

NCCN Request for Proposals (RFP): Phase I/II Clinical Trials and Correlative Trials of Tivozanib for Selected Cancers

1.0 Purpose

National Comprehensive Cancer Network® (NCCN®) has received a research grant from AVEO Pharmaceuticals, Inc. and Astellas Pharmaceuticals, Inc., (hereafter, “Grantors”) to support NCCN Member Institution(s) faculty for the performance of clinical and correlative studies of tivozanib in the treatment of specific solid tumors. NCCN will serve as the funding organization for these grants that are available only to NCCN investigators.

Proposed trials should not duplicate or compete with trials already in progress for this compound (see below).

These clinical trials should focus on developing innovative single agent and combination studies of tivozanib in specific solid tumors. Studies that evaluate mechanisms and markers of sensitivity and primary and acquired resistance are encouraged. The Scientific Review Committee (SRC) will also consider studies of tivozanib in other solid tumors with high unmet needs, if there is a strong scientific rationale and high feasibility of completion.

It is hoped that proposals submitted in response to this RFP will be useful in guiding further development of tivozanib. Single agent proposals and combination studies guided by strong preclinical rationale are requested. Studies with correlative endpoints are encouraged.

Collaboration between NCCN Member Institutions is strongly encouraged in order to foster the interactive sharing of knowledge and expertise, and to utilize the combined clinical strengths of members, particularly in the case of uncommon tumors.

The NCCN Request for Proposals Development Team (RFPDT) has developed a Request for Proposals (RFP) with a formalized review procedure to accept applications and select the proposals of highest scientific merit. An NCCN Scientific Review Committee (SRC) composed of some members of this group and other NCCN clinical leaders will perform the review of applications.

2.0 Background

NCCN has received a grant from the Grantors for the design and performance of clinical studies using tivozanib to treat solid tumors.

Mechanism of Action

Tivozanib (AV-951) is a potent and selective small molecule inhibitor of the VEGFR-1, -2, and -3 tyrosine kinases. It has been shown to block various VEGF-induced biologic responses at picomolar concentrations in endothelial cells *in vitro* (Table 1). By inhibiting VEGF-induced VEGFR activation, tivozanib inhibits angiogenesis and vascular permeability in tumor tissues, leading indirectly to inhibition of tumor growth.

Table 1. Selectivity of Inhibition of Phosphorylation of RTKs by Tivozanib

	Cell	IC ₅₀ (nmol/L)
VEGFR-2	HUVEC	0.16
VEGFR-1	Flt-1-3T3 ^a	0.21
VEGFR-3	HUVEC	0.24
c-Kit	KU812F	1.63
PDGFR β	NHDF	1.72
FGFR1	NHDF	299
Flt3	Eol-1	422
c-Met	A431	1360
EGFR	A431	>SC ^b
IGFR-1R	HT29	>SC ^b

SC = saturation concentration of tivozanib in serum-free medium; ND = not determined

a: flt-1-transfected NIH3T3.

b: IC50 value is more than saturated concentration in the assay system.

Nonclinical Pharmacology, Pharmacokinetics, and Toxicology

Tivozanib demonstrated antitumor effects against a broad spectrum of solid tumor models after daily oral administrations. These include human tumor xenografts subcutaneously implanted into nude mice and rats, as well as genetically engineered murine tumor models bearing specific human oncogenes such as mutated KRAS and HER2.

Tivozanib is highly protein bound (99.7%).

In vitro studies have shown that the cytochrome (CYP) P450 enzyme system is involved in the metabolism of tivozanib. The primary human hepatic isoform shown to be involved in the biotransformation of tivozanib was CYP 3A4.

Nonclinical toxicology studies were conducted in rats, mice, rabbits, and monkeys to test the safety of tivozanib after single-dose and repeat-dose (up to 39 weeks) administration. Toxicities were similar across species and were consistent with toxicities expected for this class of agents, namely hypertension, growth plate hypertrophy, adrenal necrosis/degeneration, and renal and gastrointestinal effects. Higher drug doses caused more profound toxicities, including death, presumably attributable to direct pharmacological effects. In general, adverse findings resolved or showed signs of ongoing reversal after withdrawal of treatment.

A cardiovascular study in conscious telemetered cynomolgus monkeys did not show any effects on QTc interval.

Experience in Humans

There are 17 completed or ongoing clinical studies of tivozanib. At least some clinical data are available for 14 studies (for 12 studies in subjects with cancer and for 2 of the 5 studies in healthy volunteers, Studies AV-951-09-109 and AV-951-10-111).

