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The Efficacy and Safety of Tivozanib in Recurrent, Platinum-Resistant Ovarian, Fallopian Tube or Primary Peritoneal Cancer

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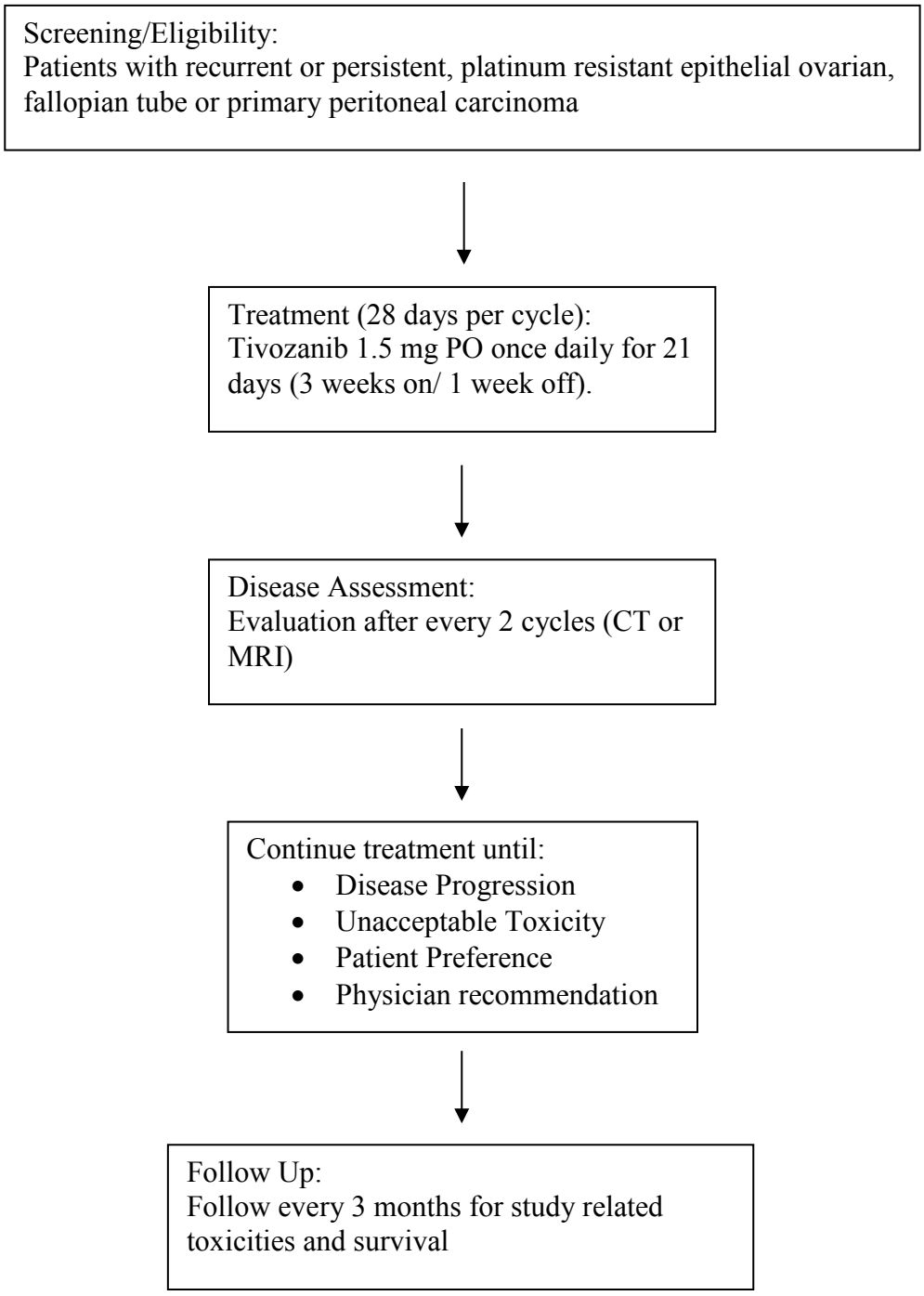
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
H&PE	History & Physical Exam
HUVECs	Human Umbilical Vein Endothelial Cells
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cells

STUDY SCHEMA



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STUDY SUMMARY

Title	The Efficacy and Safety of Tivozanib in Recurrent, Platinum-Resistant Ovarian, Fallopian Tube or Primary Peritoneal Cancer
Protocol Date	Revised January 3, 2019 (Amendment 8)
Study Duration	24 Months
Study Center(s)	Robert H. Lurie Comprehensive Cancer Center at Northwestern University
Objectives	Primary: The primary objective of this single-arm, phase II clinical trial will be to determine the clinical activity of tivozanib in patients with platinum-resistant, recurrent ovarian, fallopian tube or primary peritoneal cancer. Secondary: To determine the potential survival advantage and characterizing the safety of single agent tivozanib in patients with platinum-resistant ovarian cancer.
Number of Subjects	30
Diagnosis and Key Eligibility Criteria	Women with measurable and non-measurable recurrent or persistent, platinum resistant epithelial ovarian, fallopian tube or primary peritoneal carcinoma.
Treatment Plan	Tivozanib 1.5mg orally given daily for 3 weeks with one week off to complete a 4 week cycle until disease progression or adverse effects prohibit further therapy.
Statistical Methodology	Statistical analyses will focus on estimation of overall response rates in patients with platinum-resistant ovarian cancer as stated in the Primary Objective. For the secondary objective, the Kaplan-Meier method will be utilized to estimate the median and overall distribution of progression-free survival. Toxicity will also be evaluated as a secondary objective and grades will be summarized by counts and frequencies.

