



A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib Hydrochloride to Sorafenib in Subjects With Refractory Advanced Renal Cell Carcinoma

PROTOCOL: AV-951-15-303

IND Number: 75,547

EUDRACT Number: 2015-003607-30

AVEO PHARMACEUTICALS, INC.

1 Broadway

Cambridge, MA USA 02142

Tel: (617) 531-8292

Fax: (617) 902-2577

www.aveooncology.com

AVEO Pharma Limited

59-60 Thames Street

Windsor, UK, SL4 1TX

Version	Country(ies)	Date
1.0	Global	26-Aug-2015 (not distributed)
2.0	Global	01-Oct-2015
2.1	France	19-Jan-2016
2.2	UK	20-Jan-2016
3.0	Global	06-Jul-2016
3.1	France	20-Jul-2016
3.2	UK	20-Jul-2016
4.0	Global	01-Oct-2018

CONFIDENTIAL AND PROPRIETARY

This document is the confidential property of AVEO Pharmaceuticals, Inc. (the sponsor), and is intended solely for the guidance of this clinical investigation. The information contained herein may not be disclosed to parties not associated with this clinical investigation without the written authorization of the sponsor. No part of this document may be reproduced, referenced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the written authorization of the sponsor. The foregoing shall not apply to disclosure required by applicable laws or governmental regulations;

however, you will give notice to the sponsor of any such disclosure as soon as practicable.

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

Chief Medical Officer:

Name: Michael N Needle, MD
Aveo Oncology
1 Broadway, 14th Floor
Cambridge, MA 02142
Mobile: (303) 524-0376
mneedle@aveooncology.com

PAREXEL Medical Monitor:

Name: Gamal Elsawah, MD
PAREXEL International
2 Federal Street
Billerica MA 01821
Phone: (610) 721-2255
Gamal.Elsawah@PAREXEL.com

For urgent medical study questions, please contact the AVEO Chief Medical Officer or PAREXEL Medical Monitor. After business hours, weekends, and on holidays, please send an email message and a response will be placed.

PROTOCOL SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.



Michael Needle, MD
Chief Medical Officer
AVEO Pharmaceuticals, Inc.



Date of Signature
(dd-mmm-yyyy)

Investigator Signature

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed of the study requirements and procedures. I understand that the study may be terminated or enrollment suspended at any time by the sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice (GCP).

Investigator's Signature

Date of Signature
(dd-mmm-yyyy)

Investigator's Name (print)

1 SYNOPSIS

Name of sponsor/company: AVEO Pharmaceuticals, Inc.	
Name of investigational product: Tivozanib Hydrochloride (AV-951) capsules	
Title of study: A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib Hydrochloride to Sorafenib in Subjects With Refractory Advanced Renal Cell Carcinoma	
Study Number: AV-951-15-303	
Estimated number of study center(s): Approximately 160-190 centers	
Study duration (years): Estimated date first subject enrolled: June 2016 Estimated date last subject enrolled: August 2017 Established data cut-off date: 04 October 2018	Phase of development: 3
Objectives: Primary: <ul style="list-style-type: none">To compare the progression-free survival (PFS) of subjects with refractory advanced renal cell carcinoma (RCC) randomized to treatment with tivozanib hydrochloride (tivozanib) or sorafenib as assessed by blinded independent radiological review (IRR) of computerized tomography (CT) or magnetic resonance imaging (MRI). Secondary: <ul style="list-style-type: none">To compare the overall survival (OS) of subjects randomized to treatment with tivozanib or sorafenibTo compare objective response rate (ORR) and duration of response (DoR) of subjects randomized to treatment with tivozanib or sorafenibTo compare the safety and tolerability of tivozanib and sorafenib. Tertiary: <ul style="list-style-type: none">To explore any relationship between:<ul style="list-style-type: none">tivozanib and sorafenib drug levels and activitytivozanib and sorafenib drug levels and adverse events (AEs)	
Methodology: Open-label, randomized, controlled, multi-national, multi-center, parallel-arm study. Subjects will be randomized in a 1:1 ratio (tivozanib: sorafenib) stratified by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk category (favorable; intermediate; poor) and prior therapy (two prior vascular endothelial growth factor [VEGF] receptor tyrosine kinase inhibitors [VEGFR TKIs]; a prior checkpoint	

Name of sponsor/company: AVEO Pharmaceuticals, Inc.
Name of investigational product: Tivozanib Hydrochloride (AV-951) capsules
inhibitor [programmed cell death -1 protein (PD-1) or PD-1 ligand (PD1-L) inhibitor] plus a prior VEGFR TKI; a prior VEGFR TKI plus any other systemic agent). Once the strata have been identified, treatment will be randomly assigned to a subject within the strata using a complete permuted block design, in an unblinded fashion (open-label). In the event a subject had both 2 TKIs and a checkpoint inhibitor, the subject will be stratified according to the most recent line of therapy. Subjects must begin treatment with study drug within 14 days after randomization.
Number of subjects (planned): Approximately 322 subjects will be enrolled (161 per treatment arm)
Diagnosis and main criteria for inclusion: Subjects may be male or female, and must meet the following criteria to be included: <ol style="list-style-type: none">1. ≥ 18-years of age.2. Subjects with metastatic RCC who have failed 2 or 3 prior systemic regimens, one of which includes a VEGFR TKI other than sorafenib or tivozanib.<ol style="list-style-type: none">a. Postoperative or adjuvant systemic therapy will not be counted as a prior therapy unless recurrence is detected within 6 months of completion of treatment, in which case it will be counted as a prior therapy for metastatic disease.b. Subjects must be off all systemic anti-cancer therapy or radiotherapy for at least 2 weeks prior to Cycle 1 Day 1.3. Subjects must have recovered from the AEs of prior therapy or returned to baseline. Controlled AEs such as hypothyroidism or hypertension are permitted.4. Histologically or cytologically confirmed RCC with a clear cell component (subjects with pure papillary cell tumor or other non-clear cell histologies, including collecting duct, medullary, chromophobe, and unclassified RCC are excluded).5. Measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) criteria Version 1.1.6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.7. Life expectancy ≥ 3 months.8. If female and of childbearing potential, documentation of negative pregnancy test prior to enrollment.9. Ability to give written informed consent and comply with protocol requirements.10. Sexually active pre-menopausal female subjects (and female partners of male subjects) must use adequate contraceptive measures, while on study and for at least 90 days after the last dose of study drug. Sexually active male subjects must use adequate contraceptive measures, while on study and for at least 90 days after the last dose of study drug. All fertile male and female subjects and their partners must agree to use a

Name of sponsor/company: AVEO Pharmaceuticals, Inc.

Name of investigational product: Tivozanib Hydrochloride (AV-951) capsules

highly effective method of contraception. Effective birth control includes (a) intrauterine device (IUD) plus one barrier method; or (b) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm). (Note: Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are not considered effective for female subjects in this study)

Subjects to be excluded

1. Prior treatment with sorafenib or tivozanib.
2. More than 3 prior regimens for metastatic RCC.
3. Known central nervous system (CNS) metastases other than stable, treated brain metastases. Subjects with previously treated brain metastasis will be allowed if the brain metastasis has been stable by neuroimaging without steroid treatment for at least 3 months following prior treatment (radiotherapy or surgery).
4. Any of the following hematologic abnormalities:
 - Hemoglobin < 9.0 g/dL (packed red blood cell transfusion is permitted)
 - Absolute neutrophil count (ANC) < 1500 per mm³
 - Platelet count < 100,000 per mm³
5. Any of the following serum chemistry abnormalities:
 - Total bilirubin > 1.5 × upper limit of normal (ULN) (or > 2.5 × ULN for subjects with Gilbert's syndrome)
 - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × ULN (or > 5 × ULN for subjects with liver metastasis)
 - Alkaline phosphatase > 2.5 × ULN (or > 5 × ULN for subjects with liver or bone metastasis)
 - Creatinine > 1.5 × ULN unless creatinine clearance > 40 mL/min. Creatinine clearance can be calculated by standard equations (e.g. Cockcroft-Gault) or measured.
6. Significant cardiovascular disease, including:
 - Active clinically symptomatic left ventricular failure
 - Uncontrolled hypertension: Systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg on 2 or more antihypertensive medications, documented on 2 consecutive measurements taken at least 2 hours apart
 - Myocardial infarction, severe angina, or unstable angina within 6 months prior to administration of first dose of study drug
 - History of serious ventricular arrhythmia (ie, ventricular tachycardia or ventricular fibrillation)

Name of sponsor/company: AVEO Pharmaceuticals, Inc.

Name of investigational product: Tivozanib Hydrochloride (AV-951) capsules

- Cardiac arrhythmias requiring anti-arrhythmic medications (except for atrial fibrillation that is well controlled with anti-arrhythmic medication)
7. Non-healing wound, bone fracture, or skin ulcer.
 8. Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal condition with increased risk of perforation; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to administration of first dose of study drug.
 9. Serious/active infection or infection requiring parenteral antibiotics.
 10. Inadequate recovery from any prior surgical procedure or major surgical procedure within 4 weeks prior to administration of first dose of study drug.
 11. Significant thromboembolic or vascular disorders within 6 months prior to administration of first dose of study drug, including but not limited to:
 - Symptomatic Pulmonary embolism
 - Cerebrovascular accident (CVA) or transient ischemic attack (TIA)
 - Peripheral arterial ischemia > Grade 2
 - Coronary or peripheral artery bypass graft
 12. Significant bleeding disorders within 6 months prior to administration of first dose of study drug, including but not limited to:
 - Hematemesis, hemochezia, melena or other gastrointestinal bleeding \geq Grade 2
 - Hemoptysis or other pulmonary bleeding \geq Grade 2
 - Hematuria or other genitourinary bleeding \geq Grade 2
 13. Currently active second primary malignancy, including hematologic malignancies (leukemia, lymphoma, multiple myeloma, etc.), other than non-melanoma skin cancers, non-muscle-invasive urothelial cancer, non-metastatic prostate cancer, in situ cervical cancer and ductal or lobular carcinoma in situ of the breast. Subjects are not considered to have a currently active malignancy if they have completed anti-cancer therapy and have been disease free for >2 years.
 14. Pregnant or lactating females.
 15. History of genetic or acquired immune suppression disease such as human immunodeficiency virus (HIV), subjects on immune suppressive therapy for organ transplant.
 16. Life-threatening illness or organ system dysfunction compromising safety evaluation.
 17. Requirement for hemodialysis or peritoneal dialysis.
 18. Inability to swallow pills, malabsorption syndrome or gastrointestinal disease that severely affects the

Name of sponsor/company: AVEO Pharmaceuticals, Inc.

Name of investigational product: Tivozanib Hydrochloride (AV-951) capsules

absorption of tivozanib or sorafenib, major resection of the stomach or small bowel, or gastric bypass procedure.

19. Psychiatric disorder or altered mental status precluding informed consent or necessary testing.
20. Participation in another interventional protocol.

Drugs and treatments to be excluded

The following medications/treatments are prohibited during the study:

1. Chemotherapy, biological therapy (including cytokines, signal transduction inhibitors, monoclonal antibodies), immunotherapy or any other therapy for RCC.
2. Systemic hormonal therapy, with the exception of:
 - Hormonal therapy for appetite stimulation or contraception
 - Nasal, ophthalmic, inhaled and topical steroid preparations
 - Androgen suppression therapy for non-metastatic prostate carcinoma
 - Hormone replacement therapy for conditions such as adrenal insufficiency, hypothyroidism, etc.
 - Low-dose maintenance steroid therapy (equivalent of prednisone ≤ 10 mg/day) for other conditions
3. Treatment with radiotherapy.
4. Herbal preparations/supplements (including daily multivitamin/mineral supplement containing herbal components) or topical ointments containing herbal components.
5. Treatment with strong cytochrome P450 (CYP3A4) inducers or inhibitors (see Appendix C).
6. Treatment with full dose oral anticoagulants such as warfarin, acenocoumarol, fenprocoumon, or similar agents unless they have been on a stable dose for more than 2 weeks prior to enrollment. Full dose anticoagulation with low molecular weight heparin or unfractionated heparin administered subcutaneously is allowed.

Investigational product, dosage and mode of administration:

Tivozanib: 1.5 mg orally once daily.

Subjects will receive 1.5 mg tivozanib once daily beginning on Day 1 for 21 days followed by 7 days off treatment.

One cycle will be defined as 4 weeks in duration, consisting of 3 weeks on treatment and a week off treatment.

Cycles will be repeated every 4 weeks.

Name of sponsor/company: AVEO Pharmaceuticals, Inc.
Name of investigational product: Tivozanib Hydrochloride (AV-951) capsules
Reference therapy, dosage and mode of administration: <p>Sorafenib: 400 mg orally twice daily</p> <p>Subjects will receive 400 mg sorafenib twice daily continuously, beginning on Day 1. One cycle will be defined as 4 weeks of treatment. Cycles will be repeated every 4 weeks.</p>
Dose reduction: <p>Tivozanib: Dose reduction will be allowed for subjects with \geq Grade 3 drug-related adverse events. The exception is hypertension, which must be treated with anti-hypertensive drugs prior to dose reduction.</p> <p>The dose of tivozanib may be reduced to 1.0 mg/day. If a subject is unable to tolerate a dose of 1.0 mg/day due to toxicities thought to be related to tivozanib, treatment should be interrupted for up to 4 weeks. Once the dose of tivozanib is reduced, it may not be re-escalated throughout the study.</p> <p>Sorafenib: Dose reduction will be allowed for subjects with \geq Grade 3 drug-related adverse events. The dose of sorafenib will be reduced to 400 mg once daily. If toxicities do not resolve, sorafenib may be further reduced to 400 mg once every other day. If a subject is unable to tolerate a dose of 400 mg once every other day due to toxicities thought to be related to sorafenib, treatment should be interrupted. If toxicities resolve to \leq Grade 1, the dose of sorafenib may be re-escalated to the previous dose level at the discretion of the investigator.</p> <p>Dose interruption (tivozanib and/or sorafenib):</p> <p>Subjects with Grade 4 drug-related toxicity, or Grade 3 drug-related toxicity that is persistent despite dose reduction and appropriate medical care, should have their treatment interrupted to allow for adequate resolution of the toxicity. Tivozanib/sorafenib may be interrupted for up to 4 weeks. If a subject is able to resume treatment after interruption of \leq 4 weeks, missed doses will not be made up (ie, cycle duration will remain unchanged). If any drug-related toxicity results in interruption of $>$ 4 weeks, the subject should be discontinued from the study unless there is clear benefit from treatment, in which case the investigator must contact the medical monitor to review the subject's condition in order to resume treatment. Subjects removed from treatment for reasons other than radiological evidence of progressive disease should still be followed with regular tumor assessments until disease progression is confirmed by an independent radiology review or start of new treatment, and for survival thereafter.</p>
Criteria for evaluation: <p>Safety:</p> <p>NCI Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) will be used for grading toxicities. Subjects will be monitored throughout the treatment and 30-day follow-up period for occurrence of adverse events (AEs; acute, delayed, and/or cumulative), as well as for changes in clinical status, vital sign measurements, and laboratory data.</p> <p>Safety parameters to be measured / assessed include eligibility assessment, medical history, vital sign measurements,</p>

Name of sponsor/company: AVEO Pharmaceuticals, Inc.
Name of investigational product: Tivozanib Hydrochloride (AV-951) capsules
physical examination, hematology, serum chemistries, thyroid function tests, coagulation parameters, urinalysis, pregnancy test, ECOG performance status, and electrocardiogram (ECG). Disease status: Data on the duration of disease stabilization or any objective response, as well as the time to disease progression will be collected for all subjects. Disease parameters to be assessed: <ul style="list-style-type: none">• Disease classification (histological/cytological type and stage of carcinoma)• Diagnostic imaging with measurement of target lesions performed by an independent review committee• Response assessment using RECIST (Version 1.1) criteria• Radiology studies (CT scan or MRI) will be performed every 8 weeks following Cycle 1, Day 1 for assessing disease status
Duration of treatment: Subjects with documented stable disease or an objective response may continue to receive therapy at the same dose and schedule until progression as long as tolerability is acceptable. Discontinuation: Subjects experiencing unacceptable toxicities will be discontinued from further study treatment. Subjects with radiological evidence of progressive disease per investigator/local radiology assessment should continue treatment until progressive disease is verified by an independent radiologist. Images should be submitted for independent review as soon as possible (see Imaging Manual for specific instructions). Verification is not required in the following circumstance: <ul style="list-style-type: none">• Significant clinical deterioration that is indicative of progressive disease Subjects who have documented disease progression will be discontinued from the study treatment. Follow-up: Each subject will be followed until death from any cause (unless the subject is lost to follow-up, withdraws consent for the entire study, or the Sponsor terminates the study early). Once discontinued from study drug treatment, all subjects are to be followed for evidence of new onset of adverse events, and to ensure resolution or stabilization of existing ongoing adverse events, for 30 days from the last dose of study drug. After the 30-Day Follow-up Visit, subjects will be contacted by the site once every 3 months to collect long-term survival data.
Statistical methods: A sample size of 322 subjects (161 subjects per treatment arm) with total number of 255 events will provide 90% power to detect a statistically significant difference between treatment arms with respect to PFS as assessed by an

Name of sponsor/company: AVEO Pharmaceuticals, Inc.

Name of investigational product: Tivozanib Hydrochloride (AV-951) capsules

IRR. The sample size was determined based on the following assumptions:

- The distribution of the PFS for the 2 treatment arms will be compared by using a Log-rank test with a two-sided 5% significance level (α)
- The median PFS for subjects receiving sorafenib and tivozanib is 4 months and 6 months, respectively, (an increase of 2 months or 50%)
- Equal numbers of subjects will be assigned to each treatment arm
- Enrollment will take 15 months
- The drop out percentage per treatment arm will be 3%

Data will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequency and percentages for discrete variables.

The primary analysis will compare the distribution of the PFS between the two treatment arms by using the stratified Log-rank test, in which the stratification factors are IMDC risk category (favorable; intermediate; poor) and prior therapy (two prior VEGF TKIs; a prior checkpoint inhibitor [PD-1 or PD1-L inhibitor] plus a prior VEGFR TKI; a prior VEGFR TKI plus any other systemic agent). PFS will be based on the CT or MRI scan assessed by the IRR. PFS graphs will be presented by treatment arm.

The first secondary analysis will compare OS between the 2 treatment arms by using the stratified Log-rank test, the stratification factors included in the primary analysis, and two-sided 0.8% significance level (utilizing a Lan-DeMets alpha spending function with an O'Brien-Fleming boundary). An interim OS analysis will be done at the time of the final PFS analysis. It is expected that 149 OS events would have occurred at the time of final PFS analysis.

An interim analysis will be performed after 128 PFS events have been observed. The interim analysis will look into the study's futility using PFS as the efficacy evaluation endpoint. This will utilize a Lan-DeMets error spending-type function with an O'Brien-Fleming stopping boundary with an estimated two-sided beta (Type II error) of 1.2 % spent during this interim look. The interim analysis will be performed by an independent statistician. The independent statistician will evaluate and interpret the results of the interim analysis and will provide corresponding recommendation whether to stop the study for futility or for the study to continue until end of study condition has been met.

Two populations will be defined for the efficacy analysis: Intent-to-treat (ITT; defined as all subjects who were randomized into the study) and per protocol (PP; defined as all subjects in the ITT population who did not have major protocol deviations, have received at least two cycles (8 weeks) of protocol treatment, and met all eligibility criteria). Primary efficacy analysis will be based on ITT where subjects will be analyzed as randomized.

The safety population (SAF) will include all subjects who received at least one dose of either study drug. Subjects will be analyzed as treated.

Name of sponsor/company: AVEO Pharmaceuticals, Inc.
Name of investigational product: Tivozanib Hydrochloride (AV-951) capsules
Safety observations and measurements, including study drug exposure, adverse events, laboratory data, concomitant medications, physical examination, vital signs, ECG, and health outcome measurements, will be summarized and presented in tables and listings using the SAF population.

Table 1: Study Design and Schedule of Assessments

STUDY PROCEDURES	SCREEN	CYCLE 1		CYCLE 2	SUBSEQUENT CYCLES	END OF TREATMENT (up to 7 days after last dose) ^f	30-DAY FOLLOW-UP (±7 days)	UNSCHED-ULED ^s	LONG TERM RESPONSE & SURVIVAL FOLLOW-UP
		1	15 ± 2 days ^p	1 ± 2 days ^p	1 ± 2 days ^p				
Cycle Day	-21 to -1								
CONSENT AND MEDICAL HISTORY									
Informed Consent ^a	X								
Medical & Disease History	X								
IMDC Risk Category	X								
SAFETY ASSESSMENTS									
Concomitant Medications	X	To be collected from the date informed consent form signed to 30 days after last dose of study drug							
Adverse Event Assessments	X	To be collected from the date informed consent form signed to 30 days after last dose of study drug							
Study Drug Administration		Daily x 3 or 4 weeks ^q		Daily x 3 or 4 weeks ^q	Daily x 3 or 4 weeks ^q				
ECOG Performance Status	X	X ⁱ	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X
Physical Examination ^b	X	X ⁱ	X	X	X	X	X	X	X
Hematology ^c	X	X ⁱ	X	X	X	X	X	X	X
Serum Chemistries ^d	X	X ⁱ	X	X	X	X	X	X	X
Coagulation Parameters ^e	X	X ⁱ	X	X	X	X	X	X	X
Thyroid Function Tests ^f	X			X	X ^g	X	X	X	X
Urinalysis with Microscopic ^h	X	X ⁱ	X	X	X	X	X	X	X
Pregnancy Test ^j	X					X		X	

Table 1: Study Design and Schedule of Assessments

STUDY PROCEDURES	SCREEN	CYCLE 1		CYCLE 2	SUBSEQUENT CYCLES	END OF TREATMENT (up to 7 days after last dose) ^f	30-DAY FOLLOW-UP (±7 days)	UNSCHED-ULED ^s	LONG TERM RESPONSE & SURVIVAL FOLLOW-UP
		1	15 ± 2 days ^p	1 ± 2 days ^p	1 ± 2 days ^p				
12-Lead ECG	X					X	X	X	
Disease / Response Assessment (CT Scan or MRI Scan)	X ^k	Every 8 weeks (±3 days) from Cycle 1, Day 1				X ^l		X	X ^m
Study Drug Diary		X	X	X	X	X		X	
Pharmacokinetics ⁿ		X	X						
Contact of subject by site ^o									X

Table 1: Study Design and Schedule of Assessments

STUDY PROCEDURES	SCREEN	CYCLE 1		CYCLE 2	SUBSEQUENT CYCLES	END OF TREATMENT (up to 7 days after last dose) ^f	30-DAY FOLLOW-UP (±7 days)	UNSCHED-ULED ^s	LONG TERM RESPONSE & SURVIVAL FOLLOW-UP
Cycle Day	-21 to -1	1	15 ± 2 days ^p	1 ± 2 days ^p	1 ± 2 days ^p				

- a. Informed consent may be obtained outside the 21-day window; however, consent must be obtained prior to any protocol-specific procedures being performed.
- b. Physical exams (PE): Complete PE at screening, including height (at Screening visit only) and weight; directed PE thereafter, including weight.
- c. Hematology to include complete blood count (CBC) with differential and platelet count.
- d. Serum chemistries to include sodium, potassium, chloride, bicarbonate (optional), blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase, calcium, magnesium, phosphorous, albumin, amylase, lipase, and total protein.
- e. Coagulation parameters to include prothrombin time (PT) and/or international normalized ratio (INR), and partial thromboplastin time (PTT).
- f. Total T3 (triiodothyronine) (optional), free T4 (thyroxine), and thyroid stimulating hormone (TSH) levels.
- g. To be performed during every even-numbered cycle beyond Cycle 2 (ie, Cycle 4, 6, 8 etc.).
- h. Urinalysis to include protein, glucose, ketones, urobilinogen, occult blood, and microscopic sediment evaluation. A 24-hour urine for protein will be performed whenever protein is 4+.
- i. Prior to Cycle 1: Must be performed prior to 1st dose; need not be assessed again if ≤ 7 days since corresponding assessment performed at screening.
- j. Pregnancy test: Serum β-hCG required for premenopausal, non-sterilized females.
- k. Screening CT/MRI scan may be performed up to 30 days prior to first dose as part of standard of care, and prior to signing of the informed consent if performed in compliance with the protocol requirements. Screening scan to include head, chest, abdomen, and pelvis.
- l. Not needed if last scan was within 30 days prior to End-of-Treatment Visit and showed progressive disease (PD), as confirmed by independent radiology review.
- m. For subjects with stable disease or objective response at the time of treatment discontinuation, who discontinue for reasons other than radiological evidence of progressive disease, tumor assessments will continue to be collected (every 2 months during the first year [beginning from the date of the last scan performed prior to treatment discontinuation], every 3 months during the second year, and every 6 months thereafter) until disease progression is confirmed by independent radiology review or start of another therapy. A ±3 day visit window applies to tumor assessments for subjects that have discontinued study drug.
- n. Two blood samples for pharmacokinetic (PK) analysis will be collected at the following time points from all subjects: Cycle 1, Day 1- 4 hours post-dose and Cycle 1, Day 15- pre-dose (within 2 hours before dosing).
- o. After the 30-Day Follow-up visit, subjects will be contacted once every 3 months by the site to collect long-term survival data. Additional contacts may be made to support key analyses, such as the analysis of overall survival at the time of the final PFS analysis, and the final analysis of overall survival. A ±7 day window applies for the scheduled long term follow-up contacts.
- p. A ±2 day window applies to all visit procedures except study drug administration.
- q. The duration of treatment for tivozanib is 21 of 28 days, and for sorafenib is 28 of 28 days.
- r. All subjects will have an EOT visit when they permanently discontinue any further study treatment. The EOT visit will occur up to 7 days after the last dose of study drug. Assessments performed within 3 days of the EOT visit need not be repeated and may be documented as the EOT assessment (except for the response assessment which does not need to be repeated if performed within 30 days and showed progressive disease). Subjects starting new anti-cancer therapy after the last dose of study drug must complete the End of Treatment Visit assessments in advance of starting the new anti-cancer therapy.
- s. If additional visits are needed, these assessments may be obtained/ performed/ measured as clinically indicated.