Completed and Ongoing Clinical Studies of Tivozanib:

Study ID	Study Design	Inclusion/ Exclusion Criteria	N / Dose	Schedule/ Route of Administration
Monotherapy:				
KRN951/03-B01	Phase I	Adult subjects with histologically or cytologically confirmed, unresponsive / untreatable solid tumors	N = 41a Tivozanib 1.0 mg (n=18) 1.5 mg (n=16) 2.0 mg (n=7)	Orally, once daily for 28 days followed by a 14-day rest period
AV-951-07-201	Phase II	Adult subjects with recurrent or metastatic RCC, or primary RCC not amenable to surgery	N = 272 Tivozanib 1.5 mg for 16 weeks, then continue open-label, randomization to tivozanib or matching placebo (or discontinuation)	Orally, once daily for 21 days followed by a 7-day rest period with no treatment
AV-951-08-105	Phase Ib	Adult subjects with histologically or cytologically confirmed NSCLC	N=17 enrolled (Phase 1b) Tivozanib 1.0 mg (n=9) 1.5 mg (n=8)	Orally, once daily continuously
AV-951-09-301	Phase III	Histologically or cytologically confirmed clear cell RCC; prior nephrectomy; no more than one prior systemic treatment	N=517 enrolled (n=516 dosed) (approximately 250 per treatment group) Tivozanib: 1.5 mg Sorafenib: 400 mg	Tivozanib orally once daily for 21 days followed by a 7-day rest period with no treatment. Sorafenib orally twice daily
AV-951-10-112	Phase I	Advanced solid tumors	N=51 enrolled (n=50 dosed) Tivozanib 1.5 mg	Tivozanib orally once daily for 21 days
AV-951-10-202	Phase II	Unresectable locally recurrent or metastatic RCC	N=100 planned Tivozanib 1.5 mg	Tivozanib orally, once daily for 21 days, followed by a 7-day rest period without treatment
Combination Therapy:				
AV-951-07-102	Phase Ib safety, PK and PG in combination with temsirolimus in subjects with metastatic RCC	Adult subjects with histologically confirmed renal cell carcinoma with a clear cell component	N=27 enrolled Tivozanib 0.5 mg (n=5) 1.0 mg (n=4) 1.5 mg (n=18) Temsirrolimus: 15 mg (n=12) 25 mg (n=15)	Tivozanib orally, once daily for 21 days, followed by a 7-day rest period without treatment Temsirrolimus: IV once weekly beginning Cycle 1, Day 8

Combination Therapy (con't):				
AV-951-07-103	Phase Ib safety and PK in combination with FOLFOX 6 in subjects with advanced colorectal or other gastrointestinal cancer	Adult subjects with histologically or cytologically confirmed, metastatic colorectal or other gastrointestinal malignancy	N=30 enrolled Tivozanib 0.5 mg (n=9) 1.0 mg (n=3) 1.5 mg (n=18) FOLFOX6c	Tivozanib orally, once daily for 21 days, followed by a 7-day rest period without treatment FOLFOX6c chemotherapy every 2 weeks
AV-951-08-104	Phase Ib multicenter safety and PK, in combination with paclitaxel in subjects with advanced or metastatic breast cancer	Adult subjects with histologically or cytologically confirmed, invasive breast cancer. Documented progressive disease (Phase 1b)	N=18 enrolled (Phase 1b); Phase 1b: Tivozanib: 0.5 mg (n=7) 1.0 mg (n=4) 1.5 mg (n=7) Paclitaxel 90 mg/m ²	Tivozanib orally, once daily for 21 days, followed by a 7-day rest period without treatment Paclitaxel IV administered over 1 hour once a week for 3 weeks, followed by 1 week off
AV-951-10-114	Phase Ib, open-label, multi-center, dose-finding study of tivozanib administered in combination with capecitabine (Xeloda®) in subjects with advanced solid tumors	Male and female subjects ≥ 18 years of age, with histologically/ cytologically confirmed advanced solid tumors	N=24 planned Tivozanib: 1.5 mg or 1.0 mg Capecitabine: 825 mg/m ² or 1000 mg/m ² or 1250 mg/m ²	Tivozanib once daily orally for 2 weeks, followed by 1 week of no drug Capecitabine twice daily orally for 2 weeks, followed by 1 week of no drug
Rollover:				
AV-951-09-901 Ongoing	Open-label, multicenter Subjects continue to receive study drug(s) as per the original (parent) protocol.	Subjects who have participated in other Phase 1 /Phase 2 tivozanib (monotherapy or combination) protocols, are tolerating study drug, and displaying clinical benefit	Tivozanib: per parent protocol Combination therapy (if any): per parent protocol	Per parent protocol
AV-951-09-902 Ongoing	Open-label, multi-center Subjects continue to receive study drug(s) as per the original (parent) protocol (AV-951-09-301).	Subjects who have participated in the Phase 3 study of tivozanib vs. sorafenib in RCC (Protocol AV-951-09-301), are tolerating study drug, and displaying clinical benefit	Tivozanib: per parent protocol Sorafenib: per parent protocol	Per parent protocol