1 INTRODUCTION - BACKGROUND & RATIONALE

1.1 Disease Background-Ovarian Cancer

Ovarian cancer is the leading cause of gynecologic cancer deaths, and the fifth most common cause of cancer deaths in women [1]. Although about 75% of patients with epithelial ovarian cancer will respond to first-line chemotherapy with carboplatin/cisplatin and paclitaxel, most patients with advanced stage epithelial ovarian cancer will recur. While there are several active cytotoxic agents for the treatment of recurrent epithelial ovarian cancer, median survival after recurrence is about 2 years. Patients who recur more than 6 months after completing their adjuvant chemotherapy are referred to as "platinum-sensitive." They are oftentimes re-treated with a platinum agent, sometimes in combination with additional chemotherapy and, generally speaking, have a durable response to subsequent therapy. Women who recur within 6 months of completing adjuvant therapy are referred to as "platinum-resistant." These patients represent an unfortunate sub-group. There are multiple agents with clinical activity in this setting but the ideal treatment modality is not known. A recent Cochrane review identified topotecan, pegylated liposomal doxorubicin and paclitaxel as having the greatest potential benefit for these patients. The overall response rate for these agents ranges from 10-15% in platinum-resistant disease. The choice of treatment is often based on the side-effect profile and the patient's specific situation [2]. Given these poor response rates, new treatment options are needed in this patient population.

1.2 Tivozanib Hydrochloride

Tivozanib hydrochloride (also known as AV-951; previously known 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 pan-vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor with significant activity against all 3 VEGF receptors (VEGFR-1, -2, and -3) [3]. In nonclinical models and studies performed in humans, tivozanib has shown strong anti-angiogenesis and antitumor activity. VEGF is a potent induction factor, playing a central role in angiogenesis and vascular permeability of tumor tissues. By inhibiting VEGF-induced VEGFR activation, tivozanib inhibits angiogenesis and vascular permeability in tumor tissues, leading indirectly to inhibition of tumor growth [4].

1.2.1 Non-clinical Studies

Tivozanib hydrochloride potently and selectively inhibited VEGF ligand-induced VEGFR-1, 2, 3 phosphorylation and proliferation of human umbilical vein endothelial cells (HUVECs). In nonclinical studies, oral tivozanib hydrochloride was highly bioavailable (70%-80%). Daily oral administration of tivozanib hydrochloride demonstrated antitumor effects against a broad panel of tumor types subcutaneously engrafted into nude mice or rats. The minimum effective dose in rats was 0.2 mg/kg/day; average blood levels of tivozanib (free base) during continuous dosing at 0.2 mg/kg/day were estimated to be 70ng/mL. At these dose levels, the antitumor effects in nude rat xenograft models correlated with inhibition of tumor angiogenesis and vascular permeability. Conversely, the inhibitory activity of tivozanib hydrochloride in vitro against the growth of various cancer cells was weak (IC50 > 1), suggesting that the anti-tumor effect of

tivozanib hydrochloride in vivo is not attributable to cytotoxicity or direct inhibition of the growth of tumor cells. This suggests that, by inhibiting VEGF-induced VEGFR activation, tivozanib hydrochloride inhibits angiogenesis and vascular permeability in tumor tissues, and such inhibition leads to an indirect but broad spectrum of inhibition of tumor growth. Neither long-term therapy nor intermittent dosing resulted in any detectable drug resistance in xenograft models.

All safety pharmacology evaluations were performed after a single oral (gavage) administration of tivozanib hydrochloride. There were no significant gross behavioral or physiological changes observed in the Irwin test carried out in rats. In the monkey telemetry study, 0.015 or 0.3 mg/kg of tivozanib hydrochloride had no significant effect on arterial blood pressure (systolic, diastolic or mean), however, 3 mg/kg tivozanib hydrochloride increased systolic, diastolic and mean arterial blood pressure transiently by as much as 14–19 mmHg. Evaluation of electrocardiograms showed that tivozanib hydrochloride had no effects on heart rate, respiration rate, PR, QT, or QTc intervals or QRS duration at any of the doses tested. Tivozanib hydrochloride produced no inhibition of human ether-a-go-go (hERG)-related channel tail current in HEK293 cells stably transfected with hERG cDNA. Finally, tivozanib hydrochloride had no significant effect on the respiration rate or tidal volume of conscious rats at any of the time points or doses (0.3–400 mg/kg) tested [5].

Nonclinical toxicology studies were conducted in multiples species (rats, mice, rabbits and nonhuman primates) to support the safety of tivozanib hydrochloride. The investigations included single-dose, repeat-dose (up to 39 weeks), genotoxicity, reproductive and developmental toxicity, mechanistic toxicology and phototoxicity studies. Toxicities were similar across species and consistent with toxicities expected for a drug of this class, namely hypertension, effects on growth plate hypertrophy, and renal and gastrointestinal effects. Higher drug doses generally 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. For all nonclinical studies, tivozanib hydrochloride was used, unless otherwise specified. For all oral nonclinical studies, tivozanib hydrochloride was suspended in 0.5% methylcellulose vehicle. For IV studies, tivozanib hydrochloride was in a 40% dimethylacetamide solution.

Tivozanib hydrochloride 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.

The pharmacokinetics of tivozanib hydrochloride has been studied in rats and monkeys. Following a single oral dose, the time to max serum concentration for tivozanib (free base) is 2-4 hours and the half- life is 7-12 hours in both species. Systemic exposure was approximately dose-proportional in both species with

slight accumulation after multiple doses, consistent with a long half-life relative to the dosing interval. The mean bioavailability of tivozanib (free base) in rats is 71.8% - 82.4%. Following oral administration of [14C]-tivozanib hydrochloride to rats, radioactivity was widely distributed throughout the tissues, reaching maximum tissue concentrations at four hours post- dosing. Following both oral and IV administration in rats, dosed radioactivity was recovered principally in the feces.

Tivozanib hydrochloride has been assayed for protein binding in plasma. The proportion of drug that is protein-bound is 97.6%, 99.3%, and 99.7% in monkey, rat, and human plasma, respectively.

In vitro studies have shown that the cytochrome (CYP) P450 enzyme system is involved in the metabolism of tivozanib hydrochloride. The primary human hepatic isoform shown to be involved in the biotransformation of tivozanib hydrochloride was CYP3A4.

A cardiovascular study in conscious telemetered cynomolgus monkeys did not show any effects on QTc interval. In the same study, oral administration of 0.015 or 0.3 mg/kg tivozanib hydrochloride to cynomolgus monkeys had no effects on arterial blood pressure; however, administration of 3.0 mg/kg tivozanib hydrochloride increased arterial blood pressure transiently by 14-19 mmHg. Tivozanib hydrochloride had no marked effects on heart rate or ECG parameters at any tested dose.