TABLE OF CONTENTS

PROCEDURES IN CASE OF EMERGENCY	2
PROTOCOL SIGNATURE PAGE	3
1 SYNOPSIS.....	4
2 LIST OF ABBREVIATIONS AND EXPANDED TERM	20
3 INTRODUCTION	23
3.1 Background.....	23
3.2 Pharmacology	23
3.3 Safety Pharmacology	24
3.4 Toxicology	24
3.5 Pharmacokinetics	26
3.6 Previous Human Experience.....	26
3.6.1 Pharmacokinetics in Subjects with Solid Tumors	26
3.6.2 Clinical Activity.....	26
3.7 Study Rationale.....	29
3.7.1 Rationale for the Tivozanib Dose	29
3.7.2 Rationale for the Tivozanib Dosing Regimen	29
3.7.3 Rationale for the Study Design.....	29
3.7.4 Use in Pregnancy	30
3.7.5 Potential Risks/Benefits of Therapy With Sorafenib (Nexavar™).....	30
4 STUDY OBJECTIVES AND PURPOSE	31
4.1 Primary Objective.....	31
4.2 Secondary Objectives.....	31
4.3 Tertiary Objectives.....	31
5 INVESTIGATIONAL PLAN.....	31
5.1 Overall Study Design and Plan: Description	31
5.2 Approximate Duration of Study.....	31
5.3 Approximate Number of Subjects	31
5.4 Subject Enrollment.....	32
5.4.1 Subject Enrollment Assignment	32
5.4.2 Treatment Randomization.....	32
6 DIAGNOSIS AND MAIN CRITERIA	32
6.1 Subject Inclusion Criteria	32
6.2 Subject Exclusion Criteria	33
6.3 Drugs and Other Treatments to be Excluded.....	35
7 TREATMENT OF SUBJECTS	36
7.1 Procedures/Parameters to be Measured	36

7.1.1	Screening Visit.....	39
7.1.2	Cycle 1, Day 1 (Baseline) Visit	40
7.1.3	Cycle 1, Day 15 Visit (\pm 2 days)	40
7.1.4	Cycle 2, Day 1 Visit (\pm 2 days)	41
7.1.5	Every 8 weeks from Cycle 1, Day 1 (\pm 3 days).....	41
7.1.6	Subsequent Cycles – Day 1 Visit (\pm 2 days)	41
7.1.7	End-of-Treatment.....	42
7.1.8	30-Day Follow-Up Visit (\pm 7 days).....	42
7.1.9	Unscheduled Visits (To Occur as Needed).....	43
7.1.10	Long Term Response and Survival Follow-Up	43
7.2	Study Drug Administration.....	44
7.2.1	Tivozanib Administration.....	44
7.2.2	Sorafenib Administration.....	44
7.2.3	Review of Safety Data During Study	44
7.2.4	Duration of Study Treatment	45
7.2.5	Duration of Follow-Up	45
7.3	Prior and Concomitant Medications	46
7.4	Randomization and Blinding	46
8	STUDY DRUG MATERIALS AND MANAGEMENT	46
8.1	Study Drug.....	46
8.2	Study Drug Packaging and Labeling	47
8.3	Study Drug Shipment.....	47
8.4	Dispensing of Study Drug and Dosing Compliance.....	47
8.5	Study Drug Storage.....	47
8.6	Study Drug Accountability	47
8.7	Study Drug Handling	47
8.7.1	Disposition of Used Supplies.....	48
8.7.2	Inventory of Unused Supplies.....	48
9	ASSESSMENT OF ACTIVITY	48
9.1	Disease Classification and Response Assessments.....	48
10	MANAGEMENT OF TOXICITY	49
10.1	Grading and Recording of Toxicity	49
10.2	Evaluation and Treatment of Toxicity	49
10.3	Management of Skin Toxicities (Sorafenib).....	50
10.4	Study Drug Administration Modification.....	50
10.4.1	Tivozanib Dose Reduction.....	51
10.4.2	Tivozanib Dose Interruption.....	51
10.4.3	Sorafenib Dose Reduction	52

10.4.4	Sorafenib Dose Interruption.....	52
11	REMOVING SUBJECTS FROM STUDY	52
11.1	Criteria for Treatment Discontinuation (Stopping Rules)	52
12	ADVERSE AND SERIOUS ADVERSE EVENTS	54
12.1	Definition of Adverse Events.....	54
12.1.1	Abnormal Laboratory Findings and Other Objective Measurements.....	55
12.1.2	Medical History	55
12.1.3	Exacerbation of Primary Malignancy.....	55
12.2	Evaluating Adverse Events.....	55
12.3	Serious Adverse Events (SAE).....	55
12.4	Protocol-Related Adverse Events	56
12.5	Reporting Period.....	57
12.6	Reporting Serious Adverse Events and Subject Deaths	57
12.6.1	Timeframe for Reporting.....	57
12.6.2	Reporting of Subject Death.....	57
12.6.3	Reporting of Overdose.....	58
12.6.4	Reporting to the Institutional Review Board/Ethics Committee	58
12.6.5	Information to be Provided by the Investigator	59
12.7	Required Follow-up for All Adverse Events and Serious Adverse Events	59
12.8	Pregnancy Reporting.....	60
13	PRECAUTIONS	60
13.1	Precautions Regarding Procreation.....	60
13.1.1	Tivozanib	61
13.1.2	Sorafenib.....	61
13.2	Additional Precautions.....	61
14	DATA EVALUATION AND STATISTICS.....	61
14.1	General Design.....	61
14.2	Sample Size Justification	62
14.3	Statistical Considerations.....	62
14.3.1	Study Populations	62
14.3.2	Subject Accountability, Demographics, and Baseline Characteristics	63
14.3.3	Protocol Deviations.....	63
14.3.4	Efficacy.....	63
14.3.5	Safety Data.....	65
14.3.6	Safety Monitoring Committee	67
14.3.7	Pharmacokinetic Parameters.....	67
14.3.8	Imaging Process.....	67
15	DIRECT ACCESS TO SOURCE DATA/DOCUMENTS.....	67

15.1	Study Monitoring	67
15.2	Audits and Inspections	68
16	QUALITY CONTROL AND QUALITY ASSURANCE	68
17	ETHICS	68
17.1	Ethical Conduct of the Study/Conditions of Testing	68
17.2	Institutional Review / Ethics Committee	69
17.3	Written Informed Consent	69
17.4	Conditions for Modifying or Terminating the Study	69
17.4.1	Modification of the Study Protocol	69
17.4.2	Modification of the Informed Consent Document	70
17.4.3	Termination of the Study	70
17.4.4	Deviation From the Protocol	70
17.5	Documents to be Submitted to the Sponsor	70
18	INVESTIGATOR RESPONSIBILITIES	71
18.1	Medical Supervision	71
18.2	Confidentiality	71
18.3	Use of Information and Publication	72
18.4	Drug Dispensing Inventory	72
18.5	Handling and Disposal of Investigational Materials	73
18.6	Recording and Processing of Data	73
18.7	Source Document Requirements	73
18.8	Laboratory Reports	74
18.9	Subject Confidentiality	74
19	DATA HANDLING AND RECORDKEEPING	74
19.1	Inspection of Records	74
19.2	Retention of Records	74
20	REFERENCES	75
21	APPENDICES	77
APPENDIX A	RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) VERSION 1.1	78
APPENDIX B	ECOG PERFORMANCE STATUS EVALUATION	83
APPENDIX C	CYTOCHROME P450 (CYP3A4) INHIBITORS AND INDUCERS	84
APPENDIX D	RECOMMENDED ANTI-HYPERTENSIVE MEDICATIONS	85
APPENDIX E	SORAFENIB PRESCRIBING INFORMATION	86
APPENDIX F	STUDY DRUG INFORMATION	105
APPENDIX G	CLINICAL SYMPTOM AND ADVERSE EVENT GRADING SCALE	108

APPENDIX H INTERNATIONAL METASTATIC RENAL CELL
CARCINOMA DATABASE CONSORTIUM (IMDC) RISK
MODEL 109

LIST OF TABLES

Table 1: Study Design and Schedule of Assessments 12
Table 2: Abbreviations and Specialist Terms 20
Table 3: Management of Skin Toxicity Associated with Sorafenib 50
Table 4: Dose Modification Guidelines for Drug-Related Adverse Events 51

2 LIST OF ABBREVIATIONS AND EXPANDED TERM

Table 2: Abbreviations and Specialist Terms

Abbreviation or Term	Expanded Term
ACE	angiotensin converting enzyme
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANC	absolute neutrophil count
AST	aspartate aminotransferase (SGOT)
AUC	area under the plasma concentration-time curve
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
C _{max}	maximum (peak) plasma concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
C _{ssav}	estimated average serum concentration
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events (NCI, Version 4.03)
CV	curriculum vitae
CVA	cerebrovascular accident
CYP	cytochrome P450
DHP	dihydropyridine
DLT	dose limiting toxicity
DoR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eCRF	electronic case report form
EU	European Union

Table 2: Abbreviations and Specialist Terms

Abbreviation or Term	Expanded Term
EudraCT	European Drug Regulatory Affairs Clinical Trials
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRR	independent radiological review
ITT	intent-to-treat
IUD	intrauterine device
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
MCH	mean cell hemoglobin
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
mPFS	median progression free survival
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	North America
NOAEL	no observed adverse effect level
NOEL	no-observable effect level
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death -1 protein
PD1-L	programmed cell death -1 ligand

Table 2: Abbreviations and Specialist Terms

Abbreviation or Term	Expanded Term
PDGFR	platelet derived growth factor receptor
PE	physical examination
PFS	progression-free survival
PK	pharmacokinetic
PP	per protocol
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SD	stable disease
SMC	safety monitoring committee
SOC	system organ class
STD	standard deviation
T3	triiodothyronine
T4	thyroxine
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
TSH	thyroid stimulating hormone
t_{max}	time to peak plasma concentration
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WHO-DD	World Health Organization Drug Dictionary

3 INTRODUCTION

Tivozanib hydrochloride (tivozanib; previously known as AV-951 and as KRN951) has the chemical name (N-{2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)urea hydrochloride monohydrate. Tivozanib is a novel and potent vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor (VEGFR TKI) that has demonstrated significant anti-tumor effects in pre-clinical experiments [1]. Tivozanib inhibits phosphorylation of VEGF receptors (VEGFR) -1, -2 and -3 at picomolar concentrations (IC₅₀ of 0.21, 0.16 and 0.24 nM respectively), and inhibits c-Kit and platelet derived growth factor receptor (PDGFR) at 10-times higher concentrations (IC₅₀ of 1.63 and 1.72 nM respectively).

Based on its biochemical profile, tivozanib appears to be one of the most potent and selective VEGF tyrosine kinase inhibitor in clinical development. Other agents used for treatment of renal cell carcinoma (RCC) such as sunitinib and sorafenib inhibit multiple tyrosine kinases in addition to the VEGF receptor tyrosine kinase, leading to off-target toxicities such as fatigue, hand-foot syndrome, stomatitis, and neutropenia. The adverse event (AE) profile of tivozanib demonstrates that it is a selective VEGF tyrosine kinase inhibitor, with minimal off-target toxicities.

3.1 Background

Approximately 208,500 new cases of kidney cancer are diagnosed in the world each year, of which 40,000 new cases are diagnosed in North America and 63,300 new cases in the European Union (EU). Renal cell carcinoma accounts for 80%-85% of all malignant kidney tumors. Advanced RCC is highly resistant to chemotherapy, and interleukin-2 and interferon- α have low levels of anti-tumor activity. Recently, drugs that block the VEGF pathway such as sunitinib, sorafenib, bevacizumab, pazopanib, and axitinib have demonstrated significant anti-tumor activity in Phase 3 trials. As a result, these drugs have become the standard of care for the treatment of subjects with advanced RCC.

The formation of new blood vessels, known as angiogenesis, is required to support growth in the embryo and to allow for repair (eg, wound healing and remodeling processes in the adult) [2]. Vascular endothelial growth factor plays a critical role during normal embryonic angiogenesis and also in the pathological angiogenesis that occurs in a number of diseases, including cancer [3,4]. Tumors use this vasculature to obtain oxygen and nutrients, both of which are required to sustain tumor growth. In addition, the new intra-tumoral blood vessels provide a way for tumor cells to enter the circulation and to metastasize to distant organs [5]. The various forms of VEGF bind to 3 tyrosine kinase receptors: the vascular endothelial growth factor receptors, VEGFR-1, VEGFR-2, and VEGFR-3 retrospectively. This binding results in phosphorylation of the receptors catalyzed by the protein kinase, and the promotion of a signal transduction cascade. Deregulation of VEGF expression contributes to the progression and spread of solid tumors by promoting tumor angiogenesis [6]. Tivozanib inhibits VEGFR-associated tyrosine kinase activity and, as a result, may offer a potential therapy for subjects with cancer by controlling tumor growth.

3.2 Pharmacology

In cellular assays, tivozanib has been shown to inhibit markedly VEGF-induced phosphorylation of intracellular VEGFR-1, VEGFR-2, and VEGFR-3 (IC₅₀ of 0.21 nmol/L,

0.16 nmol/L, and 0.24 nmol/L, respectively). Tivozanib, administered orally at 5 and 20 mg/kg once daily for 2 weeks, demonstrated a broad spectrum of anti-tumor effects against lung, colon, and prostate carcinoma xenografts in nude mice.

Even at lower doses, tivozanib demonstrated a broad spectrum of anti-tumor effects. Tivozanib given orally at a dose of 0.2 mg/kg once daily for 2 weeks showed statistically significant inhibitory effects ($P < 0.05$) on the growth of various tumor xenografts [1]. Tivozanib at a dose of 1.0 mg/kg exerted tumor regression on human breast adenocarcinoma MDA-MB231, human colon adenocarcinoma LoVo, human renal carcinoma Caki-1, and human prostate carcinoma DU145 xenografts.

Tivozanib has been shown to inhibit both angiogenesis and vascular permeability in tumor tissues. Immunostaining of endothelial cells of tumor tissues in a human lung carcinoma A549 xenograft demonstrated a dose-dependent decrease in microvessel density in tumor tissues after oral administration of tivozanib (0.04, 0.2, and 1.0 mg/kg) once daily over 1 week. When Evans blue was injected intravenously in a similar animal model to examine the transfer of dye into the tumor tissues, tivozanib reduced the quantity of dye transferred to the tumor tissues in a dose-dependent manner, suggesting a reduction in vascular permeability, which could limit the availability of nutrients to the tumor thereby inhibiting tumor growth.

Based on the above results, tivozanib is expected to exhibit a broad anti-tumor spectrum of activities against various tumors by inhibiting angiogenesis and vascular permeability.

3.3 Safety Pharmacology

Based on the Irwin Test, there were no significant behavioral or physiological changes observed in rats during the 24-hour post-dose period after receiving a single oral dose of 0.3, 3, 30, or 400 mg/kg tivozanib compared to vehicle-treated animals. In a telemetry study in monkeys, doses of 0.015 or 0.3 mg/kg tivozanib were shown to have no significant effects on arterial blood pressure; however, increasing this dose to 3.0 mg/kg resulted in transient increases in systolic, diastolic, and mean arterial blood pressure by up to 14–19 mmHg. Tivozanib was not shown to have a marked effect on any other cardiovascular or respiratory parameters.

3.4 Toxicology

Repeat-dosing studies with tivozanib have been conducted in rats and monkeys. In a 28-day rat study of 0.3 and 0.1 mg/kg/day, the 0.1 mg/kg/day dose was considered to be the no observed adverse effect level (NOAEL) in the rat as based on clinical signs, laboratory findings, and histopathological changes. In a 28-day repeat-dose study in monkeys, 0.230-0.3 mg/kg/day was considered to be the NOAEL based on clinical signs, laboratory findings, and histopathological changes.

In a 13-week, repeated-dose study in the rat at dosages of 0.01, 0.03, 0.1 and 0.3 mg/kg/day, exposure to tivozanib at 0.3 mg/kg/day resulted in 3 male and 2 female unscheduled deaths considered to be drug related. The cause of death was microscopically determined to be adrenal necrosis/degeneration in these rats. Administration of 0.1 mg/kg/day tivozanib was associated with abnormal clinical signs, such as hunched appearance, thin appearance, rough hair coat, yellow hair coat, white teeth, and malocclusion. Marked body weight loss

accompanied by significant decreases in food consumption occurred in 0.3 mg/kg/day. Hematological investigations revealed lower relative and absolute reticulocyte counts in most 0.3 mg/kg/day rats, which may represent a transient effect of tivozanib. The mean cell volume (MCV) and mean cell hemoglobin (MCH) were also elevated, and there were higher white blood cell, lymphocyte, neutrophil, and monocyte counts in the 0.3 mg/kg/day rats. In blood chemistry investigation, treatment-associated changes were noted in alanine aminotransferase (ALT), bile acids, gamma-glutamyl transferase (GGT), iron metabolism parameters, and serum iron. Histopathological examination of tissues showed abnormalities in the adrenal gland, kidney, femur, liver and bile ducts, and incisors. Pronounced changes considered secondary to bile duct inflammation were seen in the pancreas and duodenum. Most findings resolved or showed signs of ongoing reversal after the withdrawal of treatment. However, kidney lesions were not resolved at either recovery or sacrifice. Based on these findings, mechanistic studies were conducted to better understand the adverse effect on the kidney. In conclusion, based on all study findings, the no-observable effect level (NOEL) was less than 0.01 mg/kg/day. Based on body weight effects in females, the NOAEL was 0.01 mg/kg/day. Some tivozanib-related effects persisted through the end of the recovery periods, and many were seen to a much lesser degree.

In the 13-week repeat dose monkey study at doses of 0.01, 0.03, 0.1 and 0.3 mg/kg/day, no mortality occurred. Clinical observations of dehydration; hunched posture; thin appearance; hypoactivity; discolored, few/no and/or non-formed feces; low/no food consumption and/or body weight loss were seen at 1.0 mg/kg/day. Low/no food consumption and/or body weight loss were observed at 0.3 mg/kg/day, and an increased frequency of low/no food consumption was also noted at 0.1 mg/kg/day. Findings were generally unremarkable during recovery. No tivozanib effects were observed in ophthalmic and electrocardiogram (ECG) examination. There were no toxicologically significant changes in hematology, serum and urine chemistry, and urinalysis data during treatment or recovery. Tivozanib-related histopathological alterations at 1.0 mg/kg/day consisted of gastroenteropathy; decreased pancreatic zymogen granules; atrophy of the primary spongiosa and hypertrophy of the physis in the distal femur and tibia; hypertrophy of femoral articular cartilage; degeneration of the adrenal cortex; mononuclear infiltrates, thrombi, hemorrhage, and pigment deposition in the cerebral ventricular choroid; and lymphoid depletion of lymphoid organs (spleen, thymus, lymph nodes). Tivozanib-related histopathological alterations observed primarily at 0.3 mg/kg/day and in a few 0.1 mg/kg/day monkeys consisted of mononuclear cell infiltrates in the choroid plexus of the brain; adrenal cortical degeneration (increased cytoplasmic eosinophilia and/or decreased vacuolization); decreased pancreatic zymogen granules and decreased cytoplasmic granules in parotid salivary glands; lymphoid depletion in thymus, spleen and mandibular lymph node; and atrophy of the primary spongiosa of the metaphysis (femur and/or tibia/fibula). The 13-week NOAEL in monkeys was considered 0.03 mg/kg/day. Findings after recovery indicated reversal or abatement of tivozanib-related changes.

Tivozanib did not produce genotoxic effects in any of the systems tested.

**FOR ADDITIONAL INFORMATION, PLEASE REFER
TO THE TIVOZANIB (AV-951) INVESTIGATOR'S BROCHURE**

3.5 Pharmacokinetics

Pharmacokinetic (PK), toxicokinetic, and metabolic disposition studies were conducted with tivozanib in rats and monkeys, and PK data are available from a Phase 1 clinical trial in humans. In rats and monkeys, peak serum concentrations of tivozanib were attained approximately 3–6 hr after oral administration, and the $t_{1/2}$ values averaged 7-12 hr.

In the nude rat, the estimated average serum tivozanib concentration (C_{ssav}) at steady state after oral doses of 0.2 mg/kg/day (the lowest dose with minimum efficacy in this animal model) was 70 ng/mL.

In the rat and monkey, after both single and multiple oral doses of tivozanib, maximum (peak) plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) were approximately dose proportional.

3.6 Previous Human Experience

3.6.1 Pharmacokinetics in Subjects with Solid Tumors

Final PK data are available from Study KRN951/03-B01, completed in subjects with solid tumors. PK data were collected from a total of 41 subjects and included all who had taken at least one dose of tivozanib. Three doses of tivozanib were studied (1.0, 1.5, and 2.0 mg) in a regimen of 4 weeks of daily dosing followed by a 14-day rest period. Each 6-week regimen was considered one cycle.

After single and multiple doses of tivozanib, the overall rate of absorption was slow. Median time to peak serum concentration (t_{max}) of tivozanib ranged from 2 to 24 hours with substantial individual variability. The time to peak serum concentration was variable due to the occurrence of secondary peaks in the concentration versus time profiles indicating the possibility of enterohepatic recirculation of tivozanib.

Although the inter-subject variability was high, mean C_{max} and AUC values after single and multiple doses were approximately dose proportional. An evaluation of the available data predicted that tivozanib has a mean half-life across dose groups of approximately 4.7 days (112 hours) and ranging from 1.3 to 9.7 days (31 – 233 hours) (data not included in tables). Due to the unexpectedly long half-life of tivozanib in humans, sufficient timepoints to characterize the terminal phase were not available from all subjects.

AUCs on Day 28 were higher than those on Day 1 indicating drug accumulation. In the majority of subjects, pre-dose samples collected prior to the first dose of Cycle 2, (ie, 14 days after administration of the previous dose on Day 28 of Cycle 1) still had detectable concentrations of tivozanib in serum indicating ongoing drug exposure during the 14-day dosing break at the end of Cycle 1.

3.6.2 Clinical Activity

TIVO-1 (AV-951-09-301) was an open-label, randomized, controlled, multi-national, multi-centre, parallel-arm trial comparing tivozanib (1.5 mg/day for 3 weeks on, 1 week off, continuously) to sorafenib (400 mg bid continuously) in patients with advanced RCC. Patients had undergone prior nephrectomy, and approximately 70% had received no prior systemic therapy in the metastatic setting. The remaining patients had received one prior line

of therapy in the metastatic setting, the vast majority of which was cytokine treatment. Prior therapy with an anti-angiogenesis agent was not allowed.

The design of the study was such that patients with radiological evidence of progressive disease (PD) per investigator/local radiology assessment continued treatment until PD was verified by an independent radiologist. Patients randomized to the sorafenib treatment arm who had verified PD (by an independent radiologist) were discontinued from study drug treatment and given the option to receive tivozanib under a separate extension protocol (AV-951-09-902). Patients who were discontinued from sorafenib treatment owing to the development of AEs or non-radiographic confirmed progression were not eligible to receive tivozanib. Patients randomised to the tivozanib treatment arm who had radiological evidence of PD per investigator/local radiology assessment continued treatment until PD was verified by an independent radiologist, after which they were discontinued from study drug treatment but were not provided sorafenib per protocol. Instead, these patients could only receive second line therapy consistent with the practices in the patient's home country.

Superiority was shown for the primary endpoint, progression-free survival (PFS), based upon blinded independent radiological assessment (per Response Evaluation Criteria in Solid Tumors [RECIST] Version 1.0 definition). The blinded independent radiological assessment showed the Median progression free survival (mPFS) in the tivozanib arm to be 11.9 months (95% confidence interval (CI) [9.3, 14.7]), compared with 9.1 months (95% CI [7.3, 9.5]) in the sorafenib arm. This is a statistically significant improvement in mPFS, with a p-value of 0.042, and a hazard ratio (HR) of 0.797 (95% CI [0.639, 0.993]).

Additional key efficacy endpoints, including independent assessment of objective response rate (ORR) and duration of stable disease were statistically significantly improved for tivozanib, compared with sorafenib. Forest plots assessing the efficacy of tivozanib vs. sorafenib in multiple subgroups showed consistent benefit of tivozanib over sorafenib.

There was a slight difference in overall survival (OS), favoring the sorafenib randomized arm over the tivozanib randomized arm (29.3 months vs 28.8 months; p-value 0.105; HR 1.245 [95% CI: 0.954, 1.624]).

Evidence of Second Line Efficacy

The updated analysis of the second line efficacy data (cut-off date of 24th April 2014) from study AV-951-09-902 has revealed that the mPFS for patients in the sorafenib arm who received tivozanib subsequent to sorafenib treatment is 11.0 months (95% CI [7.4, 12.9]). The overall median survival for this group was 21 months from the start of tivozanib. This strong second line efficacy of tivozanib in those patients who crossed over from sorafenib to tivozanib likely drives the discordance between the PFS and OS endpoints.

Impact of the Unbalanced Use of Second Line Therapy

The one-way crossover design of the pivotal trial allowed patients who experienced radiographic disease progression on sorafenib to crossover to the experimental arm, but not vice versa. This created an imbalance in second-line treatment between arms, particularly outside the EU and United States (US) where second-line therapies were not generally available. Owing to this imbalance, significantly more patients from the sorafenib arm who experienced disease progression were subsequently treated with next line targeted therapy (the

majority of which was tivozanib) compared with patients randomized to the experimental arm (tivozanib followed by off-protocol next line targeted therapy). At the time of the prior NDA submission (September 2012) 13% of patients randomized to tivozanib had received targeted next line treatment with TKI vs 63% of patients randomized to sorafenib who received second line tivozanib. An updated analysis of the second line data indicates that as of December 2014 even more patients in the sorafenib arm (approx. 70%) have received second line tivozanib following disease progression; whereas, only 36% of the patients randomized to the tivozanib arm who subsequently experienced disease progression have received targeted next line therapy.

To further understand the effect of crossover on OS in Study AV-951-09-301 an analysis was performed on the 186 patients enrolled in the study in the EU and North America (NA) (NA; US and Canada). The participating countries were Bulgaria, Canada, Czech Republic, France, Hungary, Italy, Poland, Romania, UK, and the US. In these territories the standard of care is more likely to include second line therapies and therefore mitigate the effect of the one-way crossover. This analysis revealed that for the NA and EU region while the significant benefit for PFS remains for the tivozanib arm, the non-significant trend in OS favors the tivozanib arm as well. The OS for the tivozanib arm was 35.9 months versus 31.0 months for the sorafenib arm (p-value 0.576; HR 0.892 [95% CI: 0.599, 1.329]).

Consequently, the OS data do not provide an accurate measure of relative survival against the comparator in this study. Nevertheless, with this caveat in mind, OS values for the sorafenib arm and the tivozanib arm were amongst the longest seen in pivotal RCC trials.

To conclude, the evidence provided above indicates that the imbalance in crossover between the two treatment arms in the pivotal trial and the strong second line efficacy of tivozanib observed in the patients who crossed over from sorafenib to tivozanib confounded the OS data and likely explains the discordance between the PFS and OS endpoints seen in the overall analysis, and as such makes the OS results difficult to interpret.

Consolidated Safety Data

The AE profile for tivozanib in the TIVO-1 trial (Study AV-951-09-301) is consistent with the prior Phase 2 experience (AV-951-07-201). Comparable rates of serious adverse events (SAEs) and AEs with fatal outcomes occurred in each arm.

AEs that were more common in the tivozanib arm than in the sorafenib arm included hypertension (44.0% vs 34.2%) and dysphonia (20.5% vs 4.7%). AEs that were more common in the sorafenib arm than in the tivozanib arm included hand-foot syndrome (54.1% vs 13.1%), skin rashes (17.2% vs 4.7%); and diarrhoea (31.5% vs 21.6%). Other common AEs were similar in both arms, including fatigue, asthenia, and weight decrease (all ~15-20%). Fewer grade 3 or higher AEs occurred in the tivozanib arm than in the sorafenib arm (56.8% vs 68.5%). More grade 3 or higher hypertension events were observed in the tivozanib arm (24.7% vs 17.1%) and more grade 3 or greater hand-foot syndrome events were observed in the sorafenib arm (16.7% vs 1.9%). Ischemia cerebrovascular AEs occurred in 2.7% of patients on the tivozanib arm and in 1.6% of patients on the sorafenib arm.

Cardiovascular AEs were similar in each arm. Grade 3 or higher liver enzyme perturbations were less frequent with tivozanib compared to sorafenib and proteinuria was similar between the two arms.

Fewer patients in the tivozanib group had dose interruptions (54, [20.8%] patients) compared with those in the sorafenib group (99, [38.5%] patients). Furthermore, fewer patients who received tivozanib had dose reductions overall (29, [11.2%] patients) compared to sorafenib patients (96, [37.4%] patients). More subjects in the tivozanib group had dose interruptions for hypertension (5.4% vs 3.5%), and more subjects in the sorafenib group had dose interruptions for hand-foot syndrome, diarrhoea, and asthenia (16.7% vs 1.9% and 3.5% vs 1.9% and 1.9% vs 0.8%). More subjects in the sorafenib group had dose reductions for hand-foot syndrome, diarrhoea, hypertension, and lipase increased compared with the tivozanib group (17.9% vs 1.9%; 4.3% vs 1.5%; 4.3% vs 1.5%, and 2.3% vs 0.4% respectively). Less than 2% of subjects had a dose reduction for asthenia or fatigue in either group. These dose interruption and reduction data suggest an improved patient tolerability for tivozanib versus sorafenib.

3.7 Study Rationale

3.7.1 Rationale for the Tivozanib Dose

In Study KRN951/03-B01, 3 of 8 subjects in the 2 mg tivozanib group experienced a dose limiting toxicity (DLT), indicating that the maximum tolerated dose (MTD) had been exceeded. Based on the results of this study, the MTD was determined to be 1.5 mg/day, and the safety of this dose has been confirmed in multiple subsequent studies.