Studies in Healthy Volunteers:				
Bioequivalence:				
AV-951-09-109	Phase I, open-label, single center, randomized, 2-period, 2-treatment, crossover bioequivalence study of single doses of tivozanib in healthy volunteers	Healthy male or female, non-smoking, age 18 –55 years, with a body mass index of 19-31 kg/m ²	N=34 Tivozanib tablets 1.5 mg Tivozanib capsules 1.5 mg	Subjects randomly assigned to one of 2 treatment sequences: 1: Group A → Group B 2: Group B → Group A Group A: single oral dose of tivozanib tablet Group B: single oral dose of tivozanib capsule
Mass Balance:				
AV-951-10-111	Phase I, open-label investigation of the absorption, metabolism, and excretion of a single [14C]-tivozanib dose	Healthy adult male subjects (18 – 55 years of age) inclusive; with a body mass index range of 18.5 to 31.0 kg/m ²	N=8 enrolled (n=7 completed) [14C]-tivozanib: 1.5 mg	Single oral dose of [14C]-tivozanib
Food Effects:				
AV-951-10-115	Phase I, single center, open-label, randomized, two-period crossover food effect study of single doses of tivozanib in healthy subjects	Healthy male and female subjects aged 18 to 55 years, inclusive; with a body mass index range of 18.5 to 31.0 kg/m ²	N=30 enrolled Tivozanib 1.5 mg	Subjects randomly assigned to one of 2 treatment sequences: 1: Group A → Group B 2: Group B → Group A Group A: single oral dose of tivozanib after an approximate 10-hour fast Group B: single oral dose of tivozanib following consumption of a standard high fat breakfast
Drug-Drug Interactions:				
TBD	Phase I, open-label investigation of the effect of ketoconazole on the PK, safety, and tolerability of a single dose of tivozanib in healthy subjects	Healthy male and female subjects aged 18 to 55 years, inclusive; with a body mass index range of 18.5 to 31.0 kg/m ²	Up to 30 subjects to be enrolled (to complete approximately 24 subjects) Tivozanib: 1.5 mg Ketoconazole: 400 mg (2 x 200-mg tablets)	Period 1: oral tivozanib administered after a 10-hour fast. Period 2: Once daily doses of oral ketoconazole on Days 37 to 61, coadministered with oral tivozanib on Day 40 (fasting state)

Drug-Drug Interactions (con't):				
AV-951-11-117 Ongoing	Phase I, open-label investigation of the effect of rifampin on the PK, safety, and tolerability of a single dose of tivozanib in healthy subjects	Healthy male and female subjects aged 18 to 55 years, inclusive; with a body mass index range of 18.5 to 31.0 kg/m ²	Up to 30 subjects to be enrolled (to complete approximately 24 subjects) Tivozanib: 1.5 mg Rifampin: 600 mg	Period 1: 1.5 mg oral tivozanib administered after a 10-hour fast. Period 2: Once daily doses of oral rifampin on Days 36 to 63, coadministered with oral tivozanib on Day 42 (fasting state)
Investigator Sponsored Studies:				
	Phase II discovery and validation of predictive markers for tivozanib therapy in metastatic renal cell carcinoma	Patients with metastatic RCC	Up to 69 subjects to be enrolled at one site: Tivozanib: 1.5 mg	1.5 mg oral tivozanib for one week prior to surgery, post surgery tivozanib (3 weeks on, 1 off) until progression
	Phase II Presurgical Study of Tivozanib in Patients with Metastatic Renal Cell Carcinoma	Patients with metastatic RCC	Up to 50 subjects to be enrolled at one site: Tivozanib: 1.5 mg	tivozanib for 8 weeks, undergo restaging, cytoreductive nephrectomy within the next three weeks of treatment
	A pilot clinical trial of Neoadjuvant Tivozanib in Localized Renal Cell Carcinoma	Patients locally advanced RCC	Up to 10 subjects to be enrolled at one site: Tivozanib: 1.5 mg	tivozanib for 2 cycles (4 weeks x 2), restaged utilizing and considered for nephrectomy 25 days after the last day of cycle 2 (5 half-lives)
	Phase II, Quantitative Functional Capacity Testing in Metastatic RCC patients Treated with Either Tivozanib or Sunitinib	Patients with metastatic RCC	Up to 40 subjects to be enrolled at one site: Tivozanib: 1.5 mg	1.5 mg oral tivozanib (3 weeks on, 1 off). Tumor assessments will occur every 12 weeks as standard of care
	Phase I/II tivozanib alone or in combination with gemcitabine in metastatic refractory renal cell carcinoma: a sequential biomarker-driven study	Patients with metastatic RCC	Up to 30 subjects to be enrolled at two sites: Tivozanib: 1.5 mg	1.5 mg oral tivozanib we will attempt to adopt a 3+3 design for 3 cohorts when adding gemcitabine

Investigator Sponsored Studies (con't):				
	Phase II, A single arm, multicenter phase II trial of Tivozanib as monotherapy in the treatment of metastatic papillary renal cell cancer	Patients with metastatic papillary RCC	Up to 70 subjects to be enrolled at multiple sites in France: Tivozanib: 1.5 mg	Tivozanib 1.5 mg (3 weeks on, 1 off) until progression
	Phase I/II trial of tivozanib +erlotinib in papillary RCC	Patients with metastatic RCC	Up to 40 subjects to be enrolled at two sites: Tivozanib: 1.5 mg	1.5 mg tivozanib (3 weeks on, 1 off) plus erlotinib in patients with confirmed papillary RCC
	Randomized phase II selection trial of erlotinib +/- tivozanib for untreated NSCLC patients with veristrat good biomarker	Patients with NSCLC	Up to 100 subjects to be enrolled at multiple sites: Tivozanib: 1.5 mg	Two-thirds of untreated patients will fall into Veristrat "Good" and "Poor" and will receive tivozanib or best of care
	A Randomised Phase II Study Of Erlotinib Plus Tivozanib (ET) vs. Erlotinib Alone In Treatment Naïve EGF	Patients with NSCLC	Up to 140 subjects to be enrolled at multiple sites: Tivozanib: 1.5 mg	1.5 mg oral tivozanib (3 weeks on, 1 week off) plus 150 mg/d of erlotinib for a 4 week course
	Phase II study of Tivozanib in patients with metastatic Soft Tissue Sarcoma	Patients with metastatic soft tissue sarcoma	Up to 40 subjects to be enrolled at one site: Tivozanib: 1.5 mg	1.5 mg oral tivozanib administered (3 weeks on, 1 off)
	Phase II study: Serum IL-6 and tivozanib therapy in advanced malignant solid tumors: a prospective trial	Patients with advanced solid tumors	Up to 70 subjects to be enrolled at one site: Tivozanib: 1.5 mg	1.5 mg oral tivozanib (3 weeks on, 1 off) in patients with advanced malignant solid tumors, stratified (post-registration) into serum IL6-high and serum IL6-low groups
	A phase II trial using tivozanib and RAD001 for patients with radioiodine refractory thyroid cancer	Patients with refractory thyroid cancer	Up to 33 subjects to be enrolled at one site: Tivozanib: 1.5 mg	Patients will be treated with RAD001 10mg daily d1-28 and Tivozanib 1.5mg daily d1-21