Nonclinical cutaneous and ocular phototoxicity studies indicate that tivozanib hydrochloride has no potential phototoxicity [6].

1.2.2 Clinical Studies

The substantial growth inhibition observed with tivozanib across pre-clinical models led to a Phase I study in advanced solid tumors. Key eligibility criteria included a life expectancy of at least 3 months and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 2. Patients with symptomatic brain metastasis were excluded, as were patients with evidence of severe cardiovascular disease (i.e., uncontrollable hypertension or symptomatic heart failure). A starting dose of 2.0 mg was selected based on the no observed adverse effect level (NOAEL) in primates. Extensive pharmacokinetic (PK) sampling was performed, and pharmacodynamic studies were also performed to assess the effect of tivozanib therapy on serum VEGF and soluble VEGFR2 (sVEGFR2). A total of 41 patients were enrolled into the study. Metastatic colon cancer (n = 10), metastatic renal cell cancer (MRCC) (n = 9), and pancreatic cancer (n = 6) represented the most common tumor types represented in the study. Two patients in the 2.0 mg-daily cohort experienced dose-limiting toxicities (DLTs), specifically, grade 3 asymptomatic proteinuria in one patient and grade 3 ataxia in another. No DLTs were observed in 6 patients treated at 1.0 mg daily, and therefore, an intermediate dose of 1.5 mg daily was explored. DLTs observed at this cohort included grade 3 and 4 transaminitis, uncontrollable hypertension,

grade 3 fatigue, and grade 3 dyspnea. Given these toxicities, an expansion cohort including 12 patients treated at 1.0 mg daily was assessed. With respect to efficacy, two patients with mRCC had partial responses (one confirmed, one unconfirmed), whereas the majority of patients in the study (55.2%) had stable disease as a best response. Eight patients (20%) received therapy for more than 9 months. PK analyses accompanying the study showed a mean half- life of 4.7 days (range, 1.3 to 9.7 days). The time to achieve maximum serum concentration (tmax) was between 2 and 24 hours. Other correlative studies showed that although VEGF-A levels rose consistently at the start of tivozanib therapy in a dose-dependent manner, these levels normalized after 14 days off therapy. In contrast, sVEGFR2 levels were reduced with increasing doses of tivozanib with the most marked decrease noted toward the end of the cycle (i.e., a larger decrease was observed at day 27 of therapy versus day 14). Dynamic contrast-enhanced MRI (DCE-MRI) was performed in a small subset of patients enrolled in the study (n = 8). Consistent with pre-clinical observations, a decrease in tumor vessel density was observed over time [7].

In the setting of colorectal cancer, a Phase Ib study was conducted to assess the activity of tivozanib in combination with 5-flurouracil/oxaliplatin (FOLFOX) chemotherapy. A regimen of modified FOLFOX6 (mFOLFOX6), which incorporates an 85 mg/m2 dose of oxaliplatin, was administered on days 1 and 15 of a 28-day cycle. Escalating doses of tivozanib were administered on a 3 weeks on, 1 week off cycle. To supplement PK analyses, a single dose of tivozanib was given 5 days preceding therapy with tivozanib. A total of 30 patients were ultimately enrolled in the study, with a median age of 58 years. In total, 9 patients received tivozanib at a dose of 0.5 mg daily, 3 patients received 1.0 mg daily and 18 patients received 1.5 mg daily. The median duration of treatment was 5.2 months, and 30.8% of patients achieved a response with this combination. An additional 36% of patients had stable disease as a best response. With respect to safety, there were four DLTs observed. In dose escalation cohorts, a DLT of uncontrolled hypertension was observed. In an expansion cohort including an additional 10 patients, three DLTs were observed; specifically, two episodes of reversible transaminitis and one episode of uncontrolled hypertension. PK analyses from this Phase I experience did not suggest any appreciable interaction between mFOLFOX6 and tivozanib ---- levels of tivozanib were akin to those observed with monotherapy. The appreciable safety and efficacy associated with the combination of mFOLFOX6 and tivozanib have culminated in a larger, randomized Phase II effort. In this study, patients will be randomized to receive either mFOLFOX6 with tivozanib or bevacizumab. The primary endpoint of the study is PFS, with secondary endpoints including OS, response, and health-related quality of life (HRQoL). The study also aims to explore a variety of serum biomarkers, including VEGF-A, VEGF-C, and VEGF-D and will assess a 42-gene signature. A second ongoing effort will explore the combination of capecitabine and tivozanib in patients with all solid tumor types, but will include an expansion cohort in two malignancies ----namely, colorectal cancer and breast cancer. The primary objective of the study is to determine the safety of the

combination. If a maximally tolerated dose (MTD) is not reached in a general population of solid tumor patients, then a recommended Phase II dose will be determined and an expansion cohort including breast and colorectal cancer patients will be assessed [8].

Assessment of tivozanib in breast cancer thus far is limited to a Phase I dose-finding study in combination with paclitaxel. The primary objective of the study was to determine the safety and tolerability of tivozanib in combination with paclitaxel in patients with metastatic breast cancer and to evaluate the PK profile of this combination. Patients with metastatic breast cancer with an ECOG performance status 0 - 2 and < 4 prior lines of therapy were enrolled. Notably, patients were allowed to receive one prior taxane and there was no limit to the number of prior biologic or endocrinologic treatments, although prior treatment with a VEGF-TKI was not allowed. Key exclusion criteria included evidence of brain metastasis or pre-existing neuropathy. The treatment regimen included weekly paclitaxel (90 mg/m2 intravenous, 3 out of 4 weeks) and escalating doses of tivozanib therapy (0.5, 1.0, and 1.5 mg daily). Ultimately, a total of 18 patients were included in the study. The median age of the cohort was 48, with 56 and 22% of patients demonstrating hormone receptor and HER2-positivity. All patients had received at least one prior taxane, with 61% of patients having received taxane therapy in the adjuvant setting. Notably, over half of patients (56%) had received prior bevacizumab. Two dose-limiting toxicities (DLTs) were encountered in the study. Namely, one patient treated at the first dose level (tivozanib at 0.5 mg/day) experienced grade 1 palpitations while another patient treated at the third dose level (tivozanib at 1.5 mg/day) developed grade 2 asymptomatic pneumoperitoneum. Otherwise, fatigue and alopecia were the most commonly reported treatment-emergent adverse events. The median duration of tivozanib therapy was 5.4 months. Among the 13 patients evaluable for response, partial responses were observed in 5 patients (38%), whereas stable disease was observed in 7 patients (54%). Although detailed PK data were not available for the patients enrolled, it was suggested that the PK parameters for tivozanib in combination with paclitaxel were similar to those associated with tivozanib monotherapy [9].