3.7.2 Rationale for the Tivozanib Dosing Regimen

The initial Phase 1 clinical study (KRN951/03-B01) adopted a dosing regimen with 28-day continuous administration of tivozanib followed by 14-day rest period (during which time no study drug is administered). This study demonstrated that the MTD of tivozanib is 1.5 mg/day, and that toxicities are rapidly reversible upon stopping treatment. The dosing regimen was altered for Study AV-951-07-201 to 21-day (3 weeks) continuous administration of tivozanib followed by 7-day (1 week) rest period during which no study drug is administered. The rationale for changing the dosing regimen was to minimize the rest period during treatment but yet allow subjects to recover from any treatment-related toxicity during the 7-day break. Clinical data with sunitinib have demonstrated that subjects experience recurrence of disease-related symptoms during a 14-day break in treatment [7]. Therefore, the break in tivozanib dosing was reduced from 14-days (Study KRN951/03-B01) to 7 days (Study AV-951-07-201) in an effort to maximize clinical benefit to subjects. The 1.5 mg/day dose given continuously for 21-days followed by a 7-day break has been well tolerated in 272 subjects enrolled in Study AV-951-07-201, and to date only 23 (8.5%) subjects have required a dose reduction and 8 (2.9%) have required a dose interruption. Therefore, this dosing regimen will be used in this Phase 3 study.

3.7.3 Rationale for the Study Design

This is a randomized, controlled, open-label, multicenter study comparing tivozanib to sorafenib in subjects with refractory advanced RCC. Tivozanib has demonstrated significant activity in the second line therapy as described above. Sorafenib was chosen as a comparator for this Phase 3 trial because sorafenib is no longer the most commonly used first line VEGFR inhibitor and is used in advanced RCC. Subjects will be randomized (1:1) to treatment with tivozanib or sorafenib. As differences in such factors as co-medications, prior treatments, and palliative care may affect enrollment rates across the participating centers, the randomization

of subjects will be stratified by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk category (favorable; intermediate; poor) and prior therapy (two prior VEGFR TKIs; a prior checkpoint inhibitor [programmed cell death -1 protein (PD-1) or PD-1 ligand (PD1-L) inhibitor] plus a prior VEGFR TKI; a prior VEGFR TKI plus any other systemic agent). To protect the integrity of the primary endpoint, progression-free survival will be assessed by an outside group of independent radiology reviewers.

3.7.4 Use in Pregnancy

Tivozanib should not be administered to pregnant women, as it is known that angiogenesis plays an important role in reproductions and embryonic development. It is required that women of childbearing potential undergo a pregnancy test before treatment and must use adequate contraceptive measures while on study and for at least 90 days after the last dose of study drug. Sexually active male subjects must use adequate contraceptive measures, while on study and for at least 90 days after the last dose of study drug. Risk to male sperm is unknown. Effective contraceptive measures include (a) intrauterine device (IUD) plus one barrier method; or (b) 2 barrier methods. Effective barrier measures are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm). Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are not considered effective for this study.

**FOR ADDITIONAL INFORMATION, PLEASE REFER
TO THE TIVOZANIB (AV-951) INVESTIGATOR'S BROCHURE**

3.7.5 Potential Risks/Benefits of Therapy With Sorafenib (Nexavar™)

Sorafenib is currently approved for the treatment of advanced RCC and unresectable hepatocellular carcinoma, and locally recurrent or metastatic, progressive differentiated thyroid cancer. Sorafenib was approved in the US on 20 December 2005 as the first VEGF receptor inhibitor for the treatment of advanced RCC. Sorafenib received marketing authorization by the European Commission on 19 July 2006 for the treatment of subjects with advanced RCC who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy. These approvals were based on the demonstration of an improvement in median PFS (sorafenib 167 days [5.5 months]; placebo 84 days [2.8 months]) in a large multinational, randomized, double-blind, placebo-controlled, Phase 3 study of sorafenib vs. placebo, along with a supporting Phase 2, randomized, discontinuation trial in subjects with advanced RCC. Adverse events most frequently observed ($\geq 20\%$) with sorafenib are fatigue, weight loss, rash/desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea, and abdominal pain. Overall, the most frequently observed laboratory abnormalities include neutropenia, thrombocytopenia, anemia, lymphopenia, hypophosphatemia, and elevated lipase.

**FOR ADDITIONAL INFORMATION, PLEASE REFER TO APPENDIX E
(SORAFENIB PRESCRIBING INFORMATION) FOR A DESCRIPTION OF
TOXICITIES OBSERVED IN HUMANS TO DATE.**

4 STUDY OBJECTIVES AND PURPOSE

4.1 Primary Objective

The primary objective of this study is as follows:

- To compare the PFS of subjects with refractory advanced RCC randomized to treatment with tivozanib or sorafenib as assessed by blinded independent radiological review (IRR) of computerized tomography (CT) or magnetic resonance imaging (MRI).

4.2 Secondary Objectives

The secondary objectives of this study are as follows:

- To compare the OS of subjects randomized to treatment with tivozanib or sorafenib
- To compare ORR and duration of response (DoR) of subjects randomized to treatment with tivozanib or sorafenib
- To compare the safety and tolerability of tivozanib and sorafenib.

4.3 Tertiary Objectives

The tertiary objectives of this study are as follows:

- To explore any relationship between:
 - tivozanib and sorafenib drug levels and activity
 - tivozanib and sorafenib drug levels and AEs

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan: Description

This is an open-label, randomized, controlled, multi-national, multi-center, parallel-arm study comparing tivozanib to sorafenib in subjects with refractory advanced RCC. The study is designed to compare the PFS, OS, ORR, DoR, safety and tolerability, of tivozanib and sorafenib.

Subjects will be randomized (1:1) to treatment with tivozanib or sorafenib and stratified by IMDC risk category (favorable; intermediate; poor) and prior therapy (two prior VEGFR TKIs; a prior checkpoint inhibitor [PD-1 or PD1 L inhibitor] plus a prior VEGFR TKI; a prior VEGFR TKI plus any other systemic agent). Once the strata have been identified, treatment will be randomly assigned to a subject within the strata using a complete permuted block design, in an unblinded fashion (open-label). In the event a subject had both 2 TKIs and a checkpoint inhibitor, the subject will be stratified according to the most recent line of therapy.

Subjects must begin treatment with study drug within 14 days after randomization.

5.2 Approximate Duration of Study

It is anticipated that enrollment to this study will be completed in approximately 15 months. A follow-up period of 6 months is expected. Overall duration of subject participation is approximately 24 months.

5.3 Approximate Number of Subjects

Approximately 322 subjects with refractory advanced RCC are planned to participate in this study at approximately 160-190 sites.

Anticipated date of enrollment of first subject: June 2016

Anticipated date of enrollment of last subject: August 2017

Established data cut-off date (targeted number of 242 PFS events): 04 October 2018

5.4 Subject Enrollment

Subject enrollment will take place before the start of study drug administration. Written informed consent must be obtained and all eligibility criteria must be met at the time of enrollment. An Interactive Web Response System (IWRS) will be used for enrollment, randomization and drug management (packaging of clinical supplies, shipping to study sites, and dispensing to subjects).

5.4.1 Subject Enrollment Assignment

Each subject will be assigned a 6-digit identification code. This code will consist of:

- 3-digit site code (Example: 101): assigned by the Sponsor at the time of study initiation.
- 3-digit subject code (Example: 001): assigned by the site via IWRS at the time written informed consent is obtained and screening has begun. Each site will begin with Subject 001.

In the case of re-screening, the same screening number will be used and there is no limit on the number of times re-screening is allowed. There is no window limitation in between the different screening attempts for the same subject.

5.4.2 Treatment Randomization

Once informed consent has been obtained and all eligibility criteria have been met, subjects will be randomized 1:1 to tivozanib or sorafenib using an IWRS. Subjects must begin treatment with study drug within 14 days after randomization. Specific instructions for use of the enrollment/randomization system will be provided in a separate manual.

6 DIAGNOSIS AND MAIN CRITERIA

6.1 Subject Inclusion Criteria

Subjects may be male or female, and must meet all of the following inclusion criteria to be eligible for participation in the study.

1. \geq 18-years of age.

2. Subjects with metastatic RCC who have failed 2 or 3 prior systemic regimens, one of which includes a VEGFR TKI other than sorafenib or tivozanib.
 - a. Postoperative or adjuvant systemic therapy will not be counted as a prior therapy unless recurrence is detected within 6 months of completion of treatment, in which case it will be counted as a prior therapy for metastatic disease.
 - b. Subjects must be off all systemic anti-cancer therapy or radiotherapy for at least 2 weeks prior to Cycle 1 Day 1.
3. Subjects must have recovered from the AEs of prior therapy or returned to baseline. Controlled AEs such as hypothyroidism or hypertension are permitted.
4. Histologically or cytologically confirmed RCC with a clear cell component (subjects with pure papillary cell tumor or other non-clear cell histologies, including collecting duct, medullary, chromophobe, and unclassified RCC are excluded).
5. Measurable disease per the RECIST criteria (Version 1.1, see Appendix A).
6. ECOG performance status of 0 or 1.
7. Life expectancy \geq 3 months.
8. If female and of childbearing potential, documentation of negative pregnancy test prior to enrollment.
9. Ability to give written informed consent and comply with protocol requirements.
10. Sexually active pre-menopausal female subjects (and female partners of male subjects) must use adequate contraceptive measures, while on study and for at least 90 days after the last dose of study drug. Sexually active male subjects must use adequate contraceptive measures, while on study and for at least 90 days after the last dose of study drug. All fertile male and female subjects and their partners must agree to use a highly effective method of contraception. Effective birth control includes (a) IUD plus one barrier method; or (b) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm). (Note: oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are not considered effective for female subjects in this study.)

6.2 Subject Exclusion Criteria

Subjects meeting any of the following criteria are ineligible for participation in the study.

1. Prior treatment with sorafenib or tivozanib.
2. More than 3 prior regimens for metastatic RCC.
3. Known central nervous system (CNS) metastases other than stable, treated brain metastases. Subjects with previously treated brain metastasis will be allowed if the brain metastasis has been stable by neuroimaging without steroid treatment for at least 3 months following prior treatment (radiotherapy or surgery).
4. Any of the following hematologic abnormalities:
 - Hemoglobin $<$ 9.0 g/dL (packed red blood cell transfusion is permitted)

- Absolute neutrophil count (ANC) < 1500 per mm³
 - Platelet count < 100,000 per mm³.
5. Any of the following serum chemistry abnormalities:
- Total bilirubin > 1.5 × upper limit of normal (ULN) (or > 2.5 × ULN for subjects with Gilbert's syndrome)
 - Aspartate aminotransferase (AST) or ALT > 2.5 × ULN (or > 5 × ULN for subjects with liver metastasis)
 - Alkaline phosphatase > 2.5 × ULN (or > 5 × ULN for subjects with liver or bone metastasis)
 - Creatinine > 1.5 × ULN unless the creatinine clearance is > 40 mL/min. Creatinine clearance can be calculated by standard equations (eg, Cockcroft-Gault) or measured.
6. Significant cardiovascular disease, including:
- Active clinically symptomatic left ventricular failure.
 - Uncontrolled hypertension: Systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg on 2 or more antihypertensive medications, documented on 2 consecutive measurements taken at least 2 hours apart.
 - Myocardial infarction, severe angina, or unstable angina within 6 months prior to administration of first dose of study drug.
 - History of serious ventricular arrhythmia (ie, ventricular tachycardia or ventricular fibrillation).
 - Cardiac arrhythmias requiring anti-arrhythmic medications (except for atrial fibrillation that is well controlled with anti-arrhythmic medication).
7. Non-healing wound, bone fracture, or skin ulcer.
8. Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal condition with increased risk of perforation; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to administration of first dose of study drug.
9. Serious/active infection or infection requiring parenteral antibiotics.
10. Inadequate recovery from any prior surgical procedure or major surgical procedure within 4 weeks prior to administration of first dose of study drug.
11. Significant thromboembolic or vascular disorders within 6 months prior to administration of first dose of study drug, including but not limited to:
- Symptomatic pulmonary embolism
 - Cerebrovascular accident (CVA) or transient ischemic attack (TIA)
 - Peripheral arterial ischemia > Grade 2

- Coronary or peripheral artery bypass graft.
12. Significant bleeding disorders within 6 months prior to administration of first dose of study drug, including but not limited to:
 - Hematemesis, hematochezia, melena or other gastrointestinal bleeding \geq Grade 2
 - Hemoptysis or other pulmonary bleeding \geq Grade 2
 - Hematuria or other genitourinary bleeding \geq Grade 2.
 13. Currently active second primary malignancy, including hematologic malignancies (leukemia, lymphoma, multiple myeloma, etc), other than non-melanoma skin cancers, non muscle-invasive urothelial cancer, non-metastatic prostate cancer, in situ cervical cancer and ductal or lobular carcinoma in situ of the breast. Subjects are not considered to have a currently active malignancy if they have completed anti-cancer therapy and have been disease free for >2 years.
 14. Pregnant or lactating females.
 15. History of genetic or acquired immune suppression disease such as human immunodeficiency virus (HIV), subjects on immune suppressive therapy for organ transplant.
 16. Life-threatening illness or organ system dysfunction compromising safety evaluation.
 17. Requirement for hemodialysis or peritoneal dialysis.
 18. Inability to swallow pills, malabsorption syndrome or gastrointestinal disease that severely affects the absorption of tivozanib or sorafenib, major resection of the stomach or small bowel, or gastric bypass procedure.
 19. Psychiatric disorder or altered mental status precluding informed consent or necessary testing.
 20. Participation in another interventional protocol.

6.3 Drugs and Other Treatments to be Excluded

The following medications/treatments are prohibited during the study:

1. Chemotherapy, biological therapy (including cytokines, signal transduction inhibitors, monoclonal antibodies), immunotherapy or any other therapy for RCC.
2. Systemic hormonal therapy, with the exception of:
 - Hormonal therapy for appetite stimulation or contraception
 - Nasal, ophthalmic, inhaled and topical steroid preparations
 - Androgen suppression therapy for non-metastatic prostate carcinoma
 - Hormone replacement therapy for conditions such as adrenal insufficiency, hypothyroidism, etc.
 - Low-dose maintenance steroid therapy (equivalent of prednisone \leq 10 mg/day) for other conditions.

3. Treatment with radiotherapy.
4. Herbal preparations/supplements (including daily multivitamin/mineral supplement containing herbal components) or topical ointments containing herbal components.
5. Treatment with strong cytochrome P450 (CYP3A4) inducers or inhibitors (see [Appendix C](#)).
6. Treatment with full dose oral anticoagulants such as warfarin, acenocoumarol, fenprocoumon, or similar agents unless they have been on a stable dose for more than 2 weeks prior to enrollment. Full dose anticoagulation with low molecular weight heparin or unfractionated heparin administered subcutaneously is allowed.

7 TREATMENT OF SUBJECTS

Study drug is to be administered only to subjects who have provided informed consent and meet all of the criteria outlined in [Sections 6.1](#), Subject Inclusion Criteria, and [6.2](#), Subject Exclusion Criteria.

7.1 Procedures/Parameters to be Measured

See the Study Flowchart ([Table 1](#), beginning on page 12) for the timing of the procedures to be performed at each visit.

All subjects will be assessed by scheduled clinical, laboratory, and other diagnostic assessments throughout the study. Subjects will be treated on an outpatient basis, unless hospitalization is required for other reasons.

Subjects must voluntarily sign and date the study-specific Institutional Review Board (IRB)/Ethics Committee (EC)-approved informed consent before any study-related procedures (with the exception of disease assessment for screening if it was completed as part of standard of care) are performed.

All screening assessments are to be performed within **21 days** prior to first study drug dose, unless otherwise specified.

The day of first study drug administration will be considered **Day 1** of the study.

Clinic visits will take place according to the schedule of assessments. The visit window of ± 2 working days does not apply to study drug administration. Visit assessments will be performed prior to administration of the study drug for that day.

If significant changes from baseline are noted during the course of the study, additional unscheduled clinic visits may be undertaken by the investigator, or requested by the sponsor, in order to determine both the relevance of the finding(s) and the duration of the event(s).

All end-of-treatment assessments are to be performed within **7 days** following the last study drug dose unless delayed due to the occurrence of an adverse event. Note: subjects starting any new anti-cancer therapy must complete the End-of-Treatment Visit prior to starting the new anti-cancer therapy.

A follow-up visit will be performed **30 days (± 7 days)** following the last dose of study drug.

After the 30-Day Follow-up visit, subjects will be contacted once every 3 months by the site to collect long-term survival data.

Informed Consent

All subjects must take part in the informed consent process. Adequate time must be allowed for the subject to ask questions and make a voluntary decision. No protocol specific procedures, including screening procedures are to be performed until the subject has signed and dated an IRB/EC approved informed consent form (ICF). The signing of the ICF can occur outside of the 21-day screening period; however, all protocol related procedures must only be performed after signing of the consent.

Demographic/Medical History

A complete medical history will be taken. Information to be documented includes demographic information (age, gender, ethnicity, and race), prior and ongoing medical illnesses and conditions, and surgical procedures (not related to the primary diagnosis).

Note: Data will be collected according to local regulations.

Disease History

This information should include the date of initial diagnosis, date of most recent relapse, staging at study entry, prior anti-cancer therapies (including radiation therapy) and/or surgeries, current signs and symptoms of malignant disease, metastatic sites of disease, and measurement of target lesions. For prior antineoplastic treatments, start and end dates of treatments, and method by which disease progression was confirmed (eg, CT, MRI).

IMDC Risk Category

The IMDC risk category will be determined according to the IMDC criteria (see [Appendix H](#)).

Prior and Concomitant Medications

Prior medications will be collected at the time of screening. All concomitant medications will be collected from time the subject signs the ICF throughout the subject's participation in the study, including a period of 30 days after their last dose of study drug.

Adverse Event Assessments

Refer to Section 12 for information regarding adverse events reporting requirements.

Eastern Cooperative Oncology Group (ECOG) Performance Status

Subject's performance status will be assessed using the ECOG performance status tool (see [Appendix B](#)).

Vital Sign Measurements

Vital sign measurements will be collected after the subject has been sitting for 5 minutes. Vital sign assessments will include measurements of diastolic and systolic blood pressure (mmHg), heart rate (beats per minute), respiration rate (breaths per minute), and body temperature (Celsius).

Physical Examination

A complete physical examination (PE) will be performed at screening by a physician or staff member who is qualified to perform such examinations (eg, physician's assistant, or nurse

practitioner). The complete PE will include a thorough review of all body systems and include measurements of weight (kg) and height (cm).

At all other visits throughout the study, a directed PE, including weight (kg), will be completed in a targeted manner covering body systems related to the subject's disease or relevant findings in the complete PE performed at the Screening visit.

Hematology

Hematology assessments are to include complete blood count (CBC) with differential and platelet count. Hematology evaluations should be increased in frequency in the event of a clinically significant hematologic toxicity.

Serum Chemistries

Serum chemistry assessments are to include measurements of sodium, potassium, chloride, bicarbonate (optional), blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase, calcium, magnesium, phosphorus, albumin, amylase, lipase, and total protein.

Thyroid Function Tests

Thyroid function tests are to include measurements of thyroid stimulating hormone (TSH), total T3 (triiodothyronine) (optional), and free T4 (thyroxine).

Coagulation Parameters

Coagulation parameter assessments are to include measurements of prothrombin time (PT) and/or international normalized ratio (INR), and partial thromboplastin time (PTT).

Urinalysis

Urinalysis assessments are to include determinations of protein, glucose, ketones, urobilinogen, occult blood, and microscopic sediment evaluation. A 24-hour urine for protein will be performed whenever protein is 4+.

Pregnancy Test

A serum pregnancy test will be performed on all females of childbearing potential within 7 days prior to the first dose of study drug.

12-Lead Electrocardiogram (ECG)

ECGs will be performed after subjects have been supine for approximately 10 minutes. Assessment of normal, abnormal, not clinically significant, and abnormal, clinically significant (with reason noted) will be collected in the electronic case report form (eCRFs).

Disease/Response Assessment

Disease and response assessments will be determined using RECIST (Version 1.1, [Appendix A](#)).

Disease/response assessment is to include disease classification (including details of the primary diagnosis and histological/cytological type and stage of disease at Screening) and diagnostic imaging / measurement of lesions.

The same method of assessment and the same technique should be used throughout the study. CT and MRI will be considered the standard method for evaluating disease status. All subjects should have a CT scan or MRI of the head, chest, abdomen, and pelvis at baseline. During subsequent disease/response assessments, a CT scan or MRI of the head will only be required if the subject had brain metastasis at baseline or new symptoms suggestive of brain metastasis. The location of target and non-target lesions and dimensions of target lesions will be documented on the subject's eCRF, where such information is available.

Response assessment and updates will be performed and documented. Response assessment will continue until the time of disease progression or start of another anti-cancer therapy.

If disease progression is documented at any time, no further imaging or lesion measurements will be required. Diagnostic studies documenting disease response must be available for review by the sponsor, if requested.

In the event of an objective response, the duration of the response will be determined from the day the initial response is observed (using screening/baseline images for comparison) to the day that progression is observed. Duration of disease stabilization will also be assessed (see Appendix A). In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimal interval of 8 weeks.

Pharmacokinetics

Blood samples for the analysis of pharmacokinetic parameters of tivozanib or sorafenib will be collected from all subjects. Samples will be collected at Cycle 1, Day 1- 4 hours post-dose and at Cycle 1, Day 15- pre-dose (within 2 hours before dosing).

Study Drug Administration Diary

A Study Drug Administration Diary will be provided to the study subjects at the start of each cycle. Diary information will be recorded and/or collected from each subject during study visits.

7.1.1 Screening Visit

All subjects must provide written informed consent before any protocol-related tests are performed. All screening assessments are to be performed within 21 days prior to first study drug dose, unless otherwise specified; all other assessments will be performed prior to dosing unless otherwise stated. At the screening visit, the following procedures and evaluations will be performed:

- Medical and disease history
- Concomitant medications
- Adverse event assessments
- ECOG performance status
- IMDC risk category
- Vital sign measurements
- Complete PE

- Hematology
- Serum chemistries
- Coagulation parameters
- Thyroid function tests
- Urinalysis
- Pregnancy test (*to be performed within 7 days prior to first study drug dose*)
- 12-lead ECG
- Disease assessment (CT scan or MRI scan) of head, chest, abdomen, and pelvis – *may be performed within 30 days prior to first dose*

7.1.2 Cycle 1, Day 1 (Baseline) Visit

At the Cycle 1, Day 1 Visit, the following procedures and evaluations will be performed:

- Concomitant medications
- Adverse event assessments
- Study drug administration
- ECOG performance status
- Vital sign measurements
- Directed PE
- Hematology
- Serum chemistries
- Coagulation parameters
- Urinalysis
- Pharmacokinetics sample at hour 4 post dose
- Distribute study drug diary

Note: If ECOG performance status, PE, hematology, serum chemistry, coagulation parameters, and urinalysis were measured/performed within 7 days prior to this visit, they need not be repeated.

7.1.3 Cycle 1, Day 15 Visit (± 2 days)

At the Cycle 1, Day 15 Visit, the following procedures and evaluations will be performed:

- Concomitant medications
- Adverse event assessments
- Study drug administration
- ECOG performance status

- Vital sign measurements
- Directed PE
- Hematology
- Serum chemistries
- Coagulation parameters
- Pharmacokinetic sample pre-dose (within 2 hours before dosing)
- Urinalysis
- Review Study Drug Administration Diary

7.1.4 Cycle 2, Day 1 Visit (± 2 days)

At the Cycle 2, Day 1 Visit, the following procedures and evaluations will be performed:

- Concomitant medications
- Adverse event assessments
- Study drug administration
- ECOG performance status
- Vital sign measurements
- Directed PE
- Hematology
- Serum chemistries
- Coagulation parameters
- Thyroid function tests
- Urinalysis
- Review Study Drug Administration Diary from previous cycle
- Distribute Study Drug Administration Diary

7.1.5 Every 8 weeks from Cycle 1, Day 1 (± 3 days)

Every 8 weeks (± 3 days), the following procedures and evaluations will be performed:

- Disease/response assessment (CT scan or MRI scan)

The assessment should be done during scheduled visits where appropriate and possible.

7.1.6 Subsequent Cycles – Day 1 Visit (± 2 days)

At subsequent cycle Day 1 visits, the following procedures and evaluations will be performed:

- Concomitant medications
- Adverse event assessments

- Study drug administration
- ECOG performance status
- Vital sign measurements
- Directed PE
- Hematology
- Serum chemistries
- Coagulation parameters
- Thyroid function tests – *every even-numbered cycle beyond Cycle 2 (ie, Cycle 4, 6, 8, etc)*
- Urinalysis
- Review of Study Drug Administration Diary from previous cycle
- Distribute Study Drug Administration Diary

7.1.7 End-of-Treatment

At the End-of-Treatment Visit, the following procedures and evaluations will be performed up to 7 days after last dose of study drug:

- Concomitant medications
- Adverse event assessments
- ECOG performance status
- Vital sign measurements
- Directed PE
- Hematology
- Serum chemistries
- Coagulation parameters
- Thyroid function tests
- Urinalysis
- Pregnancy test
- 12-lead ECG
- Disease/response assessment (CT scan or MRI scan): If a subject has already undergone a tumor assessment within 30 days prior to the End-of-Treatment Visit that shows disease progression as confirmed by IRR, a repeat scan is not necessary at the End-of-Treatment Visit.
- Review Study Drug Administration Diary

Note: Assessments performed within 3 days of the End-of-Treatment Visit need not be repeated.

7.1.8 30-Day Follow-Up Visit (\pm 7 days)

At the 30-Day Follow-Up Visit, the following procedures and evaluations will be performed:

- Concomitant medications
- Adverse event assessment
- ECOG performance status
- Vital sign measurements
- Directed PE
- Hematology
- Serum chemistries
- Coagulation parameters
- Thyroid function tests
- Urinalysis
- 12-lead ECG

7.1.9 Unscheduled Visits (To Occur as Needed)

If additional visits are needed, the following procedures may be obtained/performed/measured as clinically indicated:

- Concomitant medications
- Adverse event assessments
- ECOG performance status
- Vital sign measurements
- Directed PE
- Hematology
- Serum chemistries
- Coagulation parameters
- Thyroid function tests
- Urinalysis
- Review Study Drug Administration Diary
- Pregnancy Test
- 12-Lead ECG
- Disease/Response assessment (CT scan or MRI scan)

7.1.10 Long Term Response and Survival Follow-Up

- All subjects will be followed until death from any cause (unless the subject is lost to follow-up, withdraws consent for the entire study, or the Sponsor terminates the study early). After the 30-Day Follow-up visit, subjects will be contacted once every 3 months by the site to collect long-term survival data. Additional contacts may be made to support key analyses, such as the analysis of overall survival at the time of the final PFS analysis, and the final analysis of overall survival.
- Response assessment (CT scan or MRI scan): for subjects with ongoing objective response or disease stabilization at the time of treatment discontinuation, who discontinue for reasons other than radiological evidence of progressive disease, tumor assessments will continue to be collected (every 2 months during the first year [beginning from the date of the last scan performed prior to treatment discontinuation], every 3 months during the second year, and every 6 months thereafter) until disease progression is confirmed by independent radiology review or the start of another anti-cancer therapy (see [Section 7.2.4](#)).

7.2 Study Drug Administration

7.2.1 Tivozanib Administration

Tivozanib will be administered orally, at a dose of 1.5 mg/day, beginning on Day 1 of Cycle 1. Subjects will receive tivozanib once daily for 3 weeks followed by 1 week off study drug (1 cycle = 3 weeks on, 1 week off). One cycle will be defined as 4 weeks of treatment. Cycles will be repeated every 4 weeks.

The prescribed daily dose of tivozanib is to be taken, preferably in the morning, with water. Tivozanib should be taken at least 1 hour before or 2 hours after ingesting any food or other medications. Grapefruit juice should not be ingested during the study. On days of a scheduled clinic visit, the dose of tivozanib should be taken at the clinic after visit procedures are completed. Treatment with tivozanib will continue if tolerated and in the absence of documented disease progression. If a dose is vomited or if a dose is missed for any reason, the dose should not be made up. If Day 1 of a cycle is delayed for any reason, the complete 21 days of tivozanib should be administered once the cycle is started. Only one tivozanib capsule should be taken each day.