Investigator Sponsored Studies (con't):				
	Phase I/II of tivozanib in combination with vemurafenib (bRAF inhibitor) in metastatic melanoma	Patients with metastatic melanoma	Up to 40 subjects to be enrolled at one site: Tivozanib: 1.5 mg	Patients will be treated Tivozanib 1.5mg daily d1-21 plus vemurafenib mg po to determine the MTD
	Phase I/II study of tivozanib in patients with ovarian cancer	Patients with sub-optimally debulked ovarian/peritoneal/tubal carcinoma	Up to 30 subjects to be enrolled at one site: Tivozanib: 1.5 mg	Patients will be treated with neo-adjuvant tivozanib (3 weeks on, 1 week off), paclitaxel and carboplatin to determine MTD
	Phase II study of tivozanib in patients with recurrent or progressive glioblastoma	Patients with histological confirmed recurrent GBM after radiotherapy and temozolomide	Up to 40 subjects to be enrolled at one site: Tivozanib: 1.5 mg	Patients will be treated with tivozanib 1.5 mg (3 weeks on, 1 week off) to determine PFS rate at 6 months
Abbreviations: ECOG PS = Eastern Co-operative Oncology Group performance status; mg = milligrams; MTD = maximum tolerated dose; PG = Pharmacogenomic; PK = pharmacokinetic; NSCLC=non-small cell lung cancer; RCC=renal cell carcinoma				
a: 42 subjects enrolled in Study KRN951/03-B01. One subject inadvertently received two 10-mg doses instead of 2 mg.				
b: For Study AV-951-07-201, a dose reduction to 1.0 mg of tivozanib was allowed for subjects who developed ≥ Grade 3 AEs.				
c: IV: oxaliplatin 85 mg/m ² ; leucovorin calcium 400 mg/m ² ; fluorouracil bolus 400 mg/m ² ; fluorouracil infusion 2400 mg/m ²				

Final PK data are available for 3 monotherapy studies (KRN951/03-B01, AV-951-07-201, and AV-951-08-105) and 2 combination therapy studies (AV-951-07-102 and AV-951-08-104) in subjects with cancer. Additionally, final PK data are available for 2 healthy volunteer studies (Studies AV-951-09-109 and AV-951-10-111).

In summary, across studies, median time to peak serum concentration, (t_{max}), of tivozanib, ranges from about 2 to 24 h with substantial variability between subjects. In studies from healthy volunteers with detailed sampling regimens in the first 24 h, median T_{max} is 10 h. Across the multiple studies, exposure (C_{max} and AUC) of tivozanib generally increases in a roughly dose proportional manner and accumulation at steady-state is approximately 6-7 times single dose levels. This accumulation is consistent with the long t_{1/2} of tivozanib, the mean between studies being approximately 3.6 to 4.7 days. Also, the PK of tivozanib is similar in oncology patients compared to the profile in healthy volunteers.

In combination studies of tivozanib with temsirolimus (AV-951-07-102) and in another with paclitaxel (AV-951-08-104), there was no indication of a PK interaction that influenced tivozanib levels or those of the co-administered agent.

Data from the mass balance study (Study AV-951-10-111) found that 79.3% of the total radioactivity was recovered from feces. Urine contained no detectable tivozanib but various metabolites were detected in urine and accounted for 11.8% of recovered

radioactivity. The findings are consistent with elimination of tivozanib via feces and some degree of metabolism.

In vitro data suggest the possibility that tivozanib may interact with CYP3A4 inducers and/or inhibitors. Formal drug-drug interaction studies are currently underway to assess whether such interactions may be clinically relevant. Data are not yet available from these studies.

Safety/Tolerability Profile

Tivozanib is provided in capsules of 0.5 mg, 1.0 mg, and 1.5 mg for once-daily oral dosing.

Clinical data are available for 14 completed or ongoing clinical studies of tivozanib. Adverse events were generally manageable using standard medical therapy and/or discontinuation or reduction of study drug.