A randomized Phase II discontinuation study of tivozanib in mRCC provided key insights related to the drug's activity in this disease. Eligibility in the study was limited to mRCC patients with up to one prior therapy (other than a VEGF-directed agent) and a Karnofsky performance status of >= 70%. Patients were not allowed to enroll if they had evidence of brain metastasis or had evidence of substantial cardiovascular disease (i.e., uncontrollable hypertension or clinically significant heart failure). In accordance with the randomized Phase II design, patients received open-label tivozanib at 1.5 mg oral-daily (3 weeks on, 1 week off) for a total of 16 weeks. At the end of the 16-week interval, those patients with > 25% tumor shrinkage proceeded on open label tivozanib therapy, whereas those patients with > 25% tumor growth (or progression as otherwise defined by RECIST) discontinued protocol treatment. Those patients falling between these

cutoffs were randomized in a 1:1 double-blind fashion to receive either tivozanib or placebo for the next 12 weeks, and all patients were unblinded at that point. Those patients without evidence of progression or intolerable adverse events with tivozanib were allowed to proceed on tivozanib therapy. The primary objective of the study was to determine the safety and efficacy of tivozanib, the latter defined by the objective response rate (ORR) after the first 16 weeks of open label therapy. A secondary objective was a comparison of PFS in subgroups within the randomized discontinuation phase. Ultimately, a total of 272 patients with mRCC were enrolled. The majority of patients had clear cell histology (83%), had received prior nephrectomy (73%) and were classified as intermediate risk by Memorial Sloan-Kettering Cancer Center (MSKCC) risk criteria (60%). After the 16-week open-label phase, 18 and 66% of patients achieved objective response and stable disease respectively. The median PFS among all treated patients was 11.7 months, with censoring performed at the time of allocation to placebo. This value was considerably higher (14.7 months) in the subset of patients who had undergone prior nephrectomy and had clear cell histology -- this observation accounts for the refined eligibility noted in the subsequently described Phase III effort. Within the randomized discontinuation phase, PFS was significantly higher among those patients who received tivozanib (10.3 months vs 3.3 months, $p = 0.01$). The most common non-hematologic adverse events noted with tivozanib were hypertension, dysphonia, diarrhea and asthenia. Grade 3/4 events occurred at a frequency of less than 10%, with the exception of hypertension (12%) and GGT elevation (17%) [10].

The Phase III TIVO-1 trial was initiated on the basis of the compelling data for tivozanib monotherapy in the aforementioned randomized, Phase II study in mRCC. Eligibility for the study included clear cell histology with measurable disease and ECOG performance status between 0 - 1. Furthermore, participants were required to have had prior nephrectomy. Although participants may have had 1 prior therapy, prior use of VEGF or mTOR directed agents were not permitted. Patients were stratified by geographic region, the number of prior therapies, and the number of metastatic lesions. In a 1:1 fashion, patients were randomized to receive either tivozanib at 1.5 mg/day orally, 3 weeks on, 1 week off, or sorafenib at 400 mg oral twice daily. The primary objective of the study was to determine superiority of tivozanib as compared to sorafenib in terms of PFS, with secondary objectives including assessment of response rate, safety, and survival. Ultimately, a total of 517 patients were enrolled between February and August of 2010 at a total of 76 sites with the majority (approximately 90%) derived from European sites. Patient characteristics were similar on both study arms with an identical median age (59 years for both) and proportion of patients with no prior therapy (70% for both). Notably, there were a higher proportion of patients receiving sorafenib with an ECOG performance status of 0 (54%, as compared to 45% for tivozanib; $p < 0.05$). By independent review, there was a statistically significant improvement in PFS with tivozanib therapy (11.9 months vs. 9.1 months; $p = 0.042$), and this difference was slightly higher in those patients who had received no prior therapy (12.7 vs. 9.1 months, $p = 0.037$). A

more pronounced difference in PFS was noted by investigator assessment (14.7 months vs. 9.6 months, p = 0.003). Subset analyses based on demographic or clinicopathologic characteristics showed benefit across subgroups, including distribution by MSKCC risk stratification. With respect to secondary endpoints, there was a higher proportion of objective responses with tivozanib as compared to sorafenib (33 vs. 23%, p = 0.014) [11].

1.2.3 Safety

Detailed final safety data are available for 5 completed studies of tivozanib as monotherapy in subjects with cancer. Treatment-emergent adverse events (TEAE) were defined as any adverse event (AE) not present prior to the initiation of study drug treatment or any AE already present that worsened in either grade or frequency following exposure to study drug. With the exception of Study KRN951/030B01, the severity of an AE was classified based on the CTC Grading Scale, Version 3. For Study KRN951/03-B01, the severity of an AE was classified based on the NCI CTCAE Grading Scale, Version 2.0 (Grades 1 through 4). Safety data will be presented in relation to each study.