7.2.2 Sorafenib Administration

Sorafenib will be administered orally, at an initial dose of 400 mg twice daily continuously, beginning on Day 1 of Cycle 1. One cycle will be defined as 4 weeks of treatment. Cycles will be repeated every 4 weeks.

Sorafenib should be taken without food at least 1 hour before or 2 hours after ingesting any food or other medications. On days of a scheduled clinic visit, the dose of sorafenib should be taken at the clinic after visit procedures are completed. Treatment with sorafenib will continue if tolerated and in the absence of documented disease progression. If a dose is vomited or if a dose is missed during a cycle for any reason, the dose should not be made up. If Day 1 of a cycle is delayed for any reason, the complete 28 days of sorafenib should be administered once the cycle is started.

7.2.3 Review of Safety Data During Study

The investigator(s) and medical monitor(s) will review safety data on an ongoing basis throughout the study and make decisions regarding the advisability of continuing accrual to the study. In order to do so, the following will occur:

- All serious adverse events (SAEs) must be reported to the sponsor within 24 hours of the investigator becoming aware of the SAE (see [Section 12.3](#), Serious Adverse Events).
- The Adverse Events pages of the subject's eCRF should be promptly completed (ie, within 2 weeks) of a subject's visit (or being discontinued from the study).

7.2.4 Duration of Study Treatment

Subjects with documented stable disease or an objective response may continue to receive therapy at the same dose and schedule until disease progression or unacceptable toxicities occur, or if other withdrawal criteria are met, as outlined in [Section 11.1](#).

Discontinuation: Subjects experiencing unacceptable toxicities will be discontinued from further study treatment. Subjects with radiological evidence of progressive disease (per RECIST Version 1.1) per investigator/local radiology assessment should continue treatment until progressive disease is verified by an independent radiologist. Images should be submitted for independent review as soon as possible (see Imaging Manual for specific instructions). Verification of progressive disease is not required in the following circumstance:

- Significant clinical deterioration that is compatible with progressive disease.

Subjects who have documented disease progression (as verified by an independent radiologist) will be discontinued from the study treatment.

7.2.5 Duration of Follow-Up

Follow-up safety evaluations will be conducted 30 days following the subject's last dose of study drug. This period will be extended if any observed toxicity, thought to be associated with study drug, has not resolved or returned to baseline.

Note: The occurrence of any significant post-therapy event thought to be associated with study drug must be reported to the sponsor.

Subjects starting any new anti-cancer therapy must complete the End-of-Treatment Visit prior to starting the new anti-cancer therapy. Adverse Event Assessment will be conducted in order to confirm that all events have resolved, stabilized, or returned to baseline and that no longer-term deleterious effects of study drug administration have become evident.

In the event that a subject has an ongoing objective response or disease stabilization at the time of treatment discontinuation, who discontinues for reasons other than radiological evidence of progressive disease (per RECIST Version 1.1, as confirmed by independent radiology review), tumor assessments will continue to be collected (every 2 months during the first year [beginning from the date of the last scan performed prior to treatment discontinuation], every 3 months during the second year, and every 6 months thereafter) until disease progression (per RECIST Version 1.1) is confirmed by independent radiology review

the start of another anti-cancer therapy, or discontinuation of the subject from overall study participation (ie, death, subject withdrawal of consent, or loss to follow-up, or study closure).

After discontinuation from all study treatment, follow-up information for long-term survival and subsequent anti-cancer therapy, if available, will be obtained every 3 months from the End of Treatment Visit or 30-Day Follow-up Visit (whichever is later) until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first. Additional contacts may be made to support key analyses, such as the analysis of overall survival at the time of the final PFS analysis, and the final analysis of overall survival.

7.3 Prior and Concomitant Medications

All concomitant medications or medication administered will be collected from the time the subject signs the ICF throughout their participation in the study, including a period of 30 days after last dose of study drug. These data must be recorded on the appropriate eCRF along with the indication for which it was used. The generic name of the drug must be specified along with the start date, stop date, and route of administration. Additionally, any diagnostic, therapeutic, or surgical procedure performed during the study period must be recorded on the eCRF, including the date, indication, description of the procedure(s) and any clinical finding.

Any medication considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator. Drugs and treatment specifically excluded are described in [Section 6.3, Drugs and Other Treatments to be Excluded](#).

7.4 Randomization and Blinding

The IWRS will be used for randomization and drug management (packaging of clinical supplies, shipping to study sites, and dispensing to subjects).

Subjects will be randomized in a 1:1 ratio (tivozanib: sorafenib) stratified by IMDC risk category (favorable; intermediate; poor) and prior therapy (two prior VEGFR TKIs; a prior checkpoint inhibitor [PD-1 or PD1 L inhibitor] plus a prior VEGFR TKI; a prior VEGFR TKI plus any other systemic agent). Once the strata have been identified, treatment will be randomly assigned to a subject within the strata using a complete permuted block design, in an unblinded fashion (open-label). In the event a subject had both 2 TKIs and a checkpoint inhibitor, the subject will be stratified according to the most recent line of therapy.

Subjects must begin treatment with study drug within 14 days after randomization.

8 STUDY DRUG MATERIALS AND MANAGEMENT

For purposes of this study, "study drug" will refer to either tivozanib or sorafenib. Complete study drug information (packaging, labeling, storage, disposition, etc.) is provided in [Appendix F, Tivozanib Study Drug Information](#) and [Appendix E, Sorafenib Prescribing Information](#).

All study drug information will be recorded on the Drug Dispensing Log or other appropriate study drug inventory. This inventory will be maintained throughout the duration of the study and will be periodically reviewed by a representative of the sponsor.

8.1 Study Drug

Prior to the start of the study, the sponsor will provide labeled supplies of tivozanib to the study center investigational pharmacy. Tivozanib is formulated for oral administration as a white opaque number 4 gelatin capsule containing 1.0 or 1.5 mg tivozanib. Sorafenib is formulated for oral administration as a round, biconvex, red film-coated tablet, debossed with the “Bayer cross” on one side and “200” on the other side.

8.2 Study Drug Packaging and Labeling

Tivozanib will be packaged and labeled by the sponsor according to all local legal requirements. Tivozanib will be labeled in accordance with applicable regulatory requirements.

8.3 Study Drug Shipment

Study drug will be shipped to the site via Randomization and Trial Supply Management system after the first subject has been screened, instead of after site activation or a site initiation visit. Exceptions to this process will be allowed after careful review by the sponsor.

8.4 Dispensing of Study Drug and Dosing Compliance

The amount of study drug dispensed to the subject at the beginning of each dosing cycle will be sufficient to allow for 3 weeks (21 days) of consecutive once-daily dosing of tivozanib or 4 weeks (28 days) of consecutive twice-daily dosing of sorafenib.

- The investigator (or designee) will be responsible for determining the amount of drug and the appropriate dosage strength to dispense to the subject at the beginning of each cycle.
- The investigator (or designee) will be responsible for recording this information on the Drug Dispensing Log or other appropriate study drug inventory. This inventory will be maintained throughout the duration of the study and will be periodically reviewed by a representative of the sponsor.

The investigator (or designee) will instruct the subject that all dispensed pill bottles must be returned at each follow-up visit, at which time a tablet/capsule count will be conducted to assure subject dosing compliance.

8.5 Study Drug Storage

Tivozanib does not have any special storage requirements, and may be stored at room temperature in a dry place, in a secure location. Sorafenib is to be stored at room temperature (15°–25° C) in a dry place, in a secure location.

8.6 Study Drug Accountability

The US Food and Drug Administration (FDA) and other regulatory agencies require accounting for the disposition of all investigational drugs received by each clinical site. Information on drug disposition required by law consists of the date received, date administered, quantity administered, and the subject to whom the drug was administered. The principal investigator is responsible for the accounting for all unused study drugs and all used

study drug containers. The investigator must maintain a complete and current dispensing and inventory record that has been supplied by the sponsor.

8.7 Study Drug Handling

At the termination of the study, a final drug accountability review and reconciliation must be completed and any discrepancies must be investigated and their resolution documented.

8.7.1 Disposition of Used Supplies

At the completion of a subject's participation in the study, all partially used and empty pill bottles must be returned to the investigator (or designee) so that a final subject-dosing inventory may be conducted. This information will be recorded on the Drug Dispensing Log.

8.7.2 Inventory of Unused Supplies

Periodically throughout and at the conclusion of the study, an inventory of unused bottles of study drug will be conducted by a representative of the sponsor.

9 ASSESSMENT OF ACTIVITY

9.1 Disease Classification and Response Assessments

Data on disease classification and the duration of disease stabilization or any objective response, as well as the time to disease progression, will be collected for all subjects. Subjects will undergo disease assessment at screening (within 30 days prior to first dose of study drug) and every 8 weeks following Cycle 1, Day 1 until radiological disease progression is documented and confirmed by independent radiology review. Response will be determined by RECIST (Version 1.1) criteria ([Appendix A](#)).

Disease parameters to be assessed:

- Disease classification
- Diagnostic imaging/measurement of target lesions
- Response assessment.

Disease Classification

Details of the primary diagnosis should be documented at the Screening Visit. The histological/cytological type and stage of disease should be noted on the eCRF.

Diagnostic Imaging/Measurement of Lesions

Subjects should be followed with the same imaging procedure throughout this study; if progressive disease (PD) is documented at any time per RECIST Version 1.1, no further imaging or lesion measurements will be required after PD is verified by an independent radiologist; diagnostic studies documenting response must be available for sponsor review.

Response Assessment

Response will be assessed as detailed in [Appendix A](#) using RECIST criteria Version 1.1. All subjects who receive a minimum of 2 cycles of study drug will be considered evaluable for response assessment. All subjects who develop early progressive disease (regardless of the

duration of the study treatment) prior to response evaluation will be considered to have progressed on study.

The duration of any objective response is to be measured from the date the initial response is observed to the date that disease progression is observed. In the case of SD, follow-up assessments must have met the SD criteria at least once after study entry, at a minimal interval of 8 weeks.

Response Assessment Update

In the event that a subject has an ongoing objective response or disease stabilization at the time of treatment discontinuation, who discontinues for reasons other than radiological evidence of progressive disease, tumor assessments will continue to be collected (every 8 weeks during the first year, every 3 months during the second year, and every 6 months thereafter) until disease progression is confirmed by independent radiology review or the start of another anti-cancer therapy. Data will continue to be collected on the duration of objective response or disease stabilization, as well as on the overall time to disease progression until the subject experiences disease progression as confirmed by independent radiology review, or starts another anti-cancer therapy.

10 MANAGEMENT OF TOXICITY

Comprehensive assessments of any toxicity experienced by the subject will be performed throughout the course of this study. Anticipated toxicities that may be experienced are detailed in [Section 3.1](#), Background; [Section 13](#), Precautions; and in the Investigator's Brochure (IB). Grades of toxicity (NCI Common Terminology for Adverse Events [CTCAE Version 4.03]), as well as clinical judgment, will be used to determine appropriate management of the subject experiencing any adverse event while participating in this study.

10.1 Grading and Recording of Toxicity

Any significant clinical adverse event, whether observed by the investigator, or observed or experienced by the subject, will be reported. Any clinically significant change from baseline in a laboratory parameter will be reported as an adverse event. All clinical and laboratory adverse events must be carefully evaluated for the following minimum criteria:

- Severity (see Appendix G; mild, moderate, severe, life-threatening, fatal)*
- Duration
- Relationship to study drug (Yes / No).

*Note: In cases for which further definition of an event is provided by the NCI Common Terminology Criteria for Adverse Events Version 4.03, please refer to this document for grading and severity information.

This information is to be documented on the appropriate page of the eCRF.

10.2 Evaluation and Treatment of Toxicity

The principal investigator, sub-investigator, or designated health professional must be available throughout the course of the study in order to evaluate and treat any adverse

event(s), as well as to evaluate whether continued participation in the study is warranted or advisable.

If, at any point during the study, significant changes occur in either the subject's clinical status or laboratory parameters, such changes will be followed until the parameter(s) either returns to baseline or is adequately explained.

10.3 Management of Skin Toxicities (Sorafenib)

Management of skin toxicity associated with sorafenib is outlined in Table 3. Please refer to sorafenib prescribing information for additional information (see [Appendix E](#)).

Table 3: Management of Skin Toxicity Associated with Sorafenib

Skin Toxicity Grade	Occurrence	Suggest Dose Modification
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	First occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief If no improvement within 7 days, see below.
	No improvement within 7 days or second or third occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0–1 When resuming treatment, decrease sorafenib dose by one dose level.
	Fourth occurrence	Discontinue sorafenib treatment. Continue follow-up with regular tumor assessments until disease progression or start of new treatment, and for survival thereafter.
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet or severe discomfort that causes the patient to be unable to work or perform activities of daily living	First or second occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0–1 When resuming treatment, decrease sorafenib dose by one dose level (400 mg daily or 400 mg every other day)
	Third occurrence	Discontinue sorafenib treatment. Continue follow-up with regular tumor assessments until disease progression or start of new treatment, and for survival thereafter.

10.4 Study Drug Administration Modification

Clinical judgment will be used to determine appropriate management of the subject during any AE. The criteria for dose modification for drug-related AEs (excluding hypertension and

skin toxicity) are summarized in Table 4. Further management is at the discretion of the investigator, who may discuss this with the medical monitor if necessary.

Table 4: Dose Modification Guidelines for Drug-Related Adverse Events

Drug-Related Adverse Events (excluding Hypertension¹ and Skin Toxicity²)	Intervention
Grade 1	Continue treatment at same dose
Grade 2	Continue treatment at same dose
Grade 3	Decrease dose (see Section 10.4.2 for tivozanib and Section 10.4.3 for sorafenib dose reduction guidelines)
Grade 4	Interrupt dosing; restart at lower dose as soon as toxicity improves to \leq Grade 2 (see Section 10.4.1 for tivozanib and Section 10.4.3 for sorafenib dose reduction guidelines)

¹ Hypertension must be treated as described in Section 10.4.1 prior to dose modification

² Skin toxicity should be managed as described in [Section 10.2](#)

10.4.1 Tivozanib Dose Reduction

Dose reductions of tivozanib to 1.0 mg/day will be allowed for subjects with \geq Grade 3 drug-related adverse events. The exception is hypertension, which must be treated with anti-hypertensive drugs (see [Appendix D](#)) prior to dose reduction.

The dose of tivozanib may be reduced to 1.0 mg/day. Once the dose of tivozanib is reduced, it may not be re-escalated throughout the study. If a subject is unable to tolerate a dose of 1.0 mg/day due to toxicities thought to be related to tivozanib, dosing with tivozanib should be discontinued.

Any modification of study drug administration, and the reason for such action, must be clearly noted on the subject's eCRF using the Adverse Events reporting page.

10.4.2 Tivozanib Dose Interruption

Subjects with Grade 4 drug-related toxicity, or Grade 3 drug-related toxicity that is persistent despite appropriate medical care, should have their dose interrupted to allow for resolution of the toxicity. Tivozanib may be interrupted for up to 4 weeks. If a subject is able to resume treatment after interruption of \leq 4 weeks, missed doses will not be made up (ie, cycle duration will remain unchanged). If any drug-related toxicity results in interruption of $>$ 4 weeks, the subject should be discontinued from the study unless there is clear benefit from treatment, in which case the investigator must contact the medical monitor to review the subject's condition in order to resume treatment. Subjects removed from treatment for reasons other than radiological evidence of progressive disease should still be followed with regular tumor assessments (see [Section 7.2.4](#)) until disease progression is confirmed by independent radiology review or start of new treatment, and for survival thereafter.

Any modification of study drug administration, and the reason for such action, must be clearly noted on the subject's eCRF using the Adverse Events reporting page).

10.4.3 Sorafenib Dose Reduction

Dose modification will be allowed for subjects with \geq Grade 3 drug-related adverse events. Skin toxicity associated with sorafenib should be managed as shown in [Section 10.2](#), Management of Skin Toxicities (Sorafenib), prior to dose reduction. The dose of sorafenib will be reduced to 400 mg once daily. If toxicities do not resolve, sorafenib may be further reduced to 400 mg once every other day. If a subject is unable to tolerate a dose of 400 mg once every other day due to toxicities thought to be related to sorafenib, treatment should be interrupted. If toxicities resolve to \leq Grade 1, the dose may be re-escalated to the previous dose level at the discretion of the investigator. For management of specific sorafenib-related toxicities, please refer to the sorafenib prescribing information ([Appendix E](#)).

Any modification of study drug administration, and the reason for such action, must be clearly noted on the subject's eCRF (using the Adverse Events reporting page).

10.4.4 Sorafenib Dose Interruption

Subjects with Grade 4 toxicity, or Grade 3 drug-related toxicity that is persistent despite dose reduction and appropriate medical care, should have their treatment interrupted to allow for adequate resolution of the toxicity. Sorafenib may be interrupted for up to 4 weeks. If a subject is able to resume treatment after interruption of \leq 4 weeks, missed doses will not be made up (ie, cycle duration will remain unchanged). If any drug-related toxicity results in interruption of $>$ 4 weeks, the subject should be discontinued from the study unless there is clear benefit from treatment, in which case the investigator must contact the medical monitor to review the subject's condition in order to resume treatment. Subjects removed from treatment for reasons other than radiological evidence of progressive disease should still be followed with regular tumor assessments (see [Section 7.2.4](#)) until disease progression is confirmed by an independent radiology review or start of new treatment, and for survival thereafter.

11 REMOVING SUBJECTS FROM STUDY

Every reasonable effort will be made to keep the subject in the study; however, in the event that a subject withdraws consent from study participation, every effort will be made by the investigator to complete and report the reasons for withdrawal as thoroughly as possible. This evaluation should include final observations, as required by the protocol at the time of the subject's withdrawal. The reason(s) for study termination must be clearly documented in the source documents and on the appropriate page of the eCRF. A Termination eCRF must be completed for any subject who is randomized.

11.1 Criteria for Treatment Discontinuation (Stopping Rules)

Subjects will be discontinued from further treatment with study drug in the event of any of the following:

1. Death
2. Unacceptable toxicity considered by the investigator to require removal of the subject from study treatment.

Note: Adverse events resulting in a subject's permanent discontinuation from the study treatment, regardless of seriousness or relationship to study drug, MUST be promptly reported to the sponsor/designee. Subjects removed from treatment for intolerable toxicity should still be followed with regular tumor assessments (see Section 7.2.4) until disease progression or start of new treatment, and for survival thereafter.

3. Documented progressive disease according to RECIST Version 1.1 at any time during the study.
4. Subjects with radiological evidence of progressive disease per investigator/local radiology assessment should continue treatment until progressive disease is verified by an independent radiologist. Images should be submitted for independent review as soon as possible (see Imaging Manual for specific instructions). Verification of progressive disease is not required in the following circumstance:
 - Significant clinical deterioration that is indicative of progressive disease.
5. Subjects who have documented disease progression will be discontinued from study drug treatment and will continue to be followed up for survival.
6. Clinical progression (eg, symptomatic deterioration) not meeting the RECIST Version 1.1 criteria for radiological evidence of progressive disease but considered by the investigator to require removal of the subject from study. This includes subjects with significant clinical deterioration that is indicative of progressive disease. All related signs and symptoms of clinical progression must be captured in AE eCRF page, the term "progressive disease" should not be recorded as an adverse event or captured on the eCRF page.
7. Treatment interruption for > 4 weeks (ie, total duration of interruption, including the 1 week/cycle break in dosing of tivozanib), unless there is clear benefit from treatment, in which case the investigator must contact the medical monitor to review the subject's condition in order to resume treatment.
8. Requirement for a significant surgical procedure.

Note: Subjects requiring a minor surgical procedure (eg, port placement, skin abscess drainage) may continue on study at the investigator's discretion following discussion with the medical monitor. A brief interruption in therapy (< 4 weeks) may be considered.
9. An intercurrent illness which, in the opinion of the investigator, would prevent completion of study-related evaluations.
10. Significant deviation from the protocol or eligibility criteria. Such subjects will be considered protocol violations and will be removed from study unless there is an exemption granted that is agreed upon between the investigator and the sponsor.
11. Pregnancy.
12. Noncompliance with study or follow-up procedures.
13. Subject withdrawal of consent and election to discontinue the study treatment.

Note: The subject is free to withdraw from the study drug and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. In the event of consent withdrawal, the site should make every effort to ensure that the subject is followed for AEs for a

minimum of 30 days after their last dose of study treatment. With documented subject agreement, the investigator will contact the subject for long-term survival follow-up.

14. Termination of the study by the sponsor.
15. Any other reason which, in the opinion of the investigator, would justify removing the subject from the study. In such a case, the investigator's reason for a subject's removal must be recorded on the appropriate eCRF.

Once a subject discontinues study drug treatment for any reason, every effort will be made to collect all clinical and laboratory data as scheduled for the End-of-Treatment Visit and 30-Day Follow-up Visit (see [Section 7.1.7](#) and [Section 7.1.8](#)) as well as long term response and survival follow-up ([Section 7.1.10](#)).

Subjects who are discontinued from study drug for reasons other than progression by RECIST Version 1.1 will undergo scans for tumor assessment according to the original tumor assessment schedule until any of the following occurs, whichever comes first: PD per RECIST Version 1.1 (as confirmed by independent radiology review), initiation of new anti-cancer treatment, or discontinuation of the subject from overall study participation (death, subject withdrawal of consent, loss to follow-up, or study closure).

12 ADVERSE AND SERIOUS ADVERSE EVENTS

Information regarding the occurrence of AEs will be collected from the time the subject signs the ICF throughout their participation in the study, including a period of 30 days after last dose of study drug (data on SAEs will be collected until resolution of the event unless otherwise noted).

All SAEs must be reported to the Sponsor, as delineated in [Section 12.3](#) of this protocol, within 24 hours of the Investigator becoming aware of the event.

12.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline, during a clinical study with a study drug, regardless of causal relationship and even if no study drug has been administered.

AEs may include the following types of occurrences:

- Suspected adverse drug reactions;
- Other medical experiences, regardless of their relationship with the study drug, such as injury, surgery, accidents, extensions of symptoms or apparently unrelated illnesses, and significant abnormalities in clinical laboratory values or vital signs, psychological testing or physical examination findings;
- Reactions from study drug overdose, abuse, withdrawal, sensitivity, toxicity or failure of the study drug's expected pharmacological action.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as the AE and the death as its outcome.

12.1.1 Abnormal Laboratory Findings and Other Objective Measurements

Abnormal laboratory findings or other objective measurements that meet the criteria for a SAE (see Section 12.3) result in discontinuation of the study drug, require medical intervention or are judged by the Investigator to be clinically significant changes from baseline values should be captured and reported on the AE pages of the eCRF.

12.1.2 Medical History

Medical conditions present at the initial study visit are defined as medical history, and are NOT to be considered AEs. These medical conditions should be adequately documented on the medical history page of the eCRF. However, medical history conditions, other than the disease under study, that worsen in severity or frequency during the study and are considered clinically significant by the Investigator should be recorded and reported as AEs.

12.1.3 Exacerbation of Primary Malignancy

In this protocol, symptoms and signs of exacerbation or worsening of primary malignancy will usually be captured in the context of efficacy assessment, and recorded on the pages of the appropriate eCRF. Therefore, symptoms, or signs of exacerbation or worsening of the primary malignancy will not be considered as AEs nor captured on the AE page of the eCRF unless the event is considered possibly or probably related to the study drug (ie, the worsening is not consistent with the anticipated natural progression of the disease), or the subject is discontinued from study drug due to clinical progression without documented progressive disease. In this case the events suggesting clinical progression should be recorded in the eCRF.

12.2 Evaluating Adverse Events

Data on AEs will be obtained at scheduled or unscheduled study visits, based on information spontaneously provided by the subject and/or through questioning of the subject. To elicit AEs, questioning at each study visit should begin with simple non-leading questions. For example:

- How have you felt since your last visit?
- Have you had any health problems since you were here last?

If a subject is seen by a physician not involved with the study in relation to an AE, the Investigator should make every effort to contact the treating physician in a timely manner in order to obtain all information necessary to appropriate reporting of the event.

The Investigator is required to grade the severity/intensity of each AE according to the National Cancer Institute - CTCAE, Version 4.03. A general grading (severity/intensity) scale is provided at the beginning of the NCI-CTCAE document, and specific event grades are also provided. If a particular AE's severity/intensity is not specifically graded by the guidance document, the Investigator is to revert to the general definitions of Grade 1 through Grade 5 and use his or her best medical judgment.

Note: Death is mainly regarded as an outcome and should be documented as described below.

12.3 Serious Adverse Events (SAE)

(Notify sponsor or designee within 24 hours; document on eCRF)

Any SAE requires expedited reporting to the Sponsor's Pharmacovigilance department, regardless of its relationship to the study drug.

An SAE is defined as an AE that at any dose:

- Results in death – ie, the AE causes or contributed to the death of the subject.
- Is life threatening – ie, the AE places the subject at immediate risk of death; the definition does not apply to an AE that hypothetically might cause death if it were more severe.
- Requires or prolongs inpatient hospitalization - ie, the AE requires at least a 24-hour inpatient hospitalization or prolongs a hospitalization beyond the expected length of stay.
 - Hospital admissions for surgery planned before study entry, for social reasons or for normal disease management (including treatment adjustment) is not to be considered as an SAE according to this criterion.
 - Elective hospitalizations to simplify trial treatment or trial procedures (eg, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered as SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (eg, undesirable effects of any administered treatment) must be documented and reported as SAEs.
- **Is a congenital anomaly or birth defect** - ie, an adverse outcome in a child or fetus of a subject exposed to the study drug before conception or during pregnancy.
- **Results in persistent or significant disability or incapacity** - ie, the AE resulted in a substantial disruption of the subject's ability to conduct normal activities.
- **Is a medically important condition**
Such an event may not be immediately life threatening or result in death or hospitalization, but is clearly of major clinical significance. The AE may jeopardize the subject or require intervention to prevent a serious outcome.

For the purposes of reporting, any suspected transmission of an infectious agent via a study drug is also considered a serious adverse reaction and all such cases should be reported in an expedited manner as described above.

12.4 Protocol-Related Adverse Events

AEs that are not study drug-related may nevertheless be considered by the Investigator or the Medical Monitor to be related to the conduct of the clinical study. That is, the event may be related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an event that occurs that is related to a procedure required by the protocol.

12.5 Reporting Period

AEs are collected on an ongoing basis from the time of signature of the written informed consent until 30 days after the last dose of study drug. All subjects who took at least 1 dose of study drug should be followed until 30 days after the last dose of study drug.

It is important that each reported AE (including SAEs) be accurately recorded on the AE page of the subject's eCRF. An AE report includes a description of the event, whether it is considered serious (and if so the criterion satisfied), its duration (onset and resolution dates), its severity (graded using a 5-point scale), its relationship to the study drug as assessed by the Investigator, any other potential causality factors (if known), any method of treatment given or other action taken (including dose modification or discontinuation of the study drug) and its outcome.

New AEs and changes in ongoing AEs or those with an unknown outcome must be recorded until 30 days after the last dose of study drug.

However, any SAE or medically relevant AE that has an ongoing or unknown outcome (as determined by the Medical Monitor and Sponsor's Pharmacovigilance department), will be followed until resolution or stabilization under the responsibility of the Sponsor's Pharmacovigilance department. Beyond the 30-Day Follow-up Visit period, data regarding any new, unsolicited, SAE spontaneously reported to the Sponsor by the Investigator will be collected and processed by the Sponsor's Pharmacovigilance department within the Safety Database, rather than within the Clinical Database. SAEs occurring after the 30-Day Follow-up Visit, which are assessed as related to study drug, should be reported to the Sponsor.

If a subject is documented as lost to follow-up, no further attempt will be made to follow up on ongoing AEs or AEs of unknown outcome.