Monotherapy Phase II Study 201:

All treated patients were included in the safety analysis; patients who were randomly assigned to receive the placebo were not excluded. The most common treatment-related AEs (all grades) were hypertension (45%) and dysphonia (22%). There was a low incidence of treatment-related diarrhea (all grades, 12%; grade 3, 2%), asthenia (all grades, 10%; grade 3, 3%), fatigue (all grades, 8%; grade 3, 2%), stomatitis (all grades, 4%; grade 3, 1%), hand-foot syndrome (all grades, 4%; grade 3, 1%), and proteinuria (all grades, 3%; grade 3, 2%); no overlap was reported between asthenia and fatigue. Grade 3 and 4 AEs were infrequent; the most common grade 3 and 4 AE was hypertension, which was reported in 32 patients (grade 3, 11%; grade 4, 1%). The most frequent grade 3 and 4 laboratory abnormalities (all causality, 5% of patients) were increased glutamyl transpeptidase (17%), increased uric acid (7%), lymphopenia (6%), and hypokalemia (6%). There was a low incidence of grade 3 and 4 elevations of ALT (1%), AST (1%), and bilirubin (2%); no cases met Hy's law for drug-induced hepatotoxicity. Dose reductions and interruptions as a result of AEs were required by 22 patients (8%) and 11 patients (4%), respectively. Study discontinuations as a result of AEs were required by 25 patients (9%). Of 15 on-study deaths, the most common cause was disease progression (n=8); other causes of death included ischemic stroke (n=2), acute coronary syndrome, acute respiratory failure, cerebral vascular accident, hypotension, and pulmonary embolism (n =1 each; all deaths occurred during tivozanib treatment or within 30 days of discontinuation). No deaths were considered by the investigator to be treatment related. There were 44 treatment-emergent serious AEs reported in 36 patients (13%); AEs that occurred in more than one.

Monotherapy Phase III Study 301:

The most common adverse event (AE; all grades/≥grade 3) for Tivozanib (T) was hypertension (T: 46%/26% vs. S: 36%/18%) and for Sorafenib(S) was hand-foot syndrome (T: 13%/2% vs. S: 54%/17%). Other important AEs included diarrhea (T: 22%/2% vs. S: 32%/6%), fatigue (T: 18%/5% vs. S: 16%/4%), and neutropenia (T: 10%/2% vs. S: 9%/2%).

Combination of Tivozanib (AV-951) and Temezirolimus:

Treatment-related adverse events seen in $\geq 10\%$ of pts were (number of pts with all grades/grade 3 toxicities): fatigue (14/3), decreased appetite (9/0), stomatitis (7/1), thrombocytopenia (6/1), diarrhea (6/0), nausea (6/1), vomiting (3/0), and decreased weight (3/0). There were no grade 4 events. The MTD of this combination was tivozanib 1.5 mg/d and temsirolimus 25 mg/wk, and no dose limiting toxicities were encountered.

Combination of Tivozanib and Paclitaxel:

Toxicities (all grades) occurring in $\geq 20\%$ of pts: fatigue (72%), diarrhea (44%), nausea (44%), HTN (33%), cough (33%) and vomiting (28%). Grade 3 toxicities: diarrhea (11%), fatigue (11%), HTN (11%), neutropenia (11%), and neuropathy (6%); no grade 4 toxicity was observed. The MTD was Tivozanib 1.5 mg with Paclitaxel 90 mg/m².

Combination of Tivozanib and FOLFOX6:

DLTs were observed in 2 pts receiving 0.5 mg tivozanib (reversible grade 3 diarrhea and grade 3 and 4 transaminase elevations, respectively) and in 2 pts receiving 1.5 mg tivozanib (reversible grade 3 seizures and grade 3 vertigo, respectively). Other grade 3/4 drug-related adverse events (AEs) included neutropenia, fatigue, and hypertension (n = 2 each); and pyrexia, pulmonary embolism, and thrombosis (n = 1 each). There was no indication that drug-related AEs in this study were more frequent or severe than those observed with tivozanib or FOLFOX6 alone. The MTD was 1.5 mg tivozanib with full dose FOLFOX6.

TIVO-1 Study:

Tivozanib was recently reported to improve progression free survival compared to sorafenib in the 1st line treatment of renal cell carcinoma. TIVO-1 was a global, randomized Phase 3 clinical trial evaluating the efficacy and safety of investigational drug tivozanib compared to sorafenib patients with advanced renal cell carcinoma (RCC).

Methods: Patients (pts) with clear cell advanced renal cell carcinoma (RCC), prior nephrectomy, RECIST-defined measurable disease, and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 were randomized 1:1 to tivozanib (T) 1.5 mg once daily for 3 weeks (wks) followed by 1 wk rest, or sorafenib (S) 400 mg twice daily continuously in a 4-wk cycle. Pts were treatment naïve or received no more than 1 prior systemic therapy for metastatic disease; pts receiving prior VEGF- or mTOR-targeted therapy were excluded. The primary endpoint was progression-free survival (PFS) per blinded, independent radiological review. **Results:** A total of 517 pts were randomized to T (N=260) or S (N=257). Demographics were well balanced between the 2 groups, except ECOG 0 (T: 45% vs. S: 54%, $P=0.035$). Median PFS was 11.9 m for T vs. 9.1 m for S (HR=0.797, 95% CI 0.639–0.993; $P=0.042$). In the treatment-naïve stratum (70% of pts enrolled in each arm), the median PFS was 12.7 m for T vs. 9.1 m for S (HR 0.756, 95% CI 0.580–0.985; $P=0.037$). In all pts, objective response rate (ORR) for T was 33% vs. 23% for S ($P=0.014$). The most common adverse event (AE; all grades/ \geq grade 3) for T was hypertension (T: 46%/26% vs. S: 36%/18%) and for S was hand-foot syndrome (T: 13%/2% vs. S: 54%/17%). Other important AEs included diarrhea (T: 22%/2% vs S: 32%/6%), fatigue (T: 18%/5% vs. S: 16%/4%), and neutropenia (T: 10%/2% vs S: 9%/2%). Patient-reported outcome data are being analyzed. Overall survival data are not mature.

