evaluated on an intent-to-treat analysis defined as subjects who received at least two cycles of study medication and have completed the week 8 response assessments. TTP, ORR will be assessed by standard imaging (MRI and/or CT scans, as appropriate) utilizing modified RECIST (Version 1.1) criteria. Assessments will be performed at screening and after every 2 cycles of treatment (every 8 weeks) thereafter. TTP and overall survival will be evaluated using the Kaplan-Meier method. Median TTP and median survival will be estimated with corresponding 90% confidence intervals. Subjects that are not evaluable will be replaced with subjects with evaluable data.

11.2 Safety Analysis

The clinical safety data will be summarized using descriptive statistics.

12.0 Data Disclosure and Patient Confidentiality

Patient medical information obtained as a result of this study is considered confidential. Disclosure to third parties other than to the patient's primary physician and to those noted below is prohibited. All reports and communications relating to subjects in this study will identify each patient only by his/her number (and initials if allowed by local regulations). Data generated as a

result of this study must be available for inspection upon request by the FDA (or other Health Authority or government agency), Data Safety Monitoring Board, and the IRB.

Confidentiality will be maintained at all times unless government regulation or applicable law requires disclosure. If local or national regulations are modified to require additional consent(s) or documentation for release of source documents or other medical information, required for the study, it is the responsibility of the investigator to obtain such consent and documentation with relevant approvals by the local IRB.

12.1 Data Collection
The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and data pertinent to this investigation for each subject enrolled.

12.2 Records Retention
The Investigator must retain all source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures. If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB). Notice of such transfer will be given in writing to IRB.

12.3 Protocol Deviations/Exceptions
Deviations/exceptions from listed eligibility criteria will not be allowed under any circumstances. An accidental or unintentional deviation from the approved protocol, that in the opinion of the investigator, places one or more subjects at increased risk, or affects the rights or welfare of subjects, must be reported to the IRB and DSMC immediately.

13.0 Ethical Considerations

13.1 Protection of Human Subjects from Research Risks
The study will be conducted in accordance with the Declaration of Helsinki and with rules and regulations in accord with the U.S. Office of Protection from Research Risks (OPRR).

13.2 Institutional Review Board
The study will be reviewed and approved by a duly constituted IRB before patients are screened for entry. The investigator will ensure that all aspects of the IRB review are conducted in accordance with current institutional, local, and national regulations. Amendments to the protocol will be subject to the same requirements as the original protocol. The Investigator will submit all periodic reports and updates that the IRB may require, including any final close out reports. The Investigator will inform the IRB of any reportable adverse events as required by local regulations.

13.3 Informed Consent

Each subject will be provided with oral and written information that describes the nature and duration of the study in a language he/she can understand. The required schedule for treatment and interval safety evaluations (irrespective of holidays), plus the planned follow-up schedule, should be carefully reviewed and possibly reinforced with a calendar. The patient must consent in writing to participate before undergoing therapy on the protocol. The original signed consent form will be retained. Each subject will be given a copy of his/her consent form.

14.0 Data Safety Monitoring Board

The study Principal Investigator will monitor toxicities monthly, submitting quarterly safety and monitoring reports to the Clinical Research Management Office and The Data Safety Monitoring Committee (DSMC). All unexpected on-site adverse events and serious adverse events (SAEs) are required to be submitted to the TJU IRB and the DSMC within 48 hours. Fatal adverse events which are unexpected must be reported within 24 hours to the TJU IRB and the DSMC. Fatalities not related to the study drug/device must be reported within 5 days.

A medical monitor (a physician or other member of the DSMC who has expertise in the therapeutic area of the protocol and is not directly involved in this trial) will be identified for the protocol. The medical monitor will review all adverse events (in addition to unexpected adverse events), safety data and activity data observed in the ongoing clinical trial.
The PI provides a report to the DSMC of all AE/SAEs, safety and toxicity data, and any corrective action that occurred on a quarterly basis. The medical monitor also provides a summary of their review. The summary of all discussions of adverse events are submitted to the DSMC, and these reports are reviewed during the DSMC meetings that take place quarterly. Patients are only identified by initials, and no other PHI is included in the reports.
The medical monitor may recommend reporting adverse events and relevant safety data not previously reported, and may recommend suspension or termination of the trial based on their review of AE/SAE data observed throughout the life of a clinical trial. In such circumstances, and "ad hoc" DSMC meeting will be called to discuss corrective action with the PI.
The summary of all discussions of adverse events are included in the Kimmel Cancer Center (KCC) investigator's reports to the TJU IRBs as part of its annual progress report. The DSMC and the TJU IRB may, based on the monitor's recommendation suspend or terminate the trial. The quarterly safety and monitoring reports include a statement as to whether this data has invoked any stopping criteria in the clinical protocol.

15.0 Audits

In addition to review by the DSMC, the study will be audited by an independent auditor once 10% of target accrual has been achieved. The study will be re-audited once 50% of target accrual has been achieved. However, a study can be audited at any time based on recommendations by the IRB, DSMC, CCRRC and/or the Director of Clinical Investigations, KCC. Special audits may be recommended by the IRB, DSMC or CCRRC based on prior findings, allegations of scientific misconduct and where significant irregularities are found through quality control procedures. Any irregularities identified as part of this process would result in a full audit of that study.

In addition to the audits at 10 and 50%, the CRMO randomly audits at least 10 percent of all patients entered into therapeutic KCC trials and other trials as necessary, on at least a bi-annual

basis, to verify that there is a signed and dated patient consent form, the patient has met the eligibility criteria, and that SAEs are documented and reported to the TJU IRB.

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