Study KRN951/03-B01 was a first-in-human Phase I study in patients with advanced solid tumors, 3 doses of tivozanib hydrochloride were studied (1.0, 1.5, and 2.0 mg) in a regimen of 4 weeks of daily dosing followed by a 2-week rest period. Each 6-week regimen was considered one cycle. All 41 subjects enrolled in Study KRN951/03-B01 experienced at least 1 AE. The most frequently reported AEs were fatigue (27 subjects, 65.9%), hypertension (24 subjects, 58.5%), diarrhea (23 subjects, 56.1%), hoarseness (20 subjects, 48.8%), and nausea (18 subjects, 43.9%). The proportion of subjects who were reported to have each of these AEs was higher in the 2.0 mg tivozanib hydrochloride group than the 1.0 and 1.5 mg tivozanib hydrochloride groups. There were 31 of 41 subjects with at least one Grade 3/4 AE. The most frequently reported Grade 3/4 AEs were hypertension (20 subjects, 48.8%) and fatigue (4 subjects, 9.8%). No other Grade 3/4 AE occurred in more than 2 subjects. Two deaths within 30 days of the final dose of tivozanib hydrochloride were reported in subjects participating in Study KRN951/03-B01. One subject in the 2 mg tivozanib hydrochloride group had an AE of malignant neoplasm progression during Cycle 1, which led to death. This AE was not considered related to study drug. One subject in the 1.0 mg tivozanib hydrochloride group died from disease-related causes after 3 cycles of treatment, 25 days after withdrawal from the study due to an AE (general physical health deterioration) [6].

Study AV-951-07-201 was a phase II randomized trial in 272 patients with recurrent or metastatic RCC, or primary RCC not amenable to surgery treated with 1.5 mg/day. TEAEs were reported in 242 of the 272 treated subjects (89.0%). The most frequently reported AEs were combined hypertension (125 subjects, 46.0%), dysphonia (62 subjects, 22.8%), asthenia (61 subjects, 22.4%), dyspnea (51 subjects, 18.8%), and fatigue (46 subjects, 16.9%). There were 132 treated subjects (48.6%) who had at least 1 >= grade 3 AE. The most frequently reported >=Grade 3 AEs were combined hypertension (32 subjects, 11.8%),

asthenia (23 subjects, 8.5%), dyspnea (16 subjects, (5.9%), and GGT increased (15 subjects, 5.5%). There were 15 deaths reported within 30 days of the final dose of tivozanib. None was considered to be related to study drug (as determined by the investigator) and 7 were due to disease progression [6].

Study AV-951-08-105 was a phase 1b multicenter study to evaluate the safety and activity of tivozanib in 17 subjects with NSCLC treated with either 1.0 mg or 1.5 mg daily. All 17 subjects in Study AV-95-08-105 experienced at least 1 AE during their participation in the study. The most frequently reported AEs were fatigue (13 subjects, 76.5%), nausea (9 subjects, 52.9%), diarrhea (8 subjects, 47.1%), hypertension (7 subjects, 41.2%), constipation (6 subjects, 35.3%), stomatitis (5 subjects, 29.4%), headache (5 subjects, 29.4%), cough (5 subjects, 29.4%), and decreased appetite (5 subjects, 29.4%). Twelve of the 17 subjects (70.6%) experienced at least 1 >= Grade 3 AEs occurring in more than 1 subject was hypertension (5 subjects, 29.4%), fatigue (3 subjects, 17.6%), and vomiting (2 subjects, 11.8%). Four deaths were reported in subjects participating in Study AV-951-08-105 (1 death due to respiratory failure and 3 deaths related to progressive disease/lung cancer). None of the deaths were thought to be related to the study drug [6].

Forty-five of the 50 subjects (90.0%) dosed in Study AV-951-10-112 experienced at least 1 AE. This was an investigational study of electrocardiogram and pharmacokinetic-electrocardiogram dynamics in subjects with advanced solid tumors treated with 1.5 mg daily of tivozanib. The most frequently reported AEs were hypertension (21 subjects, 42.0%), fatigue (12 subjects, 24.0%), and headache (11 subjects, 22.0%). Nineteen of the 50 dosed subjects (38.0%) had experienced at least 1 >= grade 3 TEAE. The only events reported in more than 1 subject were hypertension (9 subjects, 18.0%) and dyspnea (2 subjects, 4.0%). Two of the 50 dosed subjects died both due to progression of disease (and both deaths were considered unrelated to study drug) [6].

Study AV-951-09-301 is the recently published phase III randomized trial of 1.5 mg daily of tivozanib versus 400 mg twice daily of sorafenib in patients with metastatic renal cell carcinoma. Fewer patients receiving tivozanib (as compared to sorafenib) required dose interruptions (18% vs. 35; $p < 0.001$) or dose reductions (12 vs. 43%, $p < 0.001$) due to adverse events. The extent of drug discontinuation on account of treatment-related adverse events was similar on both arms (4% with tivozanib vs. 5% with sorafenib). Hypertension, diarrhea, and dysphonia were the most common adverse events noted with tivozanib. In comparing grade 3/4 toxicities, hypertension was more frequent with tivozanib (26 vs. 17%), whereas hand-foot syndrome was more common with sorafenib (17 vs. 2%). The development of hypertension was noted to be a clinical biomarker predictive of efficacy, a phenomenon observed among other VEGF-TKIs for mRCC. Those patients with a diastolic blood pressure greater than 90 mmHg had an improved PFS with tivozanib (18.3 months vs. 9.1 months). Similarly, a systolic pressure greater than 150 mmHg developed while on study conferred a benefit in the same endpoint (16.7 months vs. 9.0 months) [11].

1.2.4 Clinical Pharmacology

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, (tmax), of tivozanib (free base), 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 Tmax is 10 h. Across the multiple studies, exposure (Cmax and AUC) of tivozanib (free base) 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 t1⁄2 of tivozanib (free base), the mean between studies being approximately 3.6 to 4.7 days. Also, the PK of tivozanib (free base) is similar in oncology patients compared to the profile in healthy volunteers.

In combination studies of tivozanib hydrochloride 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 (free base) levels or those of the coadministered 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 (free base) but various metabolites were detected in urine and accounted for 11.8% of recovered radioactivity. The findings are consistent with elimination of tivozanib (free base) via feces and some degree of metabolism.

In vitro data suggest the possibility that tivozanib hydrochloride 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 [6].