For screening failure subjects, new SAEs and changes in SAEs will be monitored from the signing of the informed consent until the date the subject was determined to be a screening failure. Beyond that date, SAEs which occurred between the signing of informed consent and determination of screen failure will be followed-up by the Sponsor's Pharmacovigilance department.

12.6 Reporting Serious Adverse Events and Subject Deaths

12.6.1 Timeframe for Reporting

The Investigator must notify the Sponsor (or their designee) within 24 hours of becoming aware of a new SAE or of new (follow-up) information on a previously reported SAE.

To do so, the Investigator/Reporter must complete an SAE Report Form as detailed in the SAE Report Completion Instructions. The SAE Report Form will be transmitted by the Investigator/Reporter to the Sponsor's Pharmacovigilance department/designee for this study.

12.6.2 Reporting of Subject Death

The death of any subject after date of ICF signing and within 30 days of last dose of study drug, regardless of the cause, must be reported by the Investigator or qualified designee to the Sponsor within 24 hours of the day of first becoming aware of the death. Deaths occurring after the 30-day period do not need to be reported as SAEs for this study (however, deaths

occurring at any time after the 30-day follow-up period and which are assessed as related to study drug should be reported to the Sponsor as SAEs). If the report is given via telephone rather than in writing on the form designated for SAE reporting, a full description of the circumstances, including the Investigator-determined causality in relation to the study drug must be provided, so that the appropriate written report can be completed by the designated Sponsor contact.

Reports of all deaths must also be communicated as soon as possible to the appropriate IRB or EC and/or reported in accordance with local law and regulations.

12.6.3 Reporting of Overdose

An overdose of tivozanib or sorafenib is higher than the intended dispensed dose.

Information on overdoses in clinical subjects is collected by the Sponsor's Drug Safety Surveillance department. Should a subject experience an overdose during the course of the study (whether symptomatic or not), the investigator or qualified designee must report to the Sponsor within 5 working days of the investigator or qualified designee first becoming aware of the overdose. Follow-up information on the outcome of the overdose should be forwarded to the Sponsor.

Any event associated with, or observed in conjunction with, a product overdose (whether accidental or intentional) or a product abuse and/or withdrawal is considered an AE and should be reported as such (see [Sections 12.1-12.5](#)). If a serious adverse event occurs in conjunction with the overdose, then the reporting time frame for an SAE (1 working day of first becoming aware of the event) must be met. The Sponsor will provide instructions on how to collect this information.

12.6.4 Reporting to the Institutional Review Board/Ethics Committee

The Investigator must comply with any applicable requirements related to the reporting of SAEs involving his/her subjects to the IRB/EC that approved the study. In particular, all deaths must be promptly reported to the IRB/EC that approved the study.

In accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the Sponsor will inform the Investigator of “findings that could affect adversely the safety of subjects impact the conduct of the study or alter the IRB/EC’s approval/favorable opinion to continue the study.” In line with respective regulations and Sponsor’s policy, the Sponsor will inform the Investigator of adverse events that are both serious and unexpected and are considered to be possibly or probably related to the study drug by the Investigator/Reporter. The Investigator will keep copies of these safety reports in the Investigator file. National regulations with regards to Safety Report notifications to Investigators will be also taken into account.

Unless clearly defined otherwise by national or site-specific regulations, and duly documented, the responsible Investigator will promptly notify the concerned IRB/EC of any Safety Reports provided by the Sponsor and provide copies of all related correspondence to the Sponsor. The Sponsor will provide appropriate Safety Reports directly to the concerned IRB/EC and maintain records of these notifications only when specifically required by regulations.

12.6.5 Information to be Provided by the Investigator

For any new SAE, the initial notification must include the following information at a minimum:

- Clear identification of the Investigator/Reporter with full contact information.
- Subject identification details (study number, site number, initials, date of birth).
- Study drug administration details (dose and dates).
- Diagnosis of the event with the description (or a brief description of signs/symptoms/clinical course if the diagnosis is not available) and the date of onset and duration.
- Reason(s) for considering the event serious.
- Relationship of the event with the study drug or with the study procedure (eg, the causality according to the Investigator).
- Height, weight, or body surface area (where required for dose calculation).
- Underlying diagnosis and extent of disease.
- Lot number and expiration date of study drug (if available).
- Dose, route, frequency, and duration of study drug administered.
- Date of death (if applicable).
- Intervention(s) required.
- Concomitant therapy (including regimen[s] and indication).
- Pertinent laboratory data/diagnostic study (including dates).
- Pertinent medical history.
- Study drug status (dose interrupted, discontinued).
- Did event abate after interruption of study drug administration (if applicable)?
- Did event recur after study drug was reintroduced (if applicable)?

In addition, the Investigator/Reporter must respond to any request for follow-up information or questions the Sponsor may have regarding the SAE within the same timelines as for the initial reports.

12.7 Required Follow-up for All Adverse Events and Serious Adverse Events

Appropriate consultation and follow-up evaluations should be carried out until the event has returned to baseline, has become chronic or stable per the Investigator.

All SAEs must be promptly reported by the Investigator to their IRB/EC. Should the FDA or other regulatory authorities require that the Sponsor submit additional data on the event, the Investigator will be asked to provide those data to the Sponsor in a timely fashion.

Note: All subjects are to be followed for 30 days after last study drug administration in order to monitor for the occurrence of serious and non-serious AEs thought to be associated with study drug. A longer period of time may be specified by the Sponsor if required to assure the safety of the subject. Follow-up data concerning the SAE (eg, diagnostic test reports, physician's summaries, etc.) also must be submitted to the Sponsor, as they become available, preferably by telefax or e-mail transmission, until resolution of the SAE.

12.8 Pregnancy Reporting

All pregnancies in female subjects occurring from the date of Informed Consent signature until at least 30 days after the last study drug administration must be reported to the Sponsor's Pharmacovigilance department.

The Investigator must notify the Sponsor in an expedited manner (as per the same procedures and timelines described for expedited AE reporting in [Section 12.5](#)) by completing Part I of the Pregnancy Reporting and Outcome Form.

Note: Pregnancy itself is not an AE. Only pregnancies considered related to study drug by the Investigator (ie, resulting from a drug interaction with a contraceptive medication) are considered as AEs and should be recorded on the AE eCRF.

Investigators must actively follow-up, document and report to the Sponsor's Pharmacovigilance department the outcome of all these pregnancies, even if the subject was withdrawn from the study. Pregnancy outcomes are not recorded in the eCRF unless considered adverse events (eg, spontaneous abortion, congenital anomaly, etc.).

Pregnancy outcomes must be reported to Sponsor's Pharmacovigilance department by completing Part II of the same Pregnancy Reporting and Outcome Form used for the initial pregnancy notification. Timelines vary according to the nature of the pregnancy outcome:

- For normal outcomes, the Sponsor should be notified within 45 days from birth/delivery.
- For abnormal outcomes, the fully completed form must be sent to Sponsor's Pharmacovigilance department according to the same procedures and timelines described for expedited AE reporting in [Section 12.5](#).

Additional guidance can be found in the completion conventions provided by the Sponsor.

13 PRECAUTIONS

13.1 Precautions Regarding Procreation

Men and women of childbearing potential will be informed as to the unknown risk to procreation while participating in this study and will be advised that they must use effective contraception during the study and follow-up period. Sexually active pre-menopausal female subjects (and female partners of male subjects) must use adequate contraceptive measures, while on study and for at least 90 days after the last dose of study drug. Sexually active male subjects must use adequate contraceptive measures, while on study and for at least 90 days after the last dose of study drug. Effective birth control includes (a) IUD **plus** one barrier method, or (b) two barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm). Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are not considered effective for female subjects in this study.

A pregnancy test will be performed on each premenopausal female of childbearing potential prior to first study drug administration, and again at the end of the treatment and 30-Day Follow-up Visits. A negative pregnancy test prior to administration of the study drug must be documented on the appropriate eCRF.

If it is confirmed that a study participant has become pregnant while participating in this study, study drug administration will be discontinued immediately. Any pregnancy occurring during this study will be reported immediately to the sponsor. The investigator will then report follow-up information to the sponsor regarding the course of the pregnancy, including perinatal and neonatal outcome, regardless of the fact that the subject has discontinued participation in the study. Once the newborn is determined to be healthy, as defined by and agreed upon by the sponsor and investigator, additional follow-up will no longer be required.

13.1.1 Tivozanib

Studies have not been performed to determine whether tivozanib affects reproductive function in males. For this reason, men with partners of childbearing potential must take appropriate contraceptive measures while receiving tivozanib.

It is not known whether tivozanib can cause fetal harm when administered to a pregnant woman or whether tivozanib can affect reproductive capacity. There have been no studies in pregnant women. Tivozanib should only be administered to women of childbearing capability when appropriate contraceptive measures have been taken and when pregnancy tests are negative.

13.1.2 Sorafenib

Sorafenib is classified as Pregnancy Category D. Women of childbearing potential should be advised to avoid becoming pregnant while taking sorafenib.

13.2 Additional Precautions

Tivozanib

Information regarding precautions and adverse events associated with tivozanib can be found in [Section 3](#) (Introduction) and [Section 13](#) (Precautions) of this protocol and in the Investigator's Brochure. Copies of both documents will be provided by the sponsor.

Sorafenib

Information regarding precautions and adverse events associated with sorafenib can be found in [Appendix E](#), Sorafenib Prescribing Information.

14 DATA EVALUATION AND STATISTICS

14.1 General Design

This is a Phase 3, randomized, controlled, open-label, parallel-arm, multi-national, multi-center study to compare tivozanib to sorafenib in subjects with refractory advanced RCC. The primary endpoint is progression-free survival and the primary analysis is to compare the PFS of subjects treated with tivozanib to those treated with sorafenib.

14.2 Sample Size Justification

A sample size of 322 subjects (161 subjects per treatment arm) with total number of 255 events will provide 90% power to detect statistically significant differences between treatment arms with respect to progression-free survival as assessed by the independent radiology review. Analysis of the primary endpoint will occur after 255 events have occurred. A simulation indicates that the analysis could be performed ≥ 6 months after the last subject is accrued. The sample size was determined based on the following assumptions:

- The distribution of the PFS for the two treatment arms will be compared by using a Log-rank test with two-sided 5% significance level (α).
- The median PFS for subjects receiving sorafenib and tivozanib is 4 months and 6 months, respectively (an increase of 2 months or 50%).
- An equal number of subjects will be assigned to each treatment arm.
- Enrollment will take 15 months.
- The drop out percentage per treatment arm will be 3%.

The first secondary analysis will compare OS between the 2 treatment arms by using stratified Log-rank test, the stratification factors included in the primary analysis, and two-sided 0.8% significance level (utilizing a Lan-DeMets alpha spending function with an O'Brien-Fleming boundary). The interim OS analysis will be done at the time of the final PFS analysis. Assuming a median OS for sorafenib of 12 months and a median OS for tivozanib of 16 months, 245 OS events at the time of final OS analysis and 149 OS events at the time of final PFS analysis will yield approximately 61% power to demonstrate longer OS for tivozanib using the log-rank test, given 2.5% type I error (one-sided). The final OS analysis will be performed when all subjects have been lost to follow-up, have withdrawn consent, or have died, or when all subjects in follow-up have been on-study for at least 2 years, whichever occurs first.

The estimate was obtained by using East[®] statistical package Version 6.3 by Cytel Inc.

14.3 Statistical Considerations

All data collected in this study will be documented using summary tables and subject data listings. Demographic, baseline characteristics, efficacy, and safety data will be summarized by treatment arm and the summary will be provided by visit (if applicable).

Descriptive statistics will be provided for every variable. The statistics will include sample size (n), mean, median, standard deviation (STD), minimum, and maximum for continuous variables. Categorical variables will be summarized using number and percentages.

14.3.1 Study Populations

Three populations will be used in the analyses of the data:

1. The intent-to-treat (ITT) population will consist of all randomized subjects; this population will be used for efficacy analysis, including primary endpoint (progression-free survival). Subjects will be analyzed as randomized.

2. The per protocol (PP) population is defined as all randomized subjects who received at least two cycles (8 weeks) of protocol treatment (unless discontinued due to death or disease progression), have no major protocol deviations that will confound the effects of treatment, and meet all eligibility criteria. Major protocol deviations include but are not limited to failure to satisfy eligibility criteria and taking prohibited medications during the treatment phase of the study. Subjects will be analyzed as treated.
3. The safety population (SAF) will include all subjects who received at least one dose of either study drug. Subjects will be analyzed as treated.

14.3.2 Subject Accountability, Demographics, and Baseline Characteristics

All subjects enrolled (signed informed consent) in the study will be included in the summary of subject accountability by treatment arm and region. The frequency and percentages of subjects who were enrolled in the study, discontinued from treatment before having documented disease progression, or discontinued from the study due to documented disease progression will be summarized for the ITT population.

Descriptive statistics of subject demographics (age, gender, ethnicity, and race) and baseline characteristics will be summarized and presented by treatment arm.

14.3.3 Protocol Deviations

A subject will be classified as having a protocol deviation if one incurs an event belonging to any one of the following categories: 1) violation of the inclusion/exclusion criteria; 2) taking prohibited medications or treatments; 3) treatment misallocation; 4) violation of discontinuation criteria; 5) error in procedures and tests; and 6) missed visits. Other deviation categories may be identified as appropriate.

14.3.4 Efficacy

The primary efficacy endpoint (PFS) and secondary efficacy endpoints (OS, ORR, and DoR) analyses will be carried out using the ITT population. The primary efficacy endpoint of PFS also will be analyzed using the PP population.

Analysis of the Primary Endpoint

The primary analysis is to compare the PFS of subjects dosed with tivozanib with those subjects dosed with sorafenib. The null hypothesis is that the median tivozanib PFS is equal to that of sorafenib and the alternative hypothesis is that the two PFS medians are not equal. The IRR will be the primary data source for the PFS analysis.

The primary analysis will be carried out by using a stratified Log-Rank test, in which the stratification factors are IMDC risk category (favorable; intermediate; poor) and prior therapy (two prior VEGFR TKIs; a prior checkpoint inhibitor [PD-1 or PD1 L inhibitor] plus a prior VEGFR TKI; a prior VEGFR TKI plus any other systemic agent), and using a two-sided 5% significance level. The distribution of the PFS will be estimated using the Kaplan-Meier method. The median event time and 2-sided 95% confidence interval for the median will be also provided.

Interim Analysis

An interim analysis will be performed after 128 PFS events have been observed. The interim analysis will look into the study's futility using PFS as the efficacy evaluation endpoint. This will utilize a Lan-DeMets error spending-type function with an O'Brien-Fleming stopping boundary with an estimated two-sided beta (Type II error) of 1.2 % spent during this interim look.

The interim analysis will be performed by an independent statistician. The independent statistician will evaluate and interpret the results of the interim analysis and will provide corresponding recommendation whether to stop the study for futility or for the study to continue until end of study condition has been met.

Final analysis performed on PFS will be based on 255 events. This could be performed ≥ 6 months after the last subject is accrued. PFS interim and final analyses will be carried out by using a stratified Log-Rank test with IMDC risk category and prior therapy as stratification factors.

Handling of Missing Data

For the purpose of PFS analyses, the following steps will be considered in case of missing data:

- a) Subjects with missing imaging at baseline will be considered non-evaluable for PFS estimation and will be excluded from the PFS analyses
- b) Subjects who have no tumor assessment after randomization will have PFS censored at the date of randomization, unless they died before the second scheduled tumor assessment.

Further details and other cases will be described in the statistical analysis plan (SAP).

Analysis of Secondary Endpoints

The secondary endpoints (OS, ORR, and DoR) will be analyzed using the investigator and independent radiological review assessments. The degree of agreement between the investigator and the independent assessment of responses will also be summarized and presented in a table.

The first secondary analysis will compare the OS between the 2 treatment arms by using stratified Log-rank test and the stratification factors included in the primary analysis. An interim OS analysis will be carried out at the time of the Final PFS analysis.

Duration of response (DoR) will be analyzed using the same method as for the progression-free survival.

The proportion of subjects achieving confirmed ORR (complete response [CR]+partial response [PR]) will be summarized and presented by treatment arms and cycle and will be compared between the two treatment arms using Cochran-Mantel-Haenszel (CMH) test with the same stratification factors used for the PFS analysis.

Exploratory Analyses

In order to evaluate if the timing of post-baseline radiological scan influenced the primary outcome, the time from randomization to post-radiological scan will be calculated and an exploratory analyses will be conducted. Means and standard deviation of radiological scan time will be presented by treatment arms and cycle time. Log-rank test will be used to test if cumulative percentages (survival curves) are equal (median time to each cycle from randomization) by treatment arms.

Subgroup Analyses

PFS subgroup analyses by gender, race, and age (< 65 years and \geq 65 years) will be carried out using separate unadjusted Log-rank test for the ITT population.

Definition of Efficacy Endpoints

Progression-Free Survival (PFS) is defined as the time from randomization to first documentation of objective tumor progression (progressive disease [PD], radiological) according to RECIST (Version 1.1) or death due to any reasons whichever comes first. PFS data will be censored on the day following the date of last tumor assessment documenting absence of PD for subjects who do not have objective tumor progression and are still on study at the time of the analysis, are given anti-tumor treatment other than the study treatment, or are moved from treatment follow-up prior to documentation of objective tumor progression. Subjects having no tumor assessments after randomization who are not known to have died will have PFS censored on the date of randomization.

Overall survival (OS) is defined as the time from the date of randomization to date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the subject is known to be alive. Subjects lacking data beyond randomization will have their survival times censored on the date of randomization.

Overall response rate (ORR) is defined as the proportion of subjects with confirmed CR or confirmed PR according to RECIST (Version 1.1), relative to the total population of randomized subjects. Confirmed responses are those that persist on repeat imaging study at least 4 weeks after the initial documentation of response.

Duration of response (DoR) is defined as the time from the first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to any cause. DoR data will be censored on the day following the date of the last tumor assessment documenting absence of PD for subjects who do not have tumor progression and are still on the study at the time of an analysis, are given antitumor treatment other than the study treatment, are removed from the study follow-up prior to documentation of objective tumor progression, died of non-cancer related cause, including death due to unknown cause in the absence of documented disease progression. **DoR will only be calculated for the subgroup of subjects with an objective tumor response (PR or CR).**

14.3.5 Safety Data

The safety parameters (study drug exposure, adverse events, laboratory parameters, vital signs, medical history, concomitant medications, and physical examinations) will be analyzed using the SAF population.

Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA™) Dictionary (Version 18.0 or later). Summary tables will be presented for treatment emergent adverse events by treatment arm. An overall presentation of treatment emergent adverse event information will show the number and percent of subjects with at least one event by treatment arm.

Adverse event information will be also presented by NCI CTCAE severity grade and relationship to study treatment. If a subject had more than one occurrences of an adverse event, the most severe grade or most highly treatment-related category will be used in the summary tables.

All adverse events will be listed. The following listings will be also provided: 1) subjects who died during the study; 2) subjects with treatment emergent SAEs; 3) subjects who discontinued due to treatment emergent AEs; and 4) other significant treatment emergent adverse events.

Laboratory Analyses

Laboratory assessments (hematology, serum chemistry, urinalysis, and coagulation parameters) will be summarized descriptively by treatment arm and visit. The change from baseline will be summarized for all post-baseline evaluations.

The shift (based on normal ranges) from baseline will be summarized by treatment arm and visit. The significant of shifts in laboratory parameters may be evaluated within each treatment arm using generalized McNemar's test.

The signed-rank test may be used to evaluate the within-group mean change from baseline. The mean change from baseline between the treatment arms will be compared using a Rank-Sum test.

The first laboratory observation will be taken when the lab tests are repeated. However, if the first observation is missing, then the repeat value within the same visit will be used.

All laboratory values will be listed by panel. Out-of-reference range values will be flagged (L/H) and presented in a listing.

Physical Examination, Vital Signs, and Other Safety Parameters

Vital signs and ECG results will be summarized descriptively and presented by visit and treatment arm. The change from baseline in vital signs will be summarized for all post-baseline evaluations. The signed-rank test may be used to evaluate within-group mean change from baseline.

The shift from baseline in physical examination will also be presented by visit with subjects classified as having any shift from normal to abnormal, from abnormal to normal, or no change.

ECOG performance status will be summarized descriptively and presented by visit and treatment arm.

Vital signs, physical examination, ECG results, and ECOG performance status will be listed for all treated subjects.

Concomitant Medication

For each concomitant medication taken during the study, the generic component will be identified using the World Health Organization Drug Dictionary (WHO-DD; WHODDB3 ENHANCED JUN 2015). Frequencies and percentages of the subjects taking each concomitant medication will be tabulated by preferred medication term and treatment arm. A subject will only be counted once within each generic component term.

14.3.6 Safety Monitoring Committee

A safety monitoring committee (SMC) will monitor the safety data from this study on a periodic basis in order to identify any issues and risks, as well as provide recommendations regarding the study design and conduct. The SMC is composed of six members, all of whom are qualified clinicians in general oncology and renal cell carcinoma and have practical experience conducting and monitoring the safety and efficacy of clinical trials.

The first review of the cumulative safety data will occur after 50 subjects have been randomized to each treatment arm and approximately every 6 months thereafter. The frequency may be modified at the discretion of the SMC.

Full details are described in the SMC charter.

14.3.7 Pharmacokinetic Parameters

Tivozanib concentration will be summarized descriptively and presented by visit.

14.3.8 Imaging Process

Two primary radiologists will independently review the images for each subject at each time point and if the results are discordant, then a third radiologist, blinded to treatment, will perform an adjudication of the radiology results. Additionally, an independent radiologist will verify the presence of measurable disease according to RECIST Version 1.1 guidelines, at the time of screening until progressive disease.

The imaging processes will be fully described in the radiographic charter.

15 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1 Study Monitoring

The sponsor has responsibility to governing regulatory authorities to take all reasonable steps to ensure the proper conduct of the study with respect to study ethics, protocol adherence, and data integrity and validity.

This study will be closely monitored by representatives of the sponsor (and/or designee) throughout its duration. Monitoring will be in the form of personal visits with the investigator and their staff as well as any appropriate communications by telephone, telefax, mail, or e-mail transmission. The purpose of these contacts is to review study progress, investigator, and subject adherence to protocol requirements and any emergent problems associated with the conduct of the study. The following points will be usually assessed during monitoring visits at the site:

- Required regulatory documentation
- Signed informed consent documents

- Subject accrual and follow up
- Study drug inventory records
- Investigator and subject compliance to the study protocol
- Concomitant therapy use
- Adverse event documentation
- Data as accurate, complete, and verifiable when compared to source documents.

The investigator and study staff are expected to cooperate with monitors during such visits and provide them with all relevant study documents.

15.2 Audits and Inspections

The study may be evaluated by AVEO auditors (and/or designees) and government inspectors who must be allowed access to eCRFs, source documents, and other study files. AVEO reports will be kept confidential. The investigator should promptly notify AVEO of any audits scheduled by any regulatory authorities, and promptly forward copies of audit reports.

16 QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator review the protocol, Investigator's Brochure, eCRFs and instructions for their completion, procedure for obtaining informed consent, and procedure for reporting AEs and SAEs. A qualified representative of the sponsor monitors the conduct of the study by visiting the site and by contacting the site by telephone and e-mail. During these site visits, information recorded in the eCRFs is verified against source documents/hospital records.

17 ETHICS

17.1 Ethical Conduct of the Study/Conditions of Testing

In sponsoring this study, it is the intention of AVEO Pharmaceuticals, Inc. to obtain subject safety data for submission to regulatory authorities. In agreeing to conduct this investigation, the investigative facility agrees to follow all requirements stipulated in this protocol as well as regulations described in the US Code of Federal Regulations (CFR), the European Commission Directive 2001/20/EC, Directive 2005/28/EC, or by the National Regulatory Authorities concerning:

- General Responsibilities of Investigators (Title 21CFR, Part 312)
- Protection of Human Subjects (Title 21 CFR, Part 50)
- Institutional Review Boards (Title 21 CFR, Part 56).

In addition, the investigator agrees to perform the study in accordance with ICH guidelines for GCP and/or the Declaration of Helsinki.

17.2 Institutional Review / Ethics Committee

The investigator will submit this protocol, any protocol modifications, and the subject consent form to be utilized in this study, to the appropriate IRB or EC for review and approval. This committee must operate in accordance with the US Code of Federal Regulations, Title 21 CFR Part 56 or ICH GCP or European regulations. A letter confirming approval of the protocol, and the informed consent document, must be forwarded to the sponsor prior to initiation of this study. The investigator will not start the study, nor will study drug be shipped to the investigational site, before providing the sponsor with evidence of this approval.

The investigator is responsible for assuring continuing review and approval of the clinical study. The investigator must also promptly report all changes in the research activity and all unanticipated problems involving risk to the subjects or others to their IRB or EC. The investigator will not make any changes in the protocol without IRB or EC approval, except when necessary to eliminate apparent immediate hazards to the subjects. The investigator will provide progress reports to the IRB or EC as required by the IRB or EC. If the study remains in progress for more than 1 year, the investigator must obtain annual renewal and re-approval from the IRB or EC where appropriate. Documentation of renewal must be submitted to the sponsor. The investigator will provide notice to the IRB or EC of completion of participation in the study.

17.3 Written Informed Consent

The investigator agrees to protect the rights, safety, and welfare of the subjects entered into the study, including obtaining informed consent prior to performing any study-related procedures and informing each subject that the study drugs are being used for investigational purposes. A copy of all IRB- or EC-approved consent form document to be utilized during this study must be submitted to the sponsor or designee for review.

Prior to entry into this study, the purpose and nature of the study and possible adverse effects must be explained to each subject. All questions about the study should be answered to the satisfaction of the subject or the subject's legal representative. It is the responsibility of the investigator to obtain written informed consent from each subject, thereby attesting that consent was freely given. An investigator listed on the Form FDA 1572 will then co-sign the informed consent document. This consent must be obtained in accordance with the US Code of Federal Regulations, Title 21 CFR Part 50 or in accordance with the ICH GCP. A copy of the signed and dated informed consent document should then be given to the subject. The original executed version must remain in the subject's file and must be available for verification by a representative of the sponsor (or designee).

17.4 Conditions for Modifying or Terminating the Study

17.4.1 Modification of the Study Protocol

In the event that modifications in the experimental design, dosages, parameters, subject selection, etc., of the protocol are indicated or required, such changes will only be instituted following consultation between the sponsor and investigator and will be accomplished through formal amendment(s) to this protocol and approval by the appropriate review committees, except when necessary to immediately eliminate apparent hazards to subjects.

A modification to the protocol will not be made without the express written approval of the sponsor. Any amendment prepared by the sponsor will be implemented according to the sponsor's standard operation procedures and will be reported to the appropriate regulatory body, the appropriate IRB(s) or EC(s), and made a formal component of the protocol document.

17.4.2 Modification of the Informed Consent Document

In the event that modifications in the experimental design, dosages, parameters, subject selection, etc., of the protocol are indicated or required, and in the event that such modifications substantially alter the study design or increase the potential risk to subjects, the investigator will prepare a revision to the existing informed consent document. Such a revision will be reviewed and approved by the appropriate IRB(s) or EC(s), and documentation of this approval will be forwarded to the sponsor for submission to the appropriate regulatory body.

In addition, all current study participants, as well as subsequent study candidates, will be informed of the study design modification or increase in potential risk, and written informed consent for the modification/risk will be obtained as outlined above (see Section 18.3, Written Informed Consent).

17.4.3 Termination of the Study

Should the sponsor and/or the investigator(s) discover conditions, during the course of the study, that indicate that it should be discontinued, an appropriate procedure for termination will be instituted.

17.4.4 Deviation From the Protocol

The study is to be conducted as described in this protocol. Under no circumstances should the protocol be modified for any subject. If a protocol deviation should occur it is to be documented on the protocol deviation log and reported to the IRB/EC per their guidelines.

17.5 Documents to be Submitted to the Sponsor

The following documents must be submitted to the sponsor or delegate prior to study drug shipment:

1. Signed and dated FDA Form 1572 or the equivalent.

Note: In conducting this study, the investigator agrees to comply with commitments listed under Section 9 of Form 1572.