Conclusions: Tivozanib demonstrated significant improvement in PFS and ORR compared with sorafenib as initial targeted treatment for advanced RCC. The safety profile of tivozanib is favorable, and includes a low incidence of fatigue, diarrhea, myelosuppression, and hand-foot syndrome.

3.0 Scope and Aims

The following areas of research emphasis identified for this RFP should focus on developing innovative single agent and combination studies of tivozanib:

- Colorectal cancer
- Breast cancer
- Ovarian cancer
- Hepatoma
- Prostate cancer
- Other tumors of interest may be considered depending on the scientific merit of the concept
- Combinations of tivozanib with other unapproved anti-cancer therapies are acceptable

Concepts that duplicate the studies listed in section 2.0 will not be considered

Biomarker studies and/or potential combination regimens meant to evaluate mechanisms of resistance and/or makers of greater or lesser benefit are of high interest. These include but are not limited to assessment of factors in the VEGF axis, non-VEGF angiogenic factors, and myeloid and inflammatory factors, and factors related to hypoxia.

- Phase I/II studies in the identified tumor types
 - Single agent therapy in tivozanib
 - Drug combination studies in any tumor type are acceptable if the toxicity profile of the agent is appropriate for combination with tivozanib and there is sufficient data in the literature regarding the single agent activity of the combining drug so that the contribution of tivozanib can be determined
 - Combination studies including biologics with tivozanib
 - Multi-institutional Phase II trials to expedite the evaluation of tivozanib activity in specific low incidence tumor types are appropriate
- Non-clinical correlates are appropriate—PKs for combination chemotherapy studies, mechanism of action, mechanisms of resistance, etc. Examples include:
 - Correlative work to identify predictive markers; mechanisms of primary and acquired resistance, and mechanisms of toxicity
- Preference may be given to proposals for specific patient subsets of high unmet need
- No studies will utilize doses outside the range for which safety data is available (i.e., nothing greater than 1.5 mg) or a mode of administration other than oral

If you wish additional information regarding whether a concept is already planned or funded, please email ORProposals@nccn.org or call Doreen Walker at 215-690-0565.

Specific exclusions from this RFP include:

- Concepts that duplicate the studies listed in section 2.0 will not be considered

4.0 Study Time Frames

All approved studies are expected to commence, which is defined as the first patient receiving the first dose of study drug(s), within six (6) months and no later than nine (9) months of notice of study approval and are to complete accrual within two (2) years of commencement. A manuscript must be submitted to NCCN for review no later than nine (9) months after study endpoint is achieved or study termination. These studies will be funded as described in Section 9.0 and should be designed with subject number commensurate with study time frames and funding.

Studies for rarer cancers or those that require a large numbers of patients for statistical power must be multi-institutional. Network appropriate studies will be considered as long as submitting PI is from an NCCN Member Institution.

The following types of studies will be accepted for review:

Preclinical studies that can be completed within a 2 year timeframe.

Phase I studies are expected to complete accrual within 2 years of commencement.

Single-arm Phase II studies are expected to explore new approaches that can be tested in larger confirmatory studies if positive results are obtained. It is expected that these studies will complete accrual within 2 years of commencement. To meet this accrual goal, single-arm Phase II trials may be multi-institutional. Data management and monitoring of studies should be coordinated by the applying institution. Additional funding for the applying institution may be requested to support the additional resources required for this activity, if the study involves multi-institutional participation.

Correlative laboratory studies are expected to be completed within the same time frame as the corresponding clinical trial.

Larger randomized Phase II studies already supported through other mechanisms (i.e. cooperative group) will be considered for support where the support requested will be for correlative laboratory studies that are unfunded and enhance the evaluation of the patient data.

All studies will require documentation of the feasibility of accruing the targeted study population and all studies may be multi-institutional.

5.0 Proposals

In order to respond to the RFP, investigators will submit a proposal in the format delineated below to NCCN, which will be evaluated by the NCCN SRC.

Proposals are required to be submitted electronically to the NCCN research portal at <https://www.mednetstudy.com/sqs/nccn/> and include a letter of support from the governing groups of the institution verifying:

- 1) Office of Sponsored Research approval
- 2) Department Chair/Division approval
- 3) Institutional budgetary review and approval
- 4) The priority status of the research stating if there are competing trials. If there are competing trials, please verify that this trial will have a higher priority.
- 5) Documentation to support feasibility with at least one of the following:
 - Letter from institution's Feasibility Committee if applicable
 - Documentation by previous studies and accrual (if available, publications and abstracts)

Letters should be addressed to Patricia J. Goldsmith, Executive Vice President/COO, National Comprehensive Cancer Network, 275 Commerce Drive, Suite 300, Fort Washington, PA 19034.