1.2.5 Drug-Drug Interaction Studies

Results from drug-drug interaction studies conducted in vitro indicate that tivozanib hydrochloride had no inhibitory effect on CYP3A4, CYP2C8, CYP2D6, CYP1A2, CYP2C9, or CYP2C19. Further, tivozanib hydrochloride did not show any propensity to induce CYP450 isoforms in an in vitro assay system at clinically relevant exposures. Due to the low likelihood of tivozanib hydrochloride causing a drug-drug interaction by inhibiting the metabolism of a co-administered agent, no clinical studies to evaluate this question are planned.

In vitro studies with cDNA-derived CYP450 showed that only CYP1A1 (primarily extrahepatic) and CYP3A4 were capable of metabolizing tivozanib hydrochloride. Clinical trials in healthy volunteers investigating the effect of ketoconazole (AV-951-11-116) and rifampin (AV-951-11-117) are in progress [6].

1.3 Study Rationale

1.3.1 Angiogenesis and Tumor Growth

Angiogenesis is defined as the formation of new blood vessels from preexisting vasculature. Angiogenesis is classified into 2 types: physiologic and pathologic. Physiologic angiogenesis includes embryonic development, reproduction, and wound healing. Pathologic angiogenesis is involved in diseases such as cancer, rheumatoid arthritis, and diabetic retinopathy. Angiogenesis plays an important role in the control of cancer progression and metastasis. Tumors cannot grow beyond 2 to 3 mm^3 in size in the absence of the new vascularization. While angiogenesis is a complex process involving endothelial cell proliferation, survival migration, vessel morphogenesis and maturation, signaling through endothelial growth factors such as the VEGF ligands is known to be rate limiting for angiogenesis. Inhibiting tumor angiogenesis is believed to be a promising therapeutic modality [12].

1.3.1.1 Vascular Endothelial Growth Factor Pathway

The vascular endothelial growth factor (VEGF) signaling pathway appears to be the dominant pathway involved in tumor angiogenesis. The VEGF family consists of five structurally related proteins (VEGF-A, VEGF-B, VEGF-C, VEGF-D and Placental Growth Factor (PLGF), and signaling through this pathway is mediated by the binding of these growth factors to three receptors (VEGFR-1, VEGFR-2, and VEGFR-3). The ligands bind each receptor with distinct but overlapping specificity as well as distinct biological function, together acting to effect proliferation, migration and morphogenesis of endothelial cells to form functional vasculature [13].

1.3.1.2 Vascular Endothelial Growth Factor Receptor

Two high-affinity cognate endothelial receptors for VEGF have been identified. One is VEGF receptor-1 (VEGFR-1, also known as Flt1) and the other is VEGFR-2 (also known as kinase insert domain-containing receptor (KDR)/Flk1). These receptors have a characteristic structure with 7 immunoglobulin-like domains in the extracellular domain and a cytoplasmic tyrosine kinase domain with a long kinase insert region. They are members of a large family of receptor tyrosine kinases and are localized on endothelial cells. Activation of VEGFR-1 and VEGFR-2 receptors occurs through ligand binding, which facilitates receptor dimerization and autophosphorylation of tyrosine residues. VEGFR-2 is considered the major mediator of the mitogenic, angiogenic and permeability-enhancing effects of VEGF. In addition, recent studies have also suggested the role of VEGFR-3 (FLT-4), another tyrosine kinase, in tumor angiogenesis. VEGFR-3 is expressed in the tumor vasculature and targeting its activity is known to retard tumor formation by inhibiting angiogenesis [14].

Tivozanib hydrochloride is a highly potent, selective inhibitor of the

receptor tyrosine kinase activity of VEGFR-1, 2, and 3. It has been shown to block various VEGF-induced biologic responses in endothelial cells in vitro. Furthermore, tivozanib hydrochloride demonstrated a marked antitumor activity against human tumor xenograft models in nude mice and nude rats. Tivozanib hydrochloride has good pharmacokinetic profiles in various animal models. In toxicology studies conducted using Good Laboratory Practices, toxicities were similar across species, were generally dose responsive and showed signs of recovery following cessation of treatment. Tivozanib hydrochloride has exhibited significant anti-tumor effects against a wide variety of tumors in rat and mouse xenograft models. Pharmacologic studies showed that tivozanib hydrochloride is a potent inhibitor of VEGFR phosphorylation, which plays a major role in tumor angiogenesis and vascular permeability, but does not have obvious direct tumorcidal activity. These data indicated that the mechanism of the anti-tumor activity for tivozanib hydrochloride is through the inhibition of tumor angiogenesis and vascular permeability [6].

1.3.2 Rationale for Clinical Trial Design

This is a single arm phase II trial. All patients will receive 1.5 mg orally of tivozanib given daily for 3 weeks with one week off to complete a 4 week cycle. At the start of each cycle, patients will have a visit with a clinician who will obtain a pertinent history, perform a physical exam, draw serum CA-125 values and a CBC and CMP and determine if the patient is appropriate for therapy. Treatment will continue until documented disease progression or the patient is unable to tolerate further therapy due to excessive toxicity.

2 STUDY OBJECTIVES

2.1 Primary

The primary objective of this single-arm, phase II clinical trial will be to determine the clinical activity of tivozanib in patients with platinum-resistant, recurrent ovarian, fallopian tube or primary peritoneal cancer. For this protocol text, these disease entities will be referred to collectively as ovarian cancer. The primary endpoint of this trial will be the overall response rate of patients with platinum-resistant ovarian cancer to treatment with single agent tivozanib as measured by physical exam findings, serum CA-125 levels and/or measurement of index lesions via appropriate imaging studies using RECIST criteria.

2.2 Secondary

2.2.1 The secondary objectives of this trial will include determining the potential survival advantage and characterizing the safety of single agent tivozanib in patients with platinum-resistant ovarian cancer.

2.2.2 The secondary endpoints will include the duration of progression-free survival in patients with platinum-resistant ovarian cancer treated with single agent tivozanib.

Additionally, toxicity will be reported using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

2.3 Exploratory

2.3.1 The first exploratory endpoint is a retrospective analysis of archival tissue from all patients who have enrolled to measure the expression of proteins that play a role in VEGF signaling and other relevant oncogenic pathways. The level of expression will be correlated with the best response to treatment (CR, PR, SD, PD).