2. Signed and dated curriculum vitae (CV) of the principal investigator and each sub-investigator named on the FDA Form 1572. Physician CVs should be current (updated within 2 years) and should include medical license numbers if available or where applicable.

Note: A sub-investigator is defined as a clinician responsible for study-related medical decisions, diagnoses, and treatment.

1. Written, signed notification of IRB or EC approval of the study protocol.
2. Written, signed notification of the approval of the informed consent document to be used during the study.

3. The IRB- or EC-approved informed consent document to be used during the study.
4. A list of IRB committee members or certification that there is no conflict of interest.
5. Laboratory normal ranges for the local laboratories to be utilized if applicable. Name, location, certification number, and date of certification of all laboratories utilized must also be provided, where available and applicable.
6. Signed and dated Protocol Signature Page.
7. Fully executed Clinical Trial Agreement.
8. Signed and dated Financial disclosure forms for the principal investigator and each sub-investigator named on the FDA Form 1572.

18 INVESTIGATOR RESPONSIBILITIES

18.1 Medical Supervision

An investigator conducting a clinical study with an investigational agent is required to comply with regulations described in US Code of Federal Regulations, Title 21 CFR Part 312, the European Commission Directive 2001/20/EC, Directive 2005/28/EC, and ICH GCP as well as local laws and regulations.

Medical supervision for the conduct of this protocol is the responsibility of the principal investigator. The principal investigator must name all sub-investigators and may delegate certain day-to-day activities to such sub-investigators, but, retains overall responsibility for ensuring that the study is conducted properly and in accordance with the design and intent herein. A memorandum outlining the specifics of the delegation will be maintained at the investigational site, in the study files, and will be updated as appropriate. The principal investigator is responsible for ensuring that drugs and devices are available for treating possible medical emergencies. The principal investigator is required to ensure compliance with respect to the investigational drug schedule, visit schedule, and procedures required by the protocol. The principal investigator is responsible for ensuring that the study is conducted according to sound medical practices.

18.2 Confidentiality

All goods, materials, information (oral or written) and unpublished documentation provided to the investigator (or any company acting on their behalf), inclusive of this protocol, the subject case report forms, and the Investigator's Brochure are the exclusive property of the sponsor. Documents and information provided to the investigator by the sponsor may not be given or disclosed by the investigator or by any person within his authority in part or in totality to any unauthorized person without the prior written formal consent of the sponsor.

It is specified that the submission of this protocol and other necessary documentation to the IRB or EC is expressly permitted, the IRB or EC members having the same obligation of confidentiality.

The investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the study, other than that information to be disclosed to a third party mandated by applicable law.

Note: Any language relating to these issues appearing in the Clinical Trial Agreement will supersede that which is outlined in this section.

18.3 Use of Information and Publication

The investigator, the institution, and its personnel understand and agree that participation in a multi-center study involves a commitment to publish the data from the study in a cooperative publication prior to publication or oral presentation of study results on an individual basis. Upon completion of the study and evaluation by sponsor of all data from the study, or upon early termination or abandonment of the study pursuant to the terms herein, the institution and investigator may publish or disclose the results of the study, subject to the following:

1. **Review Period.** A copy of such proposed publication will be given to the sponsor for review at least sixty (60) days prior to the date of submission for publication or of public disclosure. The sponsor will complete its review within this review period and will have authority to require that the institution and/or the investigator delete any reference to confidential information (other than the results) from the disclosure.
2. **Patent Filings.** If during the review period, the sponsor notifies the institution that it desires patent applications to be filed on any sponsor's inventions (defined below) disclosed or contained in the disclosures, the institution and the investigator will defer publication or other disclosure for a period, not to exceed an additional sixty (60) days, sufficient to permit the sponsor or its designee to have filed or to file any desired patent applications.

Multi-Center Studies. No submission for publication or public disclosure by the institution or the investigator will be made until results from all centers have been received and analyzed by the sponsor, or the multi-center study has been terminated or abandoned at all centers. If a publications committee, or a committee of investigators, is formed for publication of results of the multi-center clinical study, any separate publication by the institution or the investigator will be delayed until the initial publication by the committee or a determination is made by the committee not to make such publication. If the committee does not produce an initial draft of a manuscript or abstract of results from all centers within eighteen (18) months of completion of the study at all centers and the committee has not notified the institution or investigator that it intends to produce a manuscript or abstract in a timeframe satisfactory to the institution and investigator, then the institution and investigator may publish or otherwise disclose the results for non-commercial purposes, subject to the terms mentioned in Paragraphs 1 and 2 immediately above.

Note: Any language relating to these issues appearing in the Clinical Trial Agreement will supersede that which is outlined in this section.

18.4 Drug Dispensing Inventory

Study center personnel will maintain adequate records of the receipt, dispensation, and disposition of all study drugs that the sponsor ships to the site. Records will be maintained, either on a form to be provided by the sponsor or on a reasonable facsimile authorized for use by the sponsor, and should include appropriate dates, quantities received, quantities dispensed, and the identification code of the subject who received the study drug.

The investigator agrees to administer study drug only to subjects under their personal supervision. The investigator will not supply study drug to any person not authorized to receive it.

18.5 Handling and Disposal of Investigational Materials

Study drug should be stored in a secure location, under the indicated conditions (see [Appendix F](#); Tivozanib Study Drug Information and [Appendix E](#), Sorafenib Prescribing Information). After study drug is prepared for delivery and administered, the health care professional will maintain an inventory of all used bottles of study drug, after which all such supplies may be destroyed in an appropriate manner according to institutional policy. Destruction of such supplies will be documented. Information regarding the number of bottles utilized for each subject, as well as the dose of study drug administered to the subject, will be recorded on the appropriate drug inventory form.

Periodically throughout and at the conclusion of the study, unused bottles of study drug will be inventoried by a representative of the sponsor (or designee). At the completion of this study, all unused study materials will be destroyed by the site or returned to the sponsor (or designee). Destruction of study drug by the site can only occur after the sponsor (or designee) has collected the site's SOP for drug destruction.

18.6 Recording and Processing of Data

Clinical study data for this study will be captured in an electronic format. Electronic data capture (EDC) services will be provided by the contract research organization (CRO). The investigator agrees to provide all information requested on the eCRF in an accurate manner according to instructions provided. Electronic CRFs are designed for computer processing and analysis. All data must be carefully entered to permit meaningful interpretation. Corrections to entered data will be tracked within the EDC system. Data must be entered onto eCRFs in a timely fashion.

An eCRF is required to be submitted for every subject who is randomized. This includes submission of retrievable data on subjects who withdraw before completion of the study. Prior to submission, eCRFs must be reviewed for completeness and accuracy, and signed and dated where indicated, by either the principal investigator or a physician sub-investigator whose name is listed on the Form FDA 1572 for this study.

All data from the study will be exported to the sponsor, AVEO Pharmaceuticals, Inc. (Cambridge, Massachusetts, USA).

18.7 Source Document Requirements

The investigator will maintain adequate and accurate records for each subject who is randomized. Source documents such as hospital, clinic, or office charts; laboratory reports; study worksheets; and signed informed consent documents are to be included in the investigator's files along with subject study records.

The sponsor (or designee) will check eCRF entries against source documents according to the guidelines of GCP. The consent form will include a statement by which subjects allow the sponsor (or designee), as well as authorized regulatory agencies, to have direct access to source data that support data on the eCRF (eg, subject medical files, appointment books,

original laboratory records, etc.). The sponsor (or designee), bound by secrecy, will not disclose subject identities or personal medical information.

18.8 Laboratory Reports

Local laboratories will be used for laboratory safety evaluations this study. Laboratory safety evaluations must be performed at the intervals specified. If unexplained laboratory abnormalities occur, corroborative tests will be performed until the laboratory parameter has returned to normal and/or adequate explanation of the abnormality has been provided.

Copies of any additional records pertinent to the study (eg, laboratory data, radiological reports, subject chart summaries, autopsy reports) must be made available to the sponsor or regulatory authorities, if requested, with due precaution taken to ensure subject confidentiality.

18.9 Subject Confidentiality

Every effort will be made to maintain the anonymity and confidentiality of subjects during this clinical study. Coded subject identifiers will be utilized at all times (including in any publications) when referring to a particular subject. However, because of the experimental nature of this treatment, at mutually agreeable times, the institution and investigator will give the sponsor and its designees and governing regulatory agencies (as provided by applicable law) access to all records, documentation (however stored) relating to the study or to the care of study subjects, for sponsor or designees to monitor the study for source documentation verification, and/or for audit purposes, and for the sponsor or designee, to inspect the facilities to verify compliance with this protocol and the clinical study agreement. Subjects' medical records will be made available where appropriate for the purpose of source documentation verification procedures.

19 DATA HANDLING AND RECORDKEEPING

19.1 Inspection of Records

The investigator agrees that qualified representatives of the sponsor and regulatory agencies will have the right, during and after the study, to conduct inspections and to audit and review medical records pertinent to the clinical study as permitted by the regulations. Subject confidentiality will be maintained unless disclosure is required by regulations.

At mutually agreeable times, the institution and investigator will give the sponsor and its designees and governing regulatory agencies (as provided by applicable law) access all records, documentation (however stored) relating to the study or to the care of study subjects, for sponsor or designees to monitor the study, for source document verification, and/or for audit purposes, and for sponsor or designee to inspect the facilities to verify compliance with this protocol and the clinical study agreement. Subjects' medical records will be made available where appropriate for the purpose of source document verification procedures.

19.2 Retention of Records

The investigator will maintain records for this study, which includes subject's eCRFs, medical records, laboratory reports, signed informed consent forms, safety reports, plus all other pertinent data. The investigator will retain study medication disposition records, copies of eCRFs (or electronic files), and source documents for the maximum period required by the

country in which the study will be conducted, or the period specified by the sponsor, whichever is longer.

United States federal law requires that the investigator retain copies of all files pertaining to the study (ie, records of study article disposition, signed informed consent documents, case report forms, all correspondence, dates of monitoring visits, and records which support them) for a period of 2 years following the date of marketing application approval of the drug, in the indication being investigated in the study and until there are no pending or contemplated marketing application, or 2 years following the sponsor's formally discontinuing worldwide clinical development of the study drug, as notified by the sponsor, whichever is longer.

European Commission Directive 2005/28/EC requires that investigators and sponsors shall retain the essential documents for at least 5 years after completion of a clinical study.

If the investigator relocates, retires, or withdraws for any reason from the study, study records may be transferred to an acceptable designee, such as another investigator within the institution. Prior notice of such transfer will be provided in writing to the sponsor. The investigator must obtain written permission from the sponsor prior to disposing of any records.

20 REFERENCES

-
- 1 Nakamura K, Taguchi E, Miura T, et al. KRN951, a highly potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, has antitumor activities and affects functional vascular properties. *Cancer Research*. 2006;66:9134-9142.
 - 2 Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects (abstract). *Proc Natl Acad Sci USA*. 2002;99(17):11393-11398.
 - 3 Ferrara N and Alitalo K. Clinical applications of angiogenic growth factors and their inhibitors. *Nat Med*. 1999;5(12):1359-1364.
 - 4 Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med*. 1995;1(1):27 - 31.

- 5 Liekens S, de Clercq E, and Neyts J. Angiogenesis: Regulators and clinical applications. *Biochem Pharmacol.* 2001;61:253-270.

- 6 Neufeld G, Cohen T, Gengrinovitch S, and Poltorak, Z. Vascular endothelial growth factor (VEGF) and its receptors. *FASEB J.* 1999;13:9-22.

- 7 van der Veldt AAM, Boven E, Helgason HH, et al. Predictive factors for severe toxicity of sunitinib in unselected patients with advanced renal cell cancer. *British Journal of Cancer.* 2008;99, 259 – 265.

21 APPENDICES

APPENDIX A RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) VERSION 1.1

Response criteria were adapted from: Response Evaluation Criteria in Solid Tumors (RECIST) Criteria; Version 1.1, 2009 (<http://www.eortc.be/Recist/documents/RECISTGuidelines.pdf>).

1.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only subjects with measurable disease at baseline should be included in protocols where objective tumor response is an endpoint. Measurable disease is defined by the presence of at least one measurable lesion.

A measurable lesion is defined as one that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20mm by chest X-ray.

Non-measurable lesions are defined as all other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥ 10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability:

Bone lesions:

Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if

noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

1.2 Baseline Documentation of Target and Non-Target Lesions

Baseline documentation of tumor sites may include imaging assessment of disease in the chest, abdomen, and pelvis. A baseline imaging study of the brain is also required. All baseline tumor measurements must be documented within 4 weeks prior to start of therapy.

1.2.1 Target Lesions

All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

1.2.2 Non-Target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

1.3 Tumor Response Criteria

1.3.1 Evaluation of Target Lesions

- Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

1.3.2 Evaluation of Non-Target Lesions

- Complete Response (CR):** Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
- Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
- Progressive Disease (PD):** Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

1.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. In non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

DETERMINATION OF TUMOR RESPONSE			
Target Lesions	Non-Target Lesions	New Lesions	Response Assessment
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or Not All Evaluated	No	PR
SD	Non-PD or Not All Evaluated	No	SD
Not All Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable

Note: Subjects with a global deterioration of health status, requiring discontinuation of treatment without objective evidence of disease progression at that time, should be reported as “symptomatic deterioration. ” Every effort should be made to document the objective progression, even after discontinuation of treatment.

Conditions that may define “early progression, early death, and inevaluability” are study-specific and should be clearly defined in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy), before confirming the complete response status.

1.5 Guidelines for Evaluation of Measurable Disease

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

Note: Tumor lesions in a previously irradiated area are not optimally considered measurable disease. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions will only be considered measurable when they are superficial and P10mm diameter as assessed using calipers (eg skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested.

For **Chest lesions**, Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Cross Sectional Imaging: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg for body scans).

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

1.6 Duration of Response

1.6.1 Duration of Response

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

1.6.2 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 sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

1.6.3 Time to Disease Progression

Defined as the time from the date of first day of enrollment to progression as assessed by the conventional response criteria, death, or the start of further antitumor therapy. Subjects lost to follow-up will be censored at their last known alive date.

APPENDIX B ECOG PERFORMANCE STATUS EVALUATION

Grade	Eastern Cooperative Oncology Group (ECOG)*
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Death

*Oken M, Creech RH, Tormey DC, Horton J, Davis TE, McFadden E, Carbone PP. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol.* (CCT) 1982; 5:649-655.

APPENDIX C CYTOCHROME P450 (CYP3A4) INHIBITORS AND INDUCERS

Cytochrome P450 (CYP3A4) Drug interaction table	
STRONG* INHIBITORS	STRONG* INDUCERS
Ketoconazole	Rifabutin
Nefazodone	Rifampin
Nelfinavir	
Ritonavir	

* Strong inhibition implies that it can cause a > 5-fold increase in the plasma AUC values or > 80% decrease in clearance of sensitive CYP substrates.

APPENDIX D RECOMMENDED ANTI-HYPERTENSIVE MEDICATIONS

Agent	Initial Dose	Intermediate Dose	Maximum Dose
<i>Dihydropyridine (DHP) Calcium Channel Blockers</i>			
Nifedipine XL	30 mg po qd	60 mg po qd	90 mg po qd
Amlodipine	2.5 mg po qd	5 mg po qd	10 mg po qd
Felodipine	2.5 mg po qd	5 mg po qd	10 mg po qd
<i>Angiotensin Converting Enzyme (ACE) Inhibitors</i>			
Captopril	12.5 mg po tid	25 mg po tid	50 mg po tid
Enalapril	5 mg po qd	10–20 mg po qd	40 mg po qd
Ramipril	2.5 mg po qd	5 mg po qd	10 mg po qd
Lisinopril	5 mg po qd	10–20 mg po qd	40 mg po qd
Fosinopril	10 mg po qd	20 mg po qd	40 mg po qd
Perindopril	4 mg po qd	None	8 mg po qd
Quinapril	10 mg po qd	20 mg po qd	20 mg po qd
<i>Angiotensin II Receptor Blockers</i>			
Losartan	25 mg po qd	50 mg po qd	100 mg po qd
Candesartan	4 mg po qd	8–16 mg po qd	32 mg po qd
Ibresartan	75 mg po qd	150 mg po qd	300 mg po qd
Telmisartan	40 mg po qd	None	80 mg po qd
Valsartan	80 mg po qd	None	160 mg po qd

po = oral administration; qd = once daily; tid = three times daily

Adapted from Kollmannsberger C, et al, *CUAJ*. 2007;Vol 1 (Issue 2 Suppl):S41–54.

APPENDIX E SORAFENIB PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEXAVAR safely and effectively.

See full prescribing information for NEXAVAR.

NEXAVAR (sorafenib) tablets, oral

Initial U.S. Approval: 2005

RECENT MAJOR CHANGES

Contraindications (4)	10/2010
Warnings and Precautions (5.8, 5.13, 5.14)	10/2010

INDICATIONS AND USAGE

NEXAVAR is a kinase inhibitor indicated for the treatment of

- Unresectable hepatocellular carcinoma (1.1)
- Advanced renal cell carcinoma (1.2)

DOSAGE AND ADMINISTRATION

- 400 mg (2 tablets) orally twice daily without food. (2)
- Treatment interruption and/or dose reduction may be needed to manage suspected adverse drug reactions. Dose may be reduced to 400 mg once daily or to 400 mg every other day. (2)

DOSAGE FORMS AND STRENGTHS

200 mg Tablets (3)

CONTRAINDICATIONS

- NEXAVAR is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of NEXAVAR. (4)
- NEXAVAR in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer. (4)

WARNINGS AND PRECAUTIONS

- Cardiac Ischemia and/or Infarction may occur. Consider temporary or permanent discontinuation of NEXAVAR. (5.1)
- Bleeding may occur. If bleeding necessitates medical intervention, consider discontinuation of NEXAVAR. (5.2)
- Hypertension usually occurred early in the course of treatment and was managed with antihypertensive therapy. Monitor blood pressure weekly during the first 6 weeks and periodically thereafter and treat, as required. (5.3)
- Hand-foot skin reaction and rash are common. Management may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification, or in severe or persistent cases, permanent discontinuation. (5.4)
- Gastrointestinal perforation is an uncommon adverse reaction. In the event of a gastrointestinal perforation, NEXAVAR therapy should be discontinued. (5.5)
- Temporary interruption of NEXAVAR therapy is recommended in patients undergoing major surgical procedures. (5.7)

- Caution is recommended when co-administering substances metabolized/eliminated predominantly by the UGT1A1 pathway (for example, irinotecan). (5.9, 7.2)
- Caution is recommended when co-administering docetaxel. (5.10, 7.3)
- Caution is recommended when co-administering doxorubicin. (5.11, 7.4)
- Nexavar may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant while on NEXAVAR. (5.14)

ADVERSE REACTIONS

The most common adverse reactions (>20%), which were considered to be related to NEXAVAR, are fatigue, weight loss, rash/desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea and abdominal pain (6).

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-800-842-2937, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Carboplatin and Paclitaxel: Caution, sorafenib and paclitaxel AUC increases when co-administered. (4, 5.8, 7.1)
- UGT1A1 (for example, irinotecan) and UGT1A9 substrates: Caution, drug AUC increases when co-administered with NEXAVAR. (5.9, 7.2)
- Docetaxel: Caution, docetaxel AUC increases when co-administered with NEXAVAR. (5.10, 7.3)
- Doxorubicin: Caution, doxorubicin AUC increases when co-administered with NEXAVAR. (5.11, 7.4)
- Fluorouracil: Caution, fluorouracil AUC changes when co-administered with NEXAVAR. (7.5)
- CYP2B6 and CYP2C8 substrates: Caution, systemic exposure is expected to increase when co-administered with NEXAVAR. (7.6)
- CYP3A4 Inducers: Expected to increase metabolism of sorafenib and decrease sorafenib concentrations. (2, 7.7)
- Neomycin: Caution, sorafenib AUC decreases when co-administered with oral neomycin. (5.13, 7.12)

USE IN SPECIFIC POPULATIONS

- Hepatic Impairment: No dose adjustment is necessary in HCC patients with Child-Pugh A and B hepatic impairment. NEXAVAR has not been studied in patients with Child-Pugh C hepatic impairment. (8.6)
- Renal Impairment: NEXAVAR has not been studied in patients undergoing dialysis. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

Revised: 10/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Hepatocellular Carcinoma
- 1.2 Renal Cell Carcinoma

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Risk of Cardiac Ischemia and/or Infarction
- 5.2 Risk of Hemorrhage
- 5.3 Risk of Hypertension
- 5.4 Risk of Dermatologic Toxicities
- 5.5 Risk of Gastrointestinal Perforation
- 5.6 Warfarin Co-Administration
- 5.7 Wound Healing Complications
- 5.8 Use of Nexavar in combination with Carboplatin and Paclitaxel in Non-small Cell Lung Cancer
- 5.9 Interactions with UGT1A1 Substrates
- 5.10 Interaction with Docetaxel
- 5.11 Interaction with Doxorubicin
- 5.12 Hepatic Impairment
- 5.13 Neomycin
- 5.14 Use in Pregnancy

6 ADVERSE REACTIONS

- 6.1 Adverse Reactions in HCC Study
- 6.2 Adverse Reactions in RCC Study 1
- 6.3 Additional Data from Multiple Clinical Trials

7 DRUG INTERACTIONS

- 7.1 Carboplatin and Paclitaxel
- 7.2 UGT1A1 and UGT1A9 Substrates
- 7.3 Docetaxel
- 7.4 Doxorubicin
- 7.5 Fluorouracil
- 7.6 CYP2B6 and CYP2C8 Substrates
- 7.7 CYP3A4 Inducers
- 7.8 CYP3A4 Inhibitors and CYP Isoform Substrates
- 7.9 P-glycoprotein substrates
- 7.10 In Vitro Studies: CYP Enzyme Induction
- 7.11 Combination with Other Antineoplastic Agents
- 7.12 Neomycin

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Patients with Hepatic Impairment
- 8.7 Patients with Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

- 14 CLINICAL STUDIES
 - 14.1 Hepatocellular Carcinoma
 - 14.2 Renal Cell Carcinoma
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION
 - 17.1 Cardiac Ischemia; Infarction

- 17.2 Bleeding; Gastrointestinal Perforation
 - 17.3 Skin Reactions; Hypertension
 - 17.4 Birth Defects and Fetal Loss
- *Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hepatocellular Carcinoma

NEXAVAR is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC).

1.2 Renal Cell Carcinoma

NEXAVAR is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

2 DOSAGE AND ADMINISTRATION

The recommended daily dose of NEXAVAR is 400 mg (2 x 200 mg tablets) taken twice daily without food (at least 1 hour before or 2 hours after a meal). Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of NEXAVAR therapy. When dose reduction is necessary, the NEXAVAR dose may be reduced to 400 mg once daily. If additional dose reduction is required, NEXAVAR may be reduced to a single 400 mg dose every other day [see Warnings and Precautions (5)].

Suggested dose modifications for skin toxicity are outlined in Table 1.

Table 1: Suggested Dose Modifications for Skin Toxicity

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any occurrence	Continue treatment with NEXAVAR and consider topical therapy for symptomatic relief
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1 st occurrence	Continue treatment with NEXAVAR and consider topical therapy for symptomatic relief If no improvement within 7 days, see below
	No improvement within 7 days or 2 nd or 3 rd occurrence	Interrupt NEXAVAR treatment until toxicity resolves to Grade 0–1 When resuming treatment, decrease NEXAVAR dose by one dose level (400 mg daily or 400 mg every other day)
	4 th occurrence	Discontinue NEXAVAR treatment
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1 st or 2 nd occurrence	Interrupt NEXAVAR treatment until toxicity resolves to Grade 0–1 When resuming treatment, decrease NEXAVAR dose by one dose level (400 mg daily or 400 mg every other day)
	3 rd occurrence	Discontinue NEXAVAR treatment

No dose adjustment is required on the basis of patient age, gender, or body weight.

Concomitant strong CYP3A4 inducers: The use of concomitant strong CYP3A4 inducers may decrease sorafenib plasma concentrations and should be avoided (for example, St. John's Wort, dexamethasone, phenytoin).

carbamazepine, rifampin, rifabutin, phenobarbital). Although a dose increase has not been studied, if a strong CYP3A4 inducer must be co-administered, a NEXAVAR dose increase may be considered. If the dose of NEXAVAR is increased, the patient should be monitored carefully for toxicity [see *Drug Interactions (7.7)*].

3 DOSAGE FORMS AND STRENGTHS

Tablets containing sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib.

NEXAVAR tablets are round, biconvex, red film-coated tablets, debossed with the "Bayer cross" on one side and "200" on the other side.

4 CONTRAINDICATIONS

- NEXAVAR is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of NEXAVAR.
- NEXAVAR in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer [see *Warnings and Precautions (5.8)*].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Cardiac Ischemia and/or Infarction

In the HCC study, the incidence of cardiac ischemia/infarction was 2.7% in NEXAVAR patients compared with 1.3% in the placebo group and in RCC Study 1, the incidence of cardiac ischemia/infarction was higher in the NEXAVAR group (2.9%) compared with the placebo group (0.4%). Patients with unstable coronary artery disease or recent myocardial infarction were excluded from this study. Temporary or permanent discontinuation of NEXAVAR should be considered in patients who develop cardiac ischemia and/or infarction.

5.2 Risk of Hemorrhage

An increased risk of bleeding may occur following NEXAVAR administration. In the HCC study, an excess of bleeding regardless of causality was not apparent and the rate of bleeding from esophageal varices was 2.4% in NEXAVAR patients and 4% in placebo patients. Bleeding with a fatal outcome from any site was reported in 2.4% of NEXAVAR patients and 4% in placebo patients. In RCC Study 1, bleeding regardless of causality was reported in 15.3% of patients in the NEXAVAR group and 8.2% of patients in the placebo group. The incidence of CTCAE Grade 3 and 4 bleeding was 2% and 0%, respectively, in NEXAVAR patients, and 1.3% and 0.2%, respectively, in placebo patients. There was one fatal hemorrhage in each treatment group in RCC Study 1. If any bleeding necessitates medical intervention, permanent discontinuation of NEXAVAR should be considered.

5.3 Risk of Hypertension

Blood pressure should be monitored weekly during the first 6 weeks of NEXAVAR therapy and thereafter monitored and treated, if required, in accordance with standard medical practice. In the HCC study, hypertension was reported in approximately 9.4% of NEXAVAR-treated patients and 4.3% of patients in the placebo group. In RCC Study 1, hypertension was reported in approximately 18.9% of NEXAVAR-treated patients and 1.8% of patients in the placebo group. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was managed with standard antihypertensive therapy. In cases of severe or persistent hypertension, despite institution of antihypertensive therapy, temporary or permanent discontinuation of NEXAVAR should be considered. Permanent discontinuation due to hypertension occurred in 1 of 297 NEXAVAR patients in the HCC study and 1 of 451 NEXAVAR patients in RCC Study 1.

5.4 Risk of Dermatologic Toxicities

Hand-foot skin reaction and rash represent the most common adverse reactions attributed to NEXAVAR. Rash and hand-foot skin reaction are usually CTCAE Grade 1 and 2 and generally appear during the first six weeks of treatment with NEXAVAR. Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of NEXAVAR, or in severe or persistent cases, permanent discontinuation of NEXAVAR. Permanent discontinuation of therapy due to hand-foot skin reaction occurred in 4 of 297 NEXAVAR HCC patients and 3 of 451 NEXAVAR RCC patients.

5.5 Risk of Gastrointestinal Perforation

Gastrointestinal perforation is an uncommon adverse reaction and has been reported in less than 1% of patients taking NEXAVAR. In some cases this was not associated with apparent intra-abdominal tumor. In the event of a gastrointestinal perforation, NEXAVAR therapy should be discontinued.

5.6 Warfarin Co-Administration

Infrequent bleeding or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on NEXAVAR therapy. Patients taking concomitant warfarin should be monitored regularly for changes in prothrombin time, INR or clinical bleeding episodes.

5.7 Wound Healing Complications

No formal studies of the effect of NEXAVAR on wound healing have been conducted. Temporary interruption of NEXAVAR therapy is recommended in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of NEXAVAR therapy following major surgical intervention. Therefore, the decision to resume NEXAVAR therapy following a major surgical intervention should be based on clinical judgment of adequate wound healing.