Proposals will provide concise documentation of the research plan. The proposal is expected to contain sufficient information to allow the reviewers to fully assess the scientific rigor of the proposed study. A full research project plan may be submitted as an attachment. A robust review of the statistical plan will be conducted.

Clinical trial proposals should contain detailed information regarding the following areas:

5.1 Clinical Trials

- A. Title/Tumor Type
- B. Investigators and institutional affiliations
- C. Hypothesis with primary and secondary objectives
- D. Background Information
- E. Research design
- F. Study population
 - i. Stage
 - ii. Major inclusions/exclusions
- G. Treatment plan
- H. Endpoints/Statistical analysis
- I. Feasibility
 - i. Estimated time of completion/monthly accrual
 - ii. Previous experience with trials that had similar tumor type, phase of study or prior therapy
 - iii. Collaborators' experience, including affiliates
 - iv. Competing trials - List all active, approved or in-review studies at your institution for which the same patient population is eligible
 - v. Projected Accrual Dates (Month/Year)

5.2 Correlative Studies

- A. Hypothesis (include relevant background studies)
- B. Preliminary data
- C. Study design (include methods for obtaining samples, administering forms, or performing radiologic studies)
- D. Study population
- E. Methodology
- F. Analytic plan

- G. Feasibility
 - i. Accrual
 - ii. Specimen acquisition

5.3 Budget using NCCN template

- A. Breakdown by major cost categories
- B. Justification of major costs with enough detail to demonstrate how funding for major elements in the study will be allocated
- C. For combined clinical and correlative studies, separate budgets for each component should be submitted
- D. Salaries are capped at the current NIH salary cap
- E. No travel or publication costs will be covered

5.4 Ancillary Documentation

- A. An NCI format BioSketch of the Principal Investigator
- B. An appendix of supportive literature may be provided

6.0 Proposal Requirements

6.1 Submission

All proposals must be submitted electronically using the directions below and are due by **5:00 PM (EDT) on July 23, 2012. No exceptions will be granted.**

1. Access the website at <https://www.mednetstudy.com/sgs/nccn/>
2. Register for a user account by selecting the '**Registration for New Investigators Only**' link displayed on the sign on page
3. Locate your Institution / Hospital from the pick list, apply all required (*) data into the data entry area and save
4. Access your email account to obtain your User ID and Password
5. Re-access the website and apply your User ID and Password (case sensitive)
6. Complete the website training (available in word document or video)
7. Submit your study

For technical issues with submission, please call the MedNet helpdesk at 866-258-2735.

Studies that have safety issues, are already well-funded concepts, or are not consistent with the strategy for investigation as written in this RFP will not be reviewed by the SRC.

For questions regarding the RFP, please call Doreen Walker at (215) 690-0565. NCCN will seek to provide information to potential investigators regarding ongoing or completed studies of Tivozanib in order to avoid the submission of a proposal that is already a well-studied concept, or a study concept that has already been approved by the Grantor outside of this RFP mechanism.

6.2 Requirements

6.2.1 Human Biological Specimens: All specimens must be obtained under informed consent and IRB approval appropriate for the study. A letter of assurance must be provided to NCCN that the PI's academic institution owns and has full rights to the tissue without conflicting claims from a non-Grantor commercial entity. Compliance with all federal regulations is required.

6.2.2 IRB:

6.2.2(a) Draft protocols will be reviewed by NCCN and the Grantors **prior** to IRB review. A copy of the draft protocol must be submitted to NCCN within 4 weeks after the study approval letter. The protocol must be consistent with the approved proposal and all reviewer comments must be addressed.

6.2.2(b) All investigators will submit protocols for IRB review and document approval to NCCN prior to study activation and all collaborators will furnish evidence of IRB approval. It is expected that IRB review and approval be completed **within 120 days** following NCCN notification of funding for the project.

6.2.3 Serious Adverse Event Reporting: All serious adverse events will be reported to NCCN and the Grantors in addition to local regulatory authorities.

6.2.4 Institutional Monitoring: All studies will be internally monitored in accordance with appropriate committees (e.g. institutional Data Safety and Monitoring Plan in the case of human studies). A copy of the Data Monitoring Plan for the study must be submitted to NCCN prior to NCCN approval of study activation.

6.2.5 IND:

6.2.5(a) Investigators are required to hold INDs for studies but will be allowed to cross-reference a filing to Grantor's IND.

6.2.5(b) If Tivozanib is studied in combination with an investigational agent from another pharmaceutical company, or an agent used outside of its indication, the investigator must provide documentation of that company's commitment to provide drug for the investigation as well as the agreement of that company to allow presentation and publication of results and allow cross-filing or filing of a new IND. **This documentation must be provided to NCCN along with the proposal.**

6.2.5(c) Proposals using an experimental diagnostic imaging agent that will require an IND must outline how regulatory issues will be handled in order to meet the required study time frame.