2.3.2 The second exploratory endpoint is a retrospective analysis of genetic reports from all patients who have enrolled, if available. This analysis will be used to correlate genetic mutation burden with response to treatment.

3 PATIENT SELECTION

The target population for this study is patients with recurrent or persistent, platinum resistant epithelial ovarian, fallopian tube or primary peritoneal carcinoma. This will be a multicenter trial conducted at Northwestern Medicine. Northwestern University will serve as the lead site and coordinating center for this study. Participating sites will include Northwestern Medicine Cancer Center Warrenville and the Northwestern Medicine Cancer Center Delnor and Northwestern Lake Forest Hospital.

A total of 30 subjects will be needed for this trial. Approximately 6 potentially eligible patients are seen per month, and it is anticipated that at least 3 per month will be accrued (once all sites are up and running). Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Daniela Matei, at (312) 472-4684, or to the local PI at each participating site.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 10 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

3.1.1 Patients must have recurrent or persistent, platinum resistant or refractory epithelial ovarian, fallopian tube or primary peritoneal carcinoma. Platinum-resistant disease is defined as a recurrence within 6 months of completing platinum-based chemotherapy.

3.1.2 Patients must have measurable disease or non-measurable (detectable) disease:

- Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be greater than or equal to 10 mm when measured by CT, MRI or by clinical exam; or greater than or equal to 20 mm when measured by chest x-ray. Lymph nodes must be greater than or equal to 15 mm in short axis when measured by CT or MRI.

- Non-measurable (detectable) disease in a patient is defined in this protocol as one who does not have measurable disease based on RECIST criteria but does have a CA-125 greater than or equal to two times the upper normal limit within the last 60 days (confirmatory at baseline) and at least one of the following conditions:
    - Ascites and/or pleural effusion attributed to tumor
    - Hypermetabolic lesions on PET Scan

3.1.3 Patients with measurable disease must have at least one target lesion as defined by RECIST 1.1 to be used to assess response on this protocol.

3.1.4 Patients must have an ECOG Performance Status of 0, 1, or 2.

3.1.5 Patients must have had one prior taxane and platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. This initial treatment may have included intraperitoneal therapy, consolidation, non-cytotoxic (biologic/targeted agents) or extended therapy administered after surgical or non-surgical assessment. There is no maximum number of prior regimens.
Note: Use of bevacizumab as maintenance therapy after initial adjuvant platinum-based chemotherapy is allowed so long as platinum-resistant recurrence occurred subsequent to a separate platinum-based regimen AND more than 6 months after completion of bevacizumab maintenance.

3.1.6 Patients must have signed an approved informed consent and authorization permitting the release of personal health information.

3.1.7 Patients must be willing and able to complete all study procedures.

3.1.8 Patients must have adequate organ or bone marrow function within 28 days prior to study registration, as defined below:

Hemoglobin	≥ 9.0 g/dL
Absolute neutrophil count (ANC)	≥ 1500 per mm^3
Platelet count	≥ 100,000 per mm^3
Total bilirubin[1]	≤ 1.5 × ULN (or ≤ 2.5 x ULN for subjects with asymptomatic Gilbert's syndrome)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)[1]	≤ 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	≤ 2.0 × ULN;
PT/ PTT	PT such that INR ≤ 1.5 x ULN (unless a patient is on therapeutic warfarin) or a PTT ≤ 1.5 x ULN
Proteinuria	≤ 2+ by urinalysis or urine dipstick

1. Also excluded are patients with elevations in BOTH total bilirubin > ULN **AND** AST or ALT > ULN

3.1.9 Patients must be greater than or equal to 18 years of age.

3.1.10 Females of child-bearing potential (FOCBP) and males must agree to use adequate contraception (male or female condoms, diaphragms, and spermicides, which are creams or gels that contain a chemical to kill sperm) prior to study entry, for the duration of study participation, and for 45 days following completion of therapy.

NOTE: A FOCBP is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy
- Has had menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months)

3.1.11 FOCBP must have a negative pregnancy test within 7 days prior to registration on study.

3.1.12 Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.

3.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

3.2.1 Patients who have had previous treatment with tivozanib are excluded.

3.2.2 Patients with symptomatic left ventricular dysfunction or baseline left ventricular ejection fraction (LVEF) my multigated acquisition scan (MUGA) or echocardiogram (ECHO) of ≤ 50% are not eligible.

3.2.3 Patients with uncontrolled hypertension as defined as systolic blood pressure of >140mmHg or diastolic blood pressure of >90mmHg documented on 2 consecutive measurements taken at least 24 hours apart are not eligible.
Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Following antihypertensive medication initiation or adjustment, blood pressure (BP) must be re-assessed three times at approximately 2-minute intervals. At least 24 hours must have elapsed between anti-hypertensive medication initiation or adjustment and BP measurement. These three values will be averaged to obtain the mean diastolic blood pressure and the mean systolic blood pressure. The mean SBP / DBP ratio must be < 140/90 mmHg in order for a subject to be eligible for the study (see Table 6.1 for details on BP control and reassessment).

3.2.4 Patients with significant cardiovascular disease are excluded, including:

- Myocardial infarction, severe angina, or unstable angina within 6 months prior to administration of first dose of study drug.
- History of serious ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation).

- Cardiac arrhythmias requiring anti-arrhythmic medications (except for atrial fibrillation that is well controlled with anti-arrhythmic medication).
- Coronary or peripheral artery bypass graft within 6 months of screening.
- History of Class III or IV congestive heart failure, as defined by the New York Heart Association.

3.2.5 Patients with central nervous system metastases are excluded.

Note: Subjects with previously treated (radiotherapy or surgery) brain metastasis that have been stable without steroid treatment for at least 3 months following prior treatment may be enrolled.

3.2.6 Any patient with a current non-healing wound, bone fracture, or skin ulcer is excluded.

3.2.7 Patients who are currently receiving treatment with drugs known to be strong inhibitors or inducers of isoenzyme CYP3A4 including herbal medications (See Appendix B for further information).

Note: As this list is constantly evolving, if a medication is incorrectly documented as prohibited in this protocol, documentation from the site pharmacist to the contrary will be acceptable for the purposes of registration.