5.8 Use of Nexavar in combination with Carboplatin and Paclitaxel in Non-small Cell Lung Cancer

A randomized controlled trial in chemo-naïve patients with Stage IIIB-IV Non-small Cell Lung Cancer, performed to compare the safety and efficacy of carboplatin and paclitaxel with or without sorafenib, was stopped early because overall survival was not improved with the addition of sorafenib. In the analysis of the subset of patients with squamous cell carcinoma (prospectively stratified), higher mortality was observed with the addition of sorafenib compared to those treated with carboplatin and paclitaxel alone (HR 1.81, 95% CI 1.19-2.74). No definitive cause was identified for this finding [see *Contraindications (4)*].

5.9 Interactions with UGT1A1 Substrates

Sorafenib can cause increases in plasma concentrations of drugs that are substrates of UGT1A1. Caution is recommended when administering NEXAVAR with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (for example, irinotecan) [see *Drug Interactions (7.2)*].

5.10 Interaction with Docetaxel

Sorafenib can cause increases in plasma concentrations of docetaxel. Caution is recommended when NEXAVAR is co-administered with docetaxel [see *Drug Interactions (7.3)*].

5.11 Interaction with Doxorubicin

Sorafenib can cause increases in plasma concentrations of doxorubicin. Caution is recommended when NEXAVAR is co-administered with doxorubicin [see *Drug Interactions (7.4)*].

5.12 Hepatic Impairment

Hepatic impairment may reduce plasma concentrations of sorafenib. Comparison of data across studies suggests that sorafenib levels are lower in HCC patients than in non-HCC patients (without hepatic impairment). The AUC of sorafenib is similar between HCC patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. The optimal dose in non-HCC patients with hepatic impairment is not established [see *Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

5.13 Neomycin

Co-administration of oral neomycin causes a decrease in sorafenib exposure [see *Drug Interactions (7.12)*].

5.14 Use in Pregnancy

There are no adequate and well-controlled studies in pregnant women using NEXAVAR. However, based on its mechanism of action and findings in animals, NEXAVAR may cause fetal harm when administered to a pregnant woman. Sorafenib caused embryo-fetal toxicities in animals at maternal exposures that were significantly lower than the human exposures at the recommended dose of 400 mg twice daily. Women of childbearing potential should be advised to avoid becoming pregnant while on NEXAVAR. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

6 ADVERSE REACTIONS

The following risks are discussed in greater detail in the WARNINGS AND PRECAUTIONS section (5):

- Cardiac ischemia, infarction [see *Warnings and Precautions (5.1)*]
- Hemorrhage [see *Warnings and Precautions (5.2)*]
- Hypertension [see *Warnings and Precautions (5.3)*]

- Hand-foot skin reaction and rash [see Warnings and Precautions (5.4)]
- Gastrointestinal perforation [see Warnings and Precautions (5.5)]
- Wound healing complications [see Warnings and Precautions (5.7)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in sections 6.1 and 6.2 reflect exposure to NEXAVAR in 748 patients who participated in placebo controlled studies in hepatocellular carcinoma (N=297) or advanced renal cell carcinoma (N=451).

The most common adverse reactions (≥20%), which were considered to be related to NEXAVAR, in patients with HCC or RCC are fatigue, weight loss, rash/desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea and abdominal pain.

6.1 Adverse Reactions in HCC Study

Table 2 shows the percentage of HCC patients experiencing adverse reactions that were reported in at least 10% of patients and at a higher rate in the NEXAVAR arm than the placebo arm. CTCAE Grade 3 adverse reactions were reported in 39% of patients receiving NEXAVAR compared to 24% of patients receiving placebo. CTCAE Grade 4 adverse reactions were reported in 6% of patients receiving NEXAVAR compared to 8% of patients receiving placebo.

Table 2 Adverse Reactions Reported in at Least 10% of Patients and at a Higher Rate in NEXAVAR Arm than the Placebo Arm – HCC Study

Adverse Reaction NCI-CTCAE v3 Category/Term	NEXAVAR N=297			Placebo N=302		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any Adverse Reaction	98	39	6	96	24	8
Constitutional symptoms						
Fatigue	46	9	1	45	12	2
Weight loss	30	2	0	10	1	0
Dermatology/skin						
Rash/desquamation	19	1	0	14	0	0
Pruritus	14	<1	0	11	<1	0
Hand-foot skin reaction	21	8	0	3	<1	0
Dry skin	10	0	0	6	0	0
Alopecia	14	0	0	2	0	0
Gastrointestinal						
Diarrhea	55	10	<1	25	2	0
Anorexia	29	3	0	18	3	<1
Nausea	24	1	0	20	3	0
Vomiting	15	2	0	11	2	0
Constipation	14	0	0	10	0	0
Hepatobiliary/ pancreas						
Liver dysfunction	11	2	1	8	2	1
Pain						
Pain, abdomen	31	9	0	26	5	1

Hypertension was reported in 9% of patients treated with NEXAVAR and 4% of those treated with placebo. CTCAE Grade 3 hypertension was reported in 4% of NEXAVAR treated patients and 1% of placebo treated patients. No patients were reported with CTCAE Grade 4 reactions in either treatment group.

Hemorrhage/bleeding was reported in 18% of those receiving NEXAVAR and 20% of placebo patients. The rates of CTCAE Grade 3 and 4 bleeding were also higher in the placebo group (CTCAE Grade 3 – 3% NEXAVAR and 5% placebo and CTCAE Grade 4 – 2% NEXAVAR and 4% placebo). Bleeding from esophageal varices was reported in 2.4% in NEXAVAR treated patients and 4% of placebo treated patients.

Renal failure was reported in <1% of patients treated with NEXAVAR and 3% of placebo treated patients.

The rate of adverse reactions (including those associated with progressive disease) resulting in permanent discontinuation was similar in both the NEXAVAR and placebo groups (32% of NEXAVAR patients and 35% of placebo patients).

Laboratory Abnormalities

The following laboratory abnormalities were observed in HCC patients:

Hypophosphatemia was a common laboratory finding, observed in 35% of NEXAVAR-treated patients compared to 11% of placebo patients; CTCAE Grade 3 hypophosphatemia (1–2 mg/dL) occurred in 11% of NEXAVAR-treated patients and 2% of patients in the placebo group; there was 1 case of CTCAE Grade 4 hypophosphatemia (<1 mg/dL) reported in the placebo group. The etiology of hypophosphatemia associated with NEXAVAR is not known.

Elevated lipase was observed in 40% of patients treated with NEXAVAR compared to 37% of patients in the placebo group. CTCAE Grade 3 or 4 lipase elevations occurred in 9% of patients in each group. Elevated amylase was observed in 34% of patients treated with NEXAVAR compared to 29% of patients in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 2% of patients in each group. Many of the lipase and amylase elevations were transient, and in the majority of cases NEXAVAR treatment was not interrupted. Clinical pancreatitis was reported in 1 of 297 NEXAVAR-treated patients (CTCAE Grade 2).

Elevations in liver function tests were comparable between the 2 arms of the study. Hypoalbuminemia was observed in 59% of NEXAVAR-treated patients and 47% of placebo patients; no CTCAE Grade 3 or 4 hypoalbuminemia was observed in either group.

INR elevations were observed in 42% of NEXAVAR-treated patients and 34% of placebo patients; CTCAE Grade 3 INR elevations were reported in 4% of NEXAVAR-treated patients and 2% of placebo patients; there was no CTCAE Grade 4 INR elevation in either group.

Lymphopenia was observed in 47% of NEXAVAR-treated patients and 42% of placebo patients.

Thrombocytopenia was observed in 46% of NEXAVAR-treated patients and 41% of placebo patients; CTCAE Grade 3 or 4 thrombocytopenia was reported in 4% of NEXAVAR-treated patients and less than 1% of placebo patients.

6.2 Adverse Reactions in RCC Study 1

Table 3 shows the percentage of RCC patients experiencing adverse reactions that were reported in at least 10% of patients and at a higher rate in the NEXAVAR arm than the placebo arm. CTCAE Grade 3 adverse reactions were reported in 31% of patients receiving NEXAVAR compared to 22% of patients receiving placebo. CTCAE Grade 4 adverse reactions were reported in 7% of patients receiving NEXAVAR compared to 6% of patients receiving placebo.

Table 3: Adverse Reactions Reported in at Least 10% of Patients and at a Higher Rate in NEXAVAR Arm than the Placebo Arm – RCC Study 1

Adverse Reactions NCI- CTCAE v3 Category/Term	NEXAVAR N=451			Placebo N=451		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any Adverse Reactions	95	31	7	86	22	6
Cardiovascular, General						
Hypertension	17	3	<1	2	<1	0
Constitutional symptoms						
Fatigue	37	5	<1	28	3	<1
Weight loss	10	<1	0	6	0	0
Dermatology/skin						
Rash/desquamation	40	<1	0	16	<1	0
Hand-foot skin reaction	30	6	0	7	0	0
Alopecia	27	<1	0	3	0	0
Pruritus	19	<1	0	6	0	0
Dry skin	11	0	0	4	0	0
Gastrointestinal symptoms						

Diarrhea	43	2	0	13	<1	0
Nausea	23	<1	0	19	<1	0
Anorexia	16	<1	0	13	1	0
Vomiting	16	<1	0	12	1	0
Constipation	15	<1	0	11	<1	0
Hemorrhage/bleeding						
Hemorrhage – all sites	15	2	0	8	1	<1
Neurology						
Neuropathy-sensory	13	<1	0	8	<1	0
Pain						
Pain, abdomen	11	2	0	9	2	0
Pain, joint	10	2	0	8	<1	0
Pain, headache	10	<1	0	8	<1	0
Pulmonary						
Dyspnea	14	3	<1	12	2	<1

The rate of adverse reactions (including those associated with progressive disease) resulting in permanent discontinuation was similar in both the NEXAVAR and placebo groups (10% of NEXAVAR patients and 8% of placebo patients).

Laboratory Abnormalities

The following laboratory abnormalities were observed in RCC patients in Study 1:

Hypophosphatemia was a common laboratory finding, observed in 45% of NEXAVAR-treated patients compared to 11% of placebo patients. CTCAE Grade 3 hypophosphatemia (1–2 mg/dL) occurred in 13% of NEXAVAR-treated patients and 3% of patients in the placebo group. There were no cases of CTCAE Grade 4 hypophosphatemia (<1 mg/dL) reported in either NEXAVAR or placebo patients. The etiology of hypophosphatemia associated with NEXAVAR is not known.

Elevated lipase was observed in 41% of patients treated with NEXAVAR compared to 30% of patients in the placebo group. CTCAE Grade 3 or 4 lipase elevations occurred in 12% of patients in the NEXAVAR group compared to 7% of patients in the placebo group. Elevated amylase was observed in 30% of patients treated with NEXAVAR compared to 23% of patients in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 1% of patients in the NEXAVAR group compared to 3% of patients in the placebo group. Many of the lipase and amylase elevations were transient, and in the majority of cases NEXAVAR treatment was not interrupted. Clinical pancreatitis was reported in 3 of 451 NEXAVAR-treated patients (one CTCAE Grade 2 and two Grade 4) and 1 of 451 patients (CTCAE Grade 2) in the placebo group.

Lymphopenia was observed in 23% of NEXAVAR-treated patients and 13% of placebo patients. CTCAE Grade 3 or 4 lymphopenia was reported in 13% of NEXAVAR-treated patients and 7% of placebo patients. Neutropenia was observed in 18% of NEXAVAR-treated patients and 10% of placebo patients. CTCAE Grade 3 or 4 neutropenia was reported in 5% of NEXAVAR-treated patients and 2% of placebo patients.

Anemia was observed in 44% of NEXAVAR-treated patients and 48% of placebo patients. CTCAE Grade 3 or 4 anemia was reported in 2% of NEXAVAR-treated patients and 4% of placebo patients.

Thrombocytopenia was observed in 12% of NEXAVAR-treated patients and 5% of placebo patients. CTCAE Grade 3 or 4 thrombocytopenia was reported in 1% of NEXAVAR-treated patients and 0% of placebo patients.

6.3 Additional Data from Multiple Clinical Trials

The following additional drug-related adverse reactions and laboratory abnormalities were reported from clinical trials of NEXAVAR-(*very common* 10% or greater, *common* 1 to less than 10%, *uncommon* 0.1% to less than 1%):

Cardiovascular: *Common:* congestive heart failure,^{*,†} *Uncommon:* hypertensive crisis^{*}, myocardial ischemia and/or infarction.^{*}

[†]In company sponsored clinical trials, congestive heart failure was reported as an adverse event in 1.8% of patients treated with sorafenib (N= 2278). In study 11213 (RCC), adverse events consistent with congestive heart failure were reported in 1.7% of those treated with sorafenib and in 0.7% of those receiving placebo. In study 100554 (HCC), these events were reported in 0.99% of those treated with sorafenib and in 1.1% of those receiving placebo.

Dermatologic: *Very common:* erythema *Common:* exfoliative dermatitis, acne, flushing *Uncommon:* folliculitis, eczema, erythema multiforme, keratoacanthomas/squamous cell cancer of the skin, Stevens - Johnson Syndrome

Digestive: *Very common:* increased lipase, increased amylase *Common:* mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia *Uncommon:* pancreatitis, gastrointestinal reflux, gastritis, gastrointestinal perforations*, cholecystitis, cholangitis

Note that elevations in lipase are very common (41%, see below); a diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values

General Disorders: *Very common:* hemorrhage (including gastrointestinal* & respiratory tract* and uncommon cases of cerebral hemorrhage*), asthenia, pain (including mouth, bone, and tumor pain) *Common:* decreased appetite, influenza-like illness, pyrexia *Uncommon:* infection

Hematologic: *Very common:* leukopenia, lymphopenia *Common:* anemia, neutropenia, thrombocytopenia *Uncommon:* INR abnormal

Hypersensitivity: *Uncommon:* hypersensitivity reactions (including skin reactions and urticaria)

Metabolic and Nutritional: *Very common:* hypophosphatemia *Common:* transient increases in transaminases *Uncommon:* dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hypothyroidism, hyperthyroidism

Musculoskeletal: *Common:* arthralgia, myalgia

Nervous System and Psychiatric: *Common:* depression *Uncommon:* tinnitus, reversible posterior leukoencephalopathy*

Renal and Genitourinary: *Common:* renal failure

Reproductive: *Common:* erectile dysfunction *Uncommon:* gynecomastia

Respiratory: *Common:* hoarseness *Uncommon:* rhinorrhea, interstitial lung disease-like events (includes reports of pneumonitis, radiation pneumonitis, acute respiratory distress, interstitial pneumonia, pulmonitis and lung inflammation)

*adverse reactions may have a life-threatening or fatal outcome

In addition, the following medically significant adverse reactions were uncommon during clinical trials of NEXAVAR: transient ischemic attack, arrhythmia, thromboembolism. For these adverse reactions, the causal relationship to NEXAVAR has not been established.

7 DRUG INTERACTIONS

7.1 Carboplatin and Paclitaxel

Concomitant use of carboplatin (AUC=6 mg/ml-min) and paclitaxel (225 mg/m²) once every three weeks with NEXAVAR (400 mg twice daily) resulted in a 30% increase in paclitaxel AUC, a 50% increase in sorafenib AUC, and no change in carboplatin AUC. Sorafenib in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer, due to increased mortality observed with the addition of sorafenib compared to those treated with carboplatin and paclitaxel alone. No definitive cause was identified for this finding. [see *Contraindications (4)* and *Warnings and Precautions (5.8)*].

7.2 UGT1A1 and UGT1A9 Substrates

Caution is recommended when administering NEXAVAR with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (for example, irinotecan). Sorafenib inhibits glucuronidation by the UGT1A1 (K_i value: 1 micromolar) and UGT1A9 pathways (K_i value: 2 micromolar). Systemic exposure to substrates of UGT1A1 and UGT1A9 may increase when co-administered with NEXAVAR [see *Warnings and Precautions (5.9)*].

In clinical studies, when NEXAVAR was administered with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67–120% increase in the AUC of SN-38 and a 26–42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown.

7.3 Docetaxel

Concomitant use of docetaxel (75 or 100 mg/m² administered every 21 days) with NEXAVAR (200 or 400 mg twice daily), administered with a 3-day break in dosing around administration of docetaxel, resulted in a 36–80% increase in docetaxel AUC and a 18–32% increase in docetaxel C_{max}. Caution is recommended when NEXAVAR is co-administered with docetaxel [see *Warnings and Precautions (5.10)*].

7.4 Doxorubicin

Concomitant treatment with NEXAVAR resulted in a 21% increase in the AUC of doxorubicin. Caution is recommended when administering doxorubicin with NEXAVAR. The clinical significance of these findings is unknown [see *Warnings and Precautions* (5.11)].

7.5 Fluorouracil

Both increases (21%–47%) and decreases (10%) in the AUC of fluorouracil were observed with concomitant treatment with NEXAVAR. Caution is recommended when NEXAVAR is co-administered with fluorouracil/leucovorin.

7.6 CYP2B6 and CYP2C8 Substrates

Sorafenib inhibits CYP2B6 and CYP2C8 *in vitro* with K_i values of 8 and 1–2 micromolar, respectively. Systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when co-administered with NEXAVAR. Caution is recommended when administering substrates of CYP2B6 and CYP2C8 with NEXAVAR.

7.7 CYP3A4 Inducers

Continuous concomitant administration of NEXAVAR and rifampicin resulted in an average 37% reduction of sorafenib AUC. Other inducers of CYP3A4 activity (for example, *Hypericum perforatum* also known as St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) may also increase metabolism of sorafenib and thus decrease sorafenib concentrations [see *Dosage and Administration* (2)].

7.8 CYP3A4 Inhibitors and CYP Isoform Substrates

In vitro data indicate that sorafenib is metabolized by CYP3A4 and UGT1A9 pathways. Ketoconazole (400 mg), a potent inhibitor of CYP3A4, administered once daily for 7 days did not alter the mean AUC of a single oral 50 mg dose of sorafenib in healthy volunteers. Therefore, sorafenib metabolism is unlikely to be altered by CYP3A4 inhibitors.

Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C19, CYP2D6, and CYP3A4 as indicated by K_i values of 17 micromolar, 22 micromolar, and 29 micromolar, respectively. Administration of NEXAVAR 400 mg twice daily for 28 days did not alter the exposure of concomitantly administered midazolam (CYP3A4 substrate), dextromethorphan (CYP2D6 substrate), and omeprazole (CYP2C19 substrate). This indicates that sorafenib is unlikely to alter the metabolism of substrates of these enzymes *in vivo*.

Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C9 with a K_i value of 7–8 micromolar. The possible effect of sorafenib on the metabolism of the CYP2C9 substrate warfarin was assessed indirectly by measuring PT-INR. The mean changes from baseline in PT-INR were not higher in NEXAVAR patients compared to placebo patients, suggesting that sorafenib did not inhibit warfarin metabolism *in vivo* [see *Warnings and Precautions* (5.6)].

7.9 P-glycoprotein Substrates

Sorafenib is an inhibitor of P-glycoprotein *in vitro*, therefore may increase the concentrations of concomitant drugs that are P-glycoprotein substrates.

7.10 *In Vitro* Studies: CYP Enzyme Induction

CYP1A2 and CYP3A4 activities were not altered after treatment of cultured human hepatocytes with sorafenib, indicating that sorafenib is unlikely to be an inducer of CYP1A2 or CYP3A4.

7.11 Combination with Other Antineoplastic Agents

In clinical studies, NEXAVAR has been administered with a variety of other antineoplastic agents at their commonly used dosing regimens, including gemcitabine, oxaliplatin, doxorubicin, docetaxel, and irinotecan. Sorafenib had no effect on the pharmacokinetics of gemcitabine or oxaliplatin. [see *Drug Interactions* (7.2, 7.3, 7.4 and 7.5) for information about interactions with irinotecan, docetaxel, doxorubicin and fluorouracil/leucovorin.]

7.12 Neomycin

The average plasma exposure (AUC) of sorafenib was decreased by 54% in healthy volunteers who first received neomycin 1 g three times daily for 5 days orally. Therefore, the coadministration of sorafenib with oral neomycin should be carefully considered. Effects of other antibiotics on sorafenib pharmacokinetics have not been studied [see *Warnings & Precautions* (5.13)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see 'Warnings and Precautions' section].

Based on its mechanism of action and findings in animals, NEXAVAR may cause fetal harm when administered to a pregnant woman. Sorafenib caused embryo-fetal toxicities in animals at maternal exposures that were significantly lower than the human exposures at the recommended dose of 400 mg twice daily. There are no adequate and well-controlled studies in pregnant women using NEXAVAR. Women of childbearing potential should be advised to avoid becoming pregnant while on NEXAVAR. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

When administered to rats and rabbits during the period of organogenesis, sorafenib was teratogenic and induced embryo-fetal toxicity (including increased post-implantation loss, resorptions, skeletal retardations, and retarded fetal weight). The effects occurred at doses considerably below the recommended human dose of 400 mg twice daily (approximately 500 mg/m²/day on a body surface area basis). Adverse intrauterine development effects were seen at doses \geq 0.2 mg/kg/day (1.2 mg/m²/day) in rats and 0.3 mg/kg/day (3.6 mg/m²/day) in rabbits. These doses result in exposures (AUC) approximately 0.008 times the AUC seen in patients at the recommended human dose. A NOAEL (no observed adverse effect level) was not defined for either species, since lower doses were not tested.

8.3 Nursing Mothers

It is not known whether sorafenib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NEXAVAR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Following administration of radiolabeled sorafenib to lactating Wistar rats, approximately 27% of the radioactivity was secreted into the milk. The milk to plasma AUC ratio was approximately 5:1.

8.4 Pediatric Use

The safety and effectiveness of NEXAVAR in pediatric patients have not been studied.

Repeat dosing of sorafenib to young and growing dogs resulted in irregular thickening of the femoral growth plate at daily sorafenib doses \geq 800 mg/m² (approximately 0.3 times the AUC at the recommended human dose), hypocellularity of the bone marrow adjoining the growth plate at 200 mg/m²/day (approximately 0.1 times the AUC at the recommended human dose), and alterations of the dentin composition at 800 mg/m²/day. Similar effects were not observed in adult dogs when dosed for 4 weeks or less.

8.5 Geriatric Use

In total, 50% of HCC patients treated with NEXAVAR were age 65 years or older, and 19% were 75 and older. In total, 32% of RCC patients treated with NEXAVAR were age 65 years or older, and 4% were 75 and older. No differences in safety or efficacy were observed between older and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment

In vitro and *in vivo* data indicate that sorafenib is primarily metabolized by the liver. Comparison of data across studies suggests that patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment have sorafenib AUCs that may be 23– 65% lower than subjects with normal hepatic function. Systemic exposure and safety data were comparable in HCC patients with Child-Pugh A and B hepatic impairment. NEXAVAR has not been studied in patients with Child-Pugh C hepatic impairment [see 'Warnings and Precautions' (5.12) and 'Clinical Pharmacology' (12.3)].

8.7 Patients with Renal Impairment

NEXAVAR has not been studied in patients undergoing dialysis. No dosage adjustment is necessary when administering NEXAVAR to patients with mild, moderate or severe renal impairment not undergoing dialysis [see 'Clinical Pharmacology' (12.3)].

Monitoring of fluid balance and electrolytes in patients at risk of renal dysfunction is advised.

10 OVERDOSAGE

There is no specific treatment for NEXAVAR overdose.

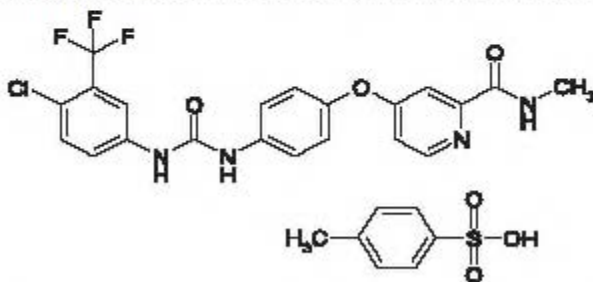
The highest dose of NEXAVAR studied clinically is 800 mg twice daily. The adverse reactions observed at this dose were primarily diarrhea and dermatologic. No information is available on symptoms of acute overdose in animals because of the saturation of absorption in oral acute toxicity studies conducted in animals.

In cases of suspected overdose, NEXAVAR should be withheld and supportive care instituted.

11 DESCRIPTION

NEXAVAR, a kinase inhibitor, is the tosylate salt of sorafenib.

Sorafenib tosylate has the chemical name 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)*N*²-methylpyridine-2-carboxamide 4-methylbenzenesulfonate and its structural formula is:



Sorafenib tosylate is a white to yellowish or brownish solid with a molecular formula of $C_{21}H_{16}ClF_3N_4O_3 \times C_7H_8O_3S$ and a molecular weight of 637.0 g/mole. Sorafenib tosylate is practically insoluble in aqueous media, slightly soluble in ethanol and soluble in PEG 400.

Each red, round NEXAVAR film-coated tablet contains sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib and the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, titanium dioxide and ferric oxide red.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sorafenib is a kinase inhibitor that decreases tumor cell proliferation *in vitro*. Sorafenib was shown to inhibit multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT-3, RET, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR- β). Several of these kinases are thought to be involved in tumor cell signaling, angiogenesis, and apoptosis. Sorafenib inhibited tumor growth and angiogenesis of human hepatocellular carcinoma and renal cell carcinoma, and several other human tumor xenografts in immunocompromised mice.

12.3 Pharmacokinetics

After administration of NEXAVAR tablets, the mean relative bioavailability is 38–49% when compared to an oral solution. The mean elimination half-life of sorafenib is approximately 25–48 hours. Multiple dosing of NEXAVAR for 7 days resulted in a 2.5- to 7-fold accumulation compared to single dose administration. Steady-state plasma sorafenib concentrations are achieved within 7 days, with a peak-to-trough ratio of mean concentrations of less than 2.

Absorption and Distribution

Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When given with a moderate-fat meal (30% fat; 700 calories), bioavailability was similar to that in the fasted state. With a high-fat meal (50% fat; 900 calories), sorafenib bioavailability was reduced by 29% compared to administration in the fasted state. It is recommended that NEXAVAR be administered without food [see *Dosage and Administration* (2)].

Mean C_{max} and AUC increased less than proportionally beyond doses of 400 mg administered orally twice daily.

In vitro binding of sorafenib to human plasma proteins is 99.5%.

Metabolism and Elimination

Sorafenib is metabolized primarily in the liver, undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9.

Sorafenib accounts for approximately 70–85% of the circulating analytes in plasma at steady-state. Eight metabolites of sorafenib have been identified, of which five have been detected in plasma. The main circulating metabolite of sorafenib in plasma, the pyridine N-oxide, shows *in vitro* potency similar to that of sorafenib. This metabolite comprises approximately 9–18% of circulating analytes at steady-state.

Following oral administration of a 100 mg dose of a solution formulation of sorafenib, 98% of the dose was recovered within 14 days, with 77% of the dose excreted in feces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in feces but not in urine.

Special Populations

Age

Analyses of demographic data suggest that no dose adjustments are necessary for age.

Gender

Analyses of demographic data suggest that no dose adjustments are necessary for gender.

Race

A study of the pharmacokinetics of sorafenib indicated that the mean AUC of sorafenib in Asians (N=78) was 30% lower than in Caucasians (N=40).

Pediatric

There are no pharmacokinetic data in pediatric patients.

Hepatic Impairment

Sorafenib is cleared primarily by the liver.

Comparison of data across studies suggests that in HCC patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, 400 mg doses of sorafenib appear to be associated with AUC values that were 23 to 65% lower than those of other subjects without hepatic impairment. The AUC of sorafenib is similar between HCC patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. The pharmacokinetics of sorafenib have not been studied in patients with severe (Child-Pugh C) hepatic impairment [see *Warnings and Precautions* (5.12) and *Use in Specific Populations* (8.6)].

Renal Impairment

In a study of drug disposition after a single oral dose of radiolabeled sorafenib to healthy subjects, 19% of the administered dose of sorafenib was excreted in urine.