6.2.6 Progress Reports: Investigators will provide interim progress reports to NCCN detailing the progress of studies monthly or quarterly,

and upon study completion. These reports will be used administratively for funding purposes. If study progress or accrual lags behind the expected rate, the Scientific Review Committee (SRC) may be asked for suggestions to improve study progress, or alternatively, to terminate the study and any further funding.

6.2.7 Specimen Transmittal: If specimens are to be transported extramurally for collaborative laboratory studies, all institutional requirements for safety and confidentiality will be met.

6.2.8 Abstracts and Publications: Abstracts for presentation at scientific meetings and all publications of study results will be submitted to NCCN and Grantors for review related to protection of company's intellectual property and confidential information **prior to any submission**. Abstracts must be submitted at least 10 days prior to submission and manuscripts at least 30 days prior to submission. Grantors may delay publication and disclosure of the manuscript or abstract for up to an additional seventy five (75) days so as to seek patent protection of intellectual property rights.

6.2.9 NCCN Multi-Institutional Studies: Collaborative studies between NCCN Member Institutions are encouraged. For these studies, the proposal feasibility section should provide information about data management, statistical analysis, and specimen handling issues. Additional funding may be provided for centralized data management and monitoring by the applying institution.

6.2.10 NCCN institutions and investigators will be responsible for conducting all studies in accordance with the applicable research plan, GCP Guidelines, and all applicable laws and regulations. NCCN institutions and investigators will be responsible for all data collection, statistical analysis and safety reporting.

6.2.11 Investigators must provide reasonable assurance that submitted studies will be able to reach completion within the time frames specified in Section 4.0.

6.2.12 Final protocols must be consistent with approved proposals. Funds will be rescinded if there are significant changes without prior NCCN approval. There will be no exceptions.

6.2.13 The Principal Investigator (PI) listed on the protocol must be the same PI listed on the proposal submission unless approved by NCCN.

6.2.14 Investigators Meeting: All studies will be presented by institutional representatives at an annual NCCN investigator meeting. The purpose of the meeting will be to discuss preliminary results and develop new research initiatives and further collaborative activities between NCCN investigators and the Grantor's scientific staff. Participation by the PIs in these meetings is a requirement of a funded study.

7.0 Drug Supply

Tivozanib will be supplied and distributed for all approved and funded studies by Grantors.

8.0 Selection Criteria

Proposals will be judged based on the following criteria:

1. Scientific value
2. Research experience of the Principal Investigator
3. Soundness of study design
4. Feasibility including reasonable assurance of achieving intended and full accrual
5. Budgetary reasonableness
6. Statistics

This grant is expected to fund approximately 4-6 studies.

9.0 Funding

NCCN and its member institutions have an agreement to include a maximum of 25% indirect costs for trials funded by NCCN. Direct funding will include all costs including investigators' salaries. For example, \$80,000 direct costs and \$20,000 indirect costs for a total grant of \$100,000. Any funds in excess of the limits stipulated in this section for direct funding will require detailed justification and review.

Phase I and Single-arm Phase II clinical trials will be funded at a cost of up to \$250,000 (total costs including direct costs and 25% indirect costs) per trial. Multi-institutional data management and monitoring of these studies should be coordinated by the applying institution. Additional funding for the applying institution may be requested to support the additional resources required for this activity.

Research Projects (Basic Research):

- 50% upon approval of funding
- 35% upon completion of research and receipt of final report by NCCN
- 15% upon submission of article for publication

Phase I trials (with or without correlative studies):

- 25% of total award for such Study after IRB approval and implementation
- Based on the per participant costs, after the initial 25% of funding has been accounted for based on participant accrual, funds will be awarded on a quarterly basis for eligible participants enrolled on Study, based on the per participant rate up to a maximum of 90% of the funding
- 10% of funds will be awarded after submission of a manuscript for publication

Phase II trials (with or without correlative studies) and stand-alone correlative studies:

- 25% of total award for such Study after IRB approval and implementation
- 35% of total award after 50% accrual
- 30% of total award after 100% accrual

- 10% of funds will be awarded after submission of a manuscript for publication.

Phase II trials with 2-Stage Design with Early Stopping Rules

- 25% of total requested grant (based on maximum number of anticipated participants) after IRB approval and implementation
- Total remainder of per participant funding for the number of participants in the first stage after all participants are accrued to the first stage of the study (total funding for the number of participants in first stage less the initial payment)
- Total per participant funding for the number of participants in the second stage less final payment after all participants are accrued to the second stage
- 10% of total requested grant (based on maximum number of anticipated participants) after submission of a manuscript for publication or of a final report

Larger Randomized Phase II trials already supported through other mechanisms (i.e. cooperative group) will be considered for support where the support requested will be for correlative laboratory studies that are unfunded and enhance the evaluation of the patient data. Correlative studies for larger randomized trials will be funded up to \$100,000.

The goal is to have rapid submission of a manuscript so as to have the data available to the wider scientific community.

Studies that do not meet the time frame requirements as stipulated in Section 4.0 will have funds rescinded and will be required to return any and all unused funds previously disbursed.

10.0 Study Agreement

A study agreement will be signed between NCCN and each participating institution. If an institution requires a separate contract with another pharmaceutical company for a study, that contract must be fully executed by the time of final contract execution with NCCN.

All aforementioned points between NCCN and the participating institution must be strictly adhered to.