In a clinical pharmacology study, the pharmacokinetics of sorafenib were evaluated following administration of a single 400 mg dose to subjects with normal renal function, and in subjects with mild (CrCl > 50–80 ml/min), moderate (CrCl 30–50 ml/min), or severe (CrCl < 30 ml/min) renal impairment, not undergoing dialysis. There was no relationship observed between sorafenib exposure and renal function. No dosage adjustment is necessary based on mild, moderate or severe renal impairment not undergoing dialysis [see *Use in Specific Populations* (8.7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with sorafenib.

Sorafenib was clastogenic when tested in an *in vitro* mammalian cell assay (Chinese hamster ovary) in the presence of metabolic activation. Sorafenib was not mutagenic in the *in vitro* Ames bacterial cell assay or clastogenic in an *in vivo* mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final drug substance (<0.15%), was positive for mutagenesis in an *in vitro* bacterial cell assay (Ames test) when tested independently.

No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. However, results from the repeat-dose toxicity studies suggest there is a potential for sorafenib to impair reproductive function and fertility. Multiple adverse effects were observed in male and female reproductive organs, with the rat being more susceptible than mice or dogs. Typical changes in rats consisted of testicular atrophy or degeneration, degeneration of epididymis, prostate, and seminal vesicles, central necrosis of the corpora lutea and arrested

follicular development. Sorafenib-related effects on the reproductive organs of rats were manifested at daily oral doses ≥ 5 mg/kg (30 mg/m²). This dose results in an exposure (AUC) that is approximately 0.5 times the AUC in patients at the recommended human dose. Dogs showed tubular degeneration in the testes at 30 mg/kg/day (600 mg/m²/day). This dose results in an exposure that is approximately 0.3 times the AUC at the recommended human dose. Oligospermia was observed in dogs at 60 mg/kg/day (1200 mg/m²/day) of sorafenib.

Adequate contraception should be used during therapy and for at least 2 weeks after completing therapy.

14 CLINICAL STUDIES

The clinical safety and efficacy of NEXAVAR have been studied in patients with hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC).

14.1 Hepatocellular Carcinoma

The HCC Study was a Phase 3, international, multicenter, randomized, double blind, placebo-controlled trial in patients with unresectable hepatocellular carcinoma. Overall survival was the primary endpoint. A total of 602 patients were randomized; 299 to NEXAVAR 400 mg twice daily and 303 to matching placebo.

Demographics and baseline disease characteristics were similar between the NEXAVAR and placebo groups with regard to age, gender, race, performance status, etiology (including hepatitis B, hepatitis C and alcoholic liver disease), TNM stage (stage I: <1% vs. <1%; stage II: 10.4% vs. 8.3%; stage III: 37.8% vs. 43.6%; stage IV: 50.8% vs. 46.9%), absence of both macroscopic vascular invasion and extrahepatic tumor spread (30.1% vs. 30.0%), and Barcelona Clinic Liver Cancer stage (stage B: 18.1% vs. 18.8%; stage C: 81.6% vs. 83.2%; stage D: <1% vs. 0%). Liver impairment by Child-Pugh score was comparable between the NEXAVAR and placebo groups (Class A: 95% vs. 98%; B: 5% vs. 2%). Only one patient with Child-Pugh class C was entered. Prior treatments included surgical resection procedures (19.1% vs. 20.5%), locoregional therapies (including radiofrequency ablation, percutaneous ethanol injection and transarterial chemoembolization; 38.8% vs. 40.6%), radiotherapy (4.3% vs. 5.0%) and systemic therapy (3.0% vs. 5.0%).

The trial was stopped for efficacy following a pre-specified second interim analysis for survival showing a statistically significant advantage for NEXAVAR over placebo for overall survival (HR: 0.69, p= 0.00058) (see Table 4 and Figure 1). This advantage was consistent across all subsets analyzed.

Final analysis of time to tumor progression (TTP) based on data from an earlier time point (by independent radiologic review) also was significantly longer in the NEXAVAR arm (HR: 0.58, p=0.000007) (see Table 4).

Table 4: Efficacy Results from HCC Study

Efficacy Parameter	NEXAVAR (N=299)	Placebo (N=303)	Hazard Ratio ¹ (95% CI)	P-value (log-rank test ²)
Overall Survival				
Median, months (95% CI)	10.7 (9.4, 13.3)	7.9 (6.8, 9.1)	0.69 (0.55, 0.87)	0.00058
No. of events	143	178		
Time to Progression³				
Median, months (95% CI)	5.5 (4.1, 6.9)	2.8 (2.7, 3.9)	0.58 (0.45, 0.74)	0.000007
No. of events	107	156		

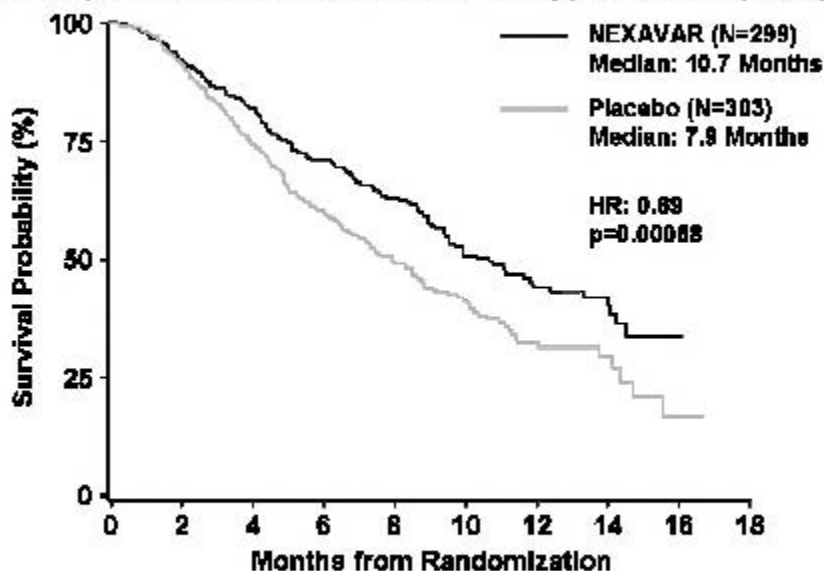
CI=Confidence interval

1. Hazard ratio, sorafenib/placebo, stratified Cox model

2. Stratified logrank (for the interim analysis of survival, the stopping boundary one-sided alpha = 0.0077)

3. The time-to-progression (TTP) analysis, based on independent radiologic review, was based on data from an earlier time point than the survival analysis

Figure 1: Kaplan-Meier Curve of Overall Survival in HCC Study (Intent-to-Treat Population)



Patients at Risk

NEXAVAR	270	234	200	140	89	48	24	1	0
Placebo	272	217	174	108	69	31	14	3	0

14.2 Renal Cell Carcinoma

The safety and efficacy of NEXAVAR in the treatment of advanced renal cell carcinoma (RCC) were studied in the following two randomized controlled clinical trials.

RCC Study 1 was a Phase 3, international, multicenter, randomized, double blind, placebo-controlled trial in patients with advanced renal cell carcinoma who had received one prior systemic therapy. Primary study endpoints included overall survival and progression-free survival (PFS). Tumor response rate was a secondary endpoint. The PFS analysis included 769 patients stratified by MSKCC (Memorial Sloan Kettering Cancer Center) prognostic risk category (low or intermediate) and country and randomized to NEXAVAR 400 mg twice daily (N=384) or to placebo (N=385).

Table 5 summarizes the demographic and disease characteristics of the study population analyzed. Baseline demographics and disease characteristics were well balanced for both treatment groups. The median time from initial diagnosis of RCC to randomization was 1.6 and 1.9 years for the NEXAVAR and placebo groups, respectively.

Table 5: Demographic and Disease Characteristics – RCC Study 1

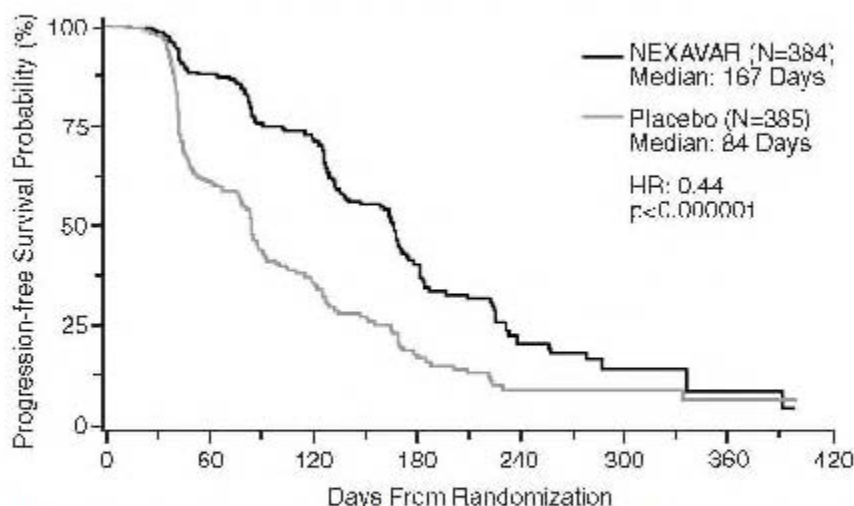
Characteristics	NEXAVAR N=384		Placebo N=385	
	n	(%)	n	(%)
Gender				
Male	267	(70)	287	(75)
Female	118	(30)	98	(25)
Race				
White	278	(72)	278	(73)
Black/Asian/ Hispanic/Other	11	(3)	10	(2)
Not reported ^a	97	(25)	97	(25)
Age group				
< 65 years	255	(67)	280	(73)
≥ 65 years	127	(33)	103	(27)
ECOG performance status at baseline				
0	184	(48)	180	(47)
1	191	(50)	201	(52)
2	6	(2)	1	(<1)
Not reported	3	(<1)	3	(<1)
MSKCC prognostic risk category				
Low	200	(52)	194	(50)
Intermediate	184	(48)	191	(50)
Prior IL-2 and/or interferon				
Yes	319	(83)	313	(81)
No	65	(17)	72	(19)

a. Race was not collected from the 186 patients enrolled in France due to local regulations. In 8 other patients, race was not available at the time of analysis.

Progression-free survival, defined as the time from randomization to progression or death from any cause, whichever occurred earlier, was evaluated by blinded independent radiological review using RECIST criteria.

Figure 2 depicts Kaplan-Meier curves for PFS. The PFS analysis was based on a two-sided Log-Rank test stratified by MSKCC prognostic risk category and country.

Figure 2: Kaplan-Meier Curves for Progression-free Survival – RCC Study 1



NOTE: HR is from Cox regression model with the following covariates: MSKCC prognostic risk category and country. P-value is from two-sided Log-Rank test stratified by MSKCC prognostic risk category and country.

The median PFS for patients randomized to NEXAVAR was 167 days compared to 84 days for patients randomized to placebo. The estimated hazard ratio (risk of progression with NEXAVAR compared to placebo) was 0.44 (95% CI: 0.35, 0.55).

A series of patient subsets were examined in exploratory univariate analyses of PFS. The subsets included age above or below 65 years, ECOG PS 0 or 1, MSKCC prognostic risk category, whether the prior therapy was for progressive metastatic disease or for an earlier disease setting, and time from diagnosis of less than or greater than 1.5 years. The effect of NEXAVAR on PFS was consistent across these subsets, including patients with no prior IL-2 or interferon therapy (N=137; 65 patients receiving NEXAVAR and 72 placebo), for whom the median PFS was 172 days on NEXAVAR compared to 85 days on placebo.

Tumor response was determined by independent radiologic review according to RECIST criteria. Overall, of 672 patients who were evaluable for response, 7 (2%) NEXAVAR patients and 0 (0%) placebo patients had a confirmed partial response. Thus the gain in PFS in NEXAVAR-treated patients primarily reflects the stable disease population.

At the time of a planned interim survival analysis, based on 220 deaths, overall survival was longer for NEXAVAR than placebo with a hazard ratio (NEXAVAR over placebo) of 0.72. This analysis did not meet the prespecified criteria for statistical significance. Additional analyses are planned as the survival data mature.

RCC Study 2 was a Phase 2 randomized discontinuation trial in patients with metastatic malignancies, including RCC. The primary endpoint was the percentage of randomized patients remaining progression-free at 24 weeks. All patients received NEXAVAR for the first 12 weeks. Radiologic assessment was repeated at week 12. Patients with <25% change in bi-dimensional tumor measurements from baseline were randomized to NEXAVAR or placebo for a further 12 weeks. Patients who were randomized to placebo were permitted to cross over to open-label NEXAVAR upon progression. Patients with tumor shrinkage $\geq 25\%$ continued NEXAVAR, whereas patients with tumor growth $\geq 25\%$ discontinued treatment.

Two hundred and two patients with advanced RCC were enrolled into RCC Study 2, including patients who had received no prior therapy and patients with tumor histology other than clear cell carcinoma. After the initial 12 weeks of NEXAVAR therapy, 79 RCC patients continued on open-label NEXAVAR, and 85 patients were randomized to NEXAVAR or placebo. After an additional 12 weeks, at week 24, for the 65 randomized patients, the progression-free rate was significantly higher in patients randomized to NEXAVAR (16/32, 50%) than in patients randomized to placebo (6/33, 18%) ($p=0.0077$). Progression-free survival was significantly longer in the NEXAVAR group (163 days) than in the placebo group (41 days) ($p=0.0001$, HR=0.29).

16 HOW SUPPLIED/STORAGE AND HANDLING

NEXAVAR tablets are supplied as round, biconvex, red film-coated tablets, debossed with the "Bayer cross" on one side and "200" on the other side, each containing sorafenib tosylate equivalent to 200 mg of sorafenib.

Bottles of 120 tablets NDC 50419-488-58

Storage

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) (see USP controlled room temperature). Store in a dry place.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling

17.1 Cardiac Ischemia; Infarction

Physicians should also discuss with patients that cardiac ischemia and/or infarction has been reported during NEXAVAR treatment, and that they should immediately report any episodes of chest pain or other symptoms of cardiac ischemia and/or infarction [see Warnings and Precautions (5.1)].

17.2 Bleeding; Gastrointestinal Perforation

Physicians should inform patients that NEXAVAR may increase the risk of bleeding and that they should promptly report any episodes of bleeding.

Patients should be advised that cases of gastrointestinal perforation have been reported in patients taking NEXAVAR [see Warnings and Precautions (5.2 and 5.5)].

17.3 Skin Reactions; Hypertension

Patients should be advised of the possible occurrence of hand-foot skin reaction and rash during NEXAVAR treatment and appropriate countermeasures.

Patients should be informed that hypertension may develop during NEXAVAR treatment, especially during the first six weeks of therapy, and that blood pressure should be monitored regularly during treatment [see Warnings and Precautions (5.3 and 5.4)].

17.4 Birth Defects and Fetal Loss

Physicians should inform female patients that NEXAVAR may cause birth defects or fetal loss and that they should not become pregnant during treatment with NEXAVAR and for at least 2 weeks after stopping treatment. Both male and female patients should be counseled to use effective birth control during treatment with NEXAVAR and for at least 2 weeks after stopping treatment. Female patients should also be advised against breast-feeding while receiving NEXAVAR [see Warnings and Precautions (5.14) and Use in Specific Populations (8.3)].

FDA-approved Patient Labeling

Patient Information:
NEXAVAR® (NEX-A-VAR)
(sorafenib)
tablets, oral

Read the Patient Information that comes with NEXAVAR before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about NEXAVAR?

NEXAVAR may cause birth defects or death of an unborn baby.

- Women should not get pregnant during treatment with NEXAVAR and for at least 2 weeks after stopping treatment.
- Men and women should use effective birth control during treatment with NEXAVAR and for at least 2 weeks after stopping treatment. Talk with your doctor about effective birth control methods.

Call your doctor right away if you become pregnant during treatment with NEXAVAR.

What is NEXAVAR?

NEXAVAR is an anticancer medicine used to treat a certain type of liver or kidney cancer called:

1. Hepatocellular carcinoma (HCC, a type of liver cancer), when it can not be treated with surgery
2. Renal cell carcinoma (RCC, a type of kidney cancer)

NEXAVAR has not been studied in children.

What should I tell my doctor before starting NEXAVAR?

Tell your doctor about all of your health conditions, including if you:

- have any allergies
- have heart problems or chest pain
- have bleeding problems
- have high blood pressure
- have kidney problems in addition to kidney cancer
- have liver problems in addition to liver cancer
- are pregnant or planning to become pregnant. See **"What is the most important information I should know about NEXAVAR?"**
- are breast-feeding or planning to breast-feed. It is not known if NEXAVAR passes into your breast milk. You and your doctor should decide if you will take NEXAVAR or breast-feed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. NEXAVAR and certain other medicines can interact with each other and cause serious side effects. **Especially, tell your doctor if you take warfarin (Coumadin®)*.**

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine. Do not take other medicines with NEXAVAR until you have talked with your doctor.

How do I take NEXAVAR?

- Take NEXAVAR exactly as prescribed by your doctor.
- The usual dose of NEXAVAR is 2 tablets taken two times a day (for a total of 4 tablets each day). Your doctor may change your dose during treatment or stop treatment for some time if you have side effects.
- Swallow NEXAVAR tablets whole with water.
- Take NEXAVAR without food (at least 1 hour before or 2 hours after a meal).
- If you miss a dose of NEXAVAR, skip the missed dose, and take your next dose at your regular time. Do not double your dose of NEXAVAR. Call your doctor right away if you take too much NEXAVAR.

What are possible side effects of NEXAVAR?

NEXAVAR may cause serious side effects, including:

- **decreased blood flow to the heart and heart attack.** Get emergency help right away and call your doctor if you get symptoms such as chest pain, shortness of breath, feel lightheaded or faint, nausea, vomiting, sweating a lot.
- **bleeding problems.** NEXAVAR may increase your chance of bleeding. Tell your doctor if you have any bleeding while taking NEXAVAR.
- **high blood pressure.** Your blood pressure should be checked every week during the first 6 weeks of starting NEXAVAR. Your blood pressure should be checked regularly and any high blood pressure should be treated while you are receiving NEXAVAR.
- **a skin problem called hand-foot skin reaction.** This causes redness, pain, swelling, or blisters on the palms of your hands or soles of your feet. If you get this side effect, your doctor may change your dose or stop treatment for some time.
- **perforation of the bowel.** Tell your doctor right away if you get high fever, nausea, vomiting, severe abdominal pain.

- **possible wound healing problems.** If you need to have a surgical or dental procedure, tell your doctor that you are taking NEXAVAR. NEXAVAR may need to be stopped until your wound heals after some types of surgery.
- **birth defects or death of an unborn baby.** See "What is the most important information I should know about NEXAVAR?"

Other side effects with NEXAVAR may include:

- rash, redness, itching or peeling of your skin
- hair thinning or patchy hair loss
- diarrhea (frequent or loose bowel movements)
- nausea or vomiting
- mouth sores
- weakness
- loss of appetite
- numbness, tingling or pain in your hands and feet
- abdominal pain
- tiredness
- weight loss

Tell your doctor if you have any side effects that bother you or that do not go away. These are not all the side effects with NEXAVAR. Ask your doctor or pharmacist for more information.

How should I store NEXAVAR?

- Store NEXAVAR tablets at room temperature between 59 to 86° F (15 to 30° C), in a dry place.
- Keep NEXAVAR and all medicines out of the reach of children.

General information about NEXAVAR

Medicines are sometimes prescribed for purposes other than those listed in the patient information leaflet. Do not use NEXAVAR for a condition for which it is not prescribed. Do not give NEXAVAR to other people even if they have the same symptoms you have. It may harm them.

This patient information leaflet summarizes the most important information about NEXAVAR. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about NEXAVAR that is written for healthcare professionals. You can visit our website at www.NEXAVAR.com, or call 1-866-NEXAVAR (1-866-639-2827).

What are the ingredients in NEXAVAR?

Active Ingredient: sorafenib tosylate

Inactive Ingredients: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, titanium dioxide and ferric oxide red.

Footnote: *Coumadin (warfarin sodium) is a trademark of Bristol-Myers Squibb Company.

Manufactured for:
Bayer HealthCare Pharmaceuticals Inc.,
Wayne, NJ 07470

Made in Germany

Onyx Pharmaceuticals, Inc.,
2100 Powell Street, Emeryville, CA 94808

Distributed and marketed by:
Bayer HealthCare Pharmaceuticals Inc.,
Wayne, NJ 07470

Marketed by:
Onyx Pharmaceuticals, Inc.
2100 Powell Street, Emeryville, CA 94808

© 2010 Bayer HealthCare Pharmaceuticals Inc. Printed in U.S.A.

APPENDIX F STUDY DRUG INFORMATION

1 STUDY MATERIALS, STUDY DRUG STORAGE

1.1 Study Drug

Tivozanib is formulated for oral administration as a white opaque number 4 gelatin capsule containing 1.0 or 1.5 mg tivozanib. The following dosage strengths will be made available:

- 1.5 mg
- 1.0 mg

Sorafenib is formulated for oral administration as a round, biconvex, red film-coated tablet, debossed with the “Bayer cross” on one side and “200” on the other side. The following dosage strength will be made available:

- 200 mg

The amount of study drug dispensed to the subject at the beginning of each dosing cycle will be sufficient to allow for 3 weeks (21 days) of consecutive once-daily dosing of tivozanib and 4 weeks (28 days) of consecutive twice-daily dosing of sorafenib. Dosing compliance will be monitored at each clinic visit.

1.2 Study Drug Storage

Tivozanib does not have any special storage requirements, and may be stored at room temperature in a dry place, in a secure location. Sorafenib is to be stored at room temperature (15°–25° C) in a dry place, in a secure location.

2 STUDY DRUG ADMINISTRATION

2.1 Route of Administration

Tivozanib and sorafenib will be administered by the oral route.

2.2 Dosing Schedule

Tivozanib: Subjects will receive tivozanib one capsule once daily for 3 weeks followed by 1 week off study drug (1 cycle = 3 weeks on, 1 week off). One cycle will be defined as 4 weeks of treatment. Cycles will be repeated every 4 weeks.

Sorafenib: Subjects will receive sorafenib 2 tablets twice daily, beginning on Day 1 of Cycle 1 and then continuously for 4 weeks. One cycle will be defined as 4 weeks of treatment. Cycles will be repeated every 4 weeks.

2.3 Doses to be Administered

Tivozanib: 1.5 mg/day

Sorafenib: 400 mg twice daily

2.4 Dosing

Tivozanib: The prescribed oral daily dose of tivozanib is to be taken, preferably in the morning, with water. Tivozanib should be taken at least 1 hour before or 2 hours after ingesting any food or other medications. Grapefruit juice should not be ingested during the study. On days of a scheduled clinic visit, the dose of tivozanib should be taken at the clinic after visit procedures are completed. Treatment with tivozanib will continue if tolerated and in the absence of documented disease progression. If a dose is vomited or if a dose is missed for any reason, the dose should not be made up. If Day 1 of a cycle is delayed for any reason, the complete 21 days of tivozanib should be administered once the cycle is started. Only one tivozanib capsule should be taken each day.

Sorafenib: The prescribed twice-daily oral dose of sorafenib should be taken without food at least 1 hour before or 2 hours after ingesting any food or other medications. On days of a scheduled clinic visit, the dose of sorafenib should be taken at the clinic after visit procedures are completed. Treatment with sorafenib will continue if tolerated and in the absence of documented disease progression. If a dose is vomited or if a dose is missed for any reason, the dose should not be made up. If Day 1 of a cycle is delayed for any reason other than an adverse event, the complete 28 days of sorafenib should be administered.

3 DISPENSING, DISPOSAL AND INVENTORY OF STUDY DRUG

1. The investigator (or designee, ie, study pharmacist) at the site will be responsible for handling study drug and maintaining required documentation. The investigator (or designee) will:
 - Prepare the appropriate dose to be dispensed, as determined by the subject's dose assignment.
 - Record pertinent information regarding the doses of study drug prepared (eg, subject identification code, date of dispensing, number of doses/bottles dispensed, etc.) on the Drug Dispensing Log, or other appropriate study drug inventory. This inventory will be maintained throughout the duration of the trial and will be periodically reviewed by a representative of the sponsor.
 - Instruct the subject that all dispensed pill bottles must be returned at each follow-up visit, at which time a tablet/capsule count will be conducted to assure subject dosing compliance.

- Inform the subject that at the completion of a subject's participation in the trial, all partially used and empty pill bottles must be returned to the investigator (or designee) so that a final subject-dosing inventory may be conducted.
2. Throughout the conduct of this trial, the investigator (or designee) will maintain a careful inventory of all partially used and empty bottles of study drug. Empty bottles may then be destroyed in an appropriate manner according to institutional policy. Destruction of such bottles will be documented, and disposition records will later be reviewed by a representative of the sponsor. All partially used bottles may be returned to the sponsor or designee (details to be provided), unless otherwise authorized in writing.

Note: No other use of tivozanib study drug intended for use in this trial is authorized by the sponsor. The investigator (or designee) will be responsible for the appropriate handling and disposition of residual study drug in partially used bottles. *Once returned to the investigator, capsules from partially used bottles will not be re-dispensed to another subject.*

3. Periodically throughout and at the conclusion of the study, an inventory of unused bottles of study drug will be conducted by a representative of the sponsor. At the completion of this trial, all unused study materials will be destroyed by the site or returned to the sponsor (or designee). Destruction of study drug by the site can only occur after the sponsor (or designee) has collected the site's SOP for drug destruction.

4 BOTTLE LABELS

Study drug bottle labels will bear the appropriate label text for investigational agents, as required by governing regulatory agencies.

5 RESUPPLY REQUESTS

An IWRS will be used for management (shipping from depots to study sites, and dispensing to subjects). Information regarding resupply via the IWRS will be in the IWRS study manual, provided separately.

APPENDIX G CLINICAL SYMPTOM AND ADVERSE EVENT GRADING SCALE

CLINICAL ADVERSE EVENT GRADING		
Severity	Grade	Definition
Mild	1	Awareness of symptom, but easily tolerated. Usually transient requiring no special treatment; does not interfere with usual status or activities
Moderate	2	May be ameliorated by simple therapeutic measures; may interfere with usual activities
Severe	3	Incapacitating; unable to perform usual activities
Life-threatening	4	Requires immediate intervention; need for emergency treatment
Fatal	5	Resulting in the subsequent death of the subject

Note: In those cases where further definition of an event is provided by the NCI Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03), please refer to that document for grading and severity information.

*There are exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists, eg. 1) tardive dyskinesia; 2) fixed drug eruptions.

APPENDIX H INTERNATIONAL METASTATIC RENAL CELL CARCINOMA DATABASE CONSORTIUM (IMDC) RISK MODEL

Predefined Database Consortium risk factors:

- Anemia (hemoglobin concentration < lower limit of normal)
- Thrombocytosis (platelet count > upper limit of normal)
- Neutrophilia (neutrophil count > upper limit of normal)
- Hypercalcemia (corrected calcium concentration > upper limit of normal)
- Karnofsky performance status <80% *
- <1 year from initial diagnosis to first treatment with a targeted agent (VEGF or mTOR)

Subject risk categories:

- Favorable risk: No risk factors
- Intermediate risk: One to two risk factors
- Poor risk: Three or more risk factors

Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol*. 2009;27:5794–5799.

Heng DYC, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. *Lancet Oncol*. 2013 February;14(2):141–148.

Ko JJ, Xie W, Kroeger N, et al. The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: a population-based study. *Lancet Oncol*. 2015 Mar;16(3):293-300.

* **Karnofsky performance status scale:**

- 100 - Normal; no complaints; no evidence of disease.
- 90 - Able to carry on normal activity; minor signs or symptoms of disease.
- 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.
- 60 - Requires occasional assistance, but is able to care for most of his personal needs.
- 50 - Requires considerable assistance and frequent medical care.
- 40 - Disabled; requires special care and assistance.
- 30 - Severely disabled; hospital admission is indicated although death not imminent.
- 20 - Very sick; hospital admission necessary; active supportive treatment necessary.
- 10 - Moribund; fatal processes progressing rapidly.
- 0 - Dead