3.2.8 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.

3.2.9 Serious/active infection or infection requiring parenteral antibiotics.

3.2.10 Patients must not have a corrected QT interval (QTc) of > 480 msec using Bazett's formula.

3.2.11 Patients who have had radiotherapy or minor surgical procedure within 14 days, or major surgical procedure within 28 days prior to administration of first dose of study drug are not eligible; patients with inadequate recovery from prior surgical procedure are also not eligible.

3.2.12 Patients with active infection requiring antibiotics are not eligible (with the exception of uncomplicated UTI and uncomplicated respiratory tract infections).

3.2.13 Patients may not have had any prior systemic therapy ≤ 21 days prior to registration for treatment of ovarian cancer.

3.2.14 Patients who have received investigational or licensed drugs that target vascular endothelial growth factor [VEGF] or VEGF receptors/pathways (such as bevacizumab, sorafenib, pazopanib, sunitinib, axitinib, cabozantinib, etc.) for the treatment of recurrent cancer are not eligible. Exceptions: prior treatment with bevacizumab in the up-front or maintenance setting is allowed, provided the patient had a favorable response to bevacizumab. Favorable response is defined as

having had a disease free interval of >6 months following completion of a bevacizumab-containing regimen. If questions, contact the PI.

3.2.15 Significant thromboembolic or vascular disorders within 6 months prior to administration of first dose of study drug, including but not limited to:

- Deep vein thrombosis
- Pulmonary embolism
- Cerebrovascular accident (CVA) or transient ischemic attack (TIA)
- Peripheral arterial ischemia > Grade 2 (per National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 4.03)

3.2.16 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 ≥ Grade 2 (per CTCAE Version 4.03)
- Hemoptysis or other pulmonary bleeding ≥ Grade 2 (per CTCAE Version 4.03)
- Hematuria or other genitourinary bleeding ≥ Grade 2 (per CTCAE Version 4.03)

3.2.17 Currently active second primary malignancy, including hematologic malignancies (leukemia, lymphoma, multiple myeloma, etc.), other than non-melanoma skin cancers, in situ cervical cancer, and ductal or lobular carcinoma in situ of the breast. Subjects are considered to have a currently active malignancy if they have completed anti-cancer therapy and have not been disease free for > 2 years.

3.2.18 Pregnant or lactating females are excluded.

3.2.19 Any patient with a history of genetic or acquired immune suppression disease such as human immunodeficiency virus (HIV) is excluded; subjects on immune suppressive therapy for organ transplant are also excluded.

3.2.20 Life-threatening illness or organ system dysfunction compromising safety evaluation.

3.2.21 Requirement for hemodialysis or peritoneal dialysis.

3.2.22 Inability to swallow capsules, malabsorption syndrome or gastrointestinal disease that severely affects the absorption of study drugs, major resection of the stomach or small bowel, or gastric bypass procedure.

3.2.23 Known hypersensitivity to drugs chemically related to tivozanib hydrochloride or sunitinib or their excipients.

3.2.24 Psychiatric disorder or altered mental status precluding informed consent or protocol-related testing.

3.2.25 Patients with clinical symptoms or signs of gastrointestinal obstruction.

4 TREATMENT PLAN

4.1 Overview

This is a single arm phase II trial. All patients will receive 1.5 mg orally of tivozanib given daily for 3 weeks with one week off to complete a 4 week cycle. At the start of each cycle, patients will have a visit with a clinician who will obtain a pertinent history,

perform a physical exam, draw serum CA-125 values and a CBC and CMP and determine if the patient is appropriate for therapy. Treatment will continue until documented disease progression or the patient is unable to tolerate further therapy due to excessive toxicity.

4.2 Study Drug Administration: Tivozanib

4.2.1 Drug Dispensing: The patient will be dispensed enough pills for 1 cycle at each monthly visit. Patient pill calendar will be reviewed by study coordinator or nurse. Pill count will be done, and any unused pills will be returned each cycle.

4.2.2 Dosing Schedule: Tivozanib hydrochloride will be administered orally, at a dose of 1.5 mg/day, beginning on Day 1 of Cycle 1. Subjects will receive tivozanib hydrochloride once daily for 3 weeks followed by 1 week off treatment. One cycle is defined as 4 weeks. Cycles will be repeated every 4 weeks in the absence of disease progression or unacceptable toxicities.

4.2.3 Dosing Information: The prescribed daily dose of tivozanib hydrochloride is to be taken, once per day, preferably in the morning, with water. Tivozanib should be taken on an empty stomach either 1 hour before or 2 hours after meals at the same time each day. The tablets should be swallowed whole and cannot be crushed or broken. Only one capsule of tivozanib hydrochloride should be taken each day. If a dose is vomited or otherwise missed that day for any reason, the dose for that day should not be made up. The next dose should be taken as prescribed at the next scheduled time (i.e., one capsule is to be taken even if the previous dose was vomited or otherwise missed; additional dose(s) should not be taken at any time to make up for any missed dose(s). Grapefruit and grapefruit juice should be avoided during the study.
In the event that tivozanib hydrochloride dosing is interrupted, the duration of cycle/treatment will not be extended; doses missed during the interruption will be captured as omitted rather than delayed.

4.2.4 Dosing Parameters: Subsequent cycles of therapy will not begin (day 1 of each cycle) until the ANC is ≥1500 cells/mcl and the platelet count is ≥ 100,000/mcl. Therapy will be delayed for a maximum of two weeks until these values are achieved. Patients who fail to recover adequate counts within a two week delay will be removed from study therapy. Grade 1 or 2 toxicity will not result in a dose reduction or treatment delay. Drug-related grade 3 or 4 toxicities will result in an interruption in treatment until the toxicity is less than or equal to grade 2. Additionally, a dose reduction will be performed. If there is no recovery to ≤ grade 2 or recurrent grade 3 or 4, then tivozanib will be discontinued.

4.3 General Concomitant Medication and Supportive Care Guidelines

4.3.1 Premedications for Study Drug-Related Toxicities

4.3.1.1 Patients should not be premedicated prior to receiving the first dose of study drug.

4.3.1.2 Thereafter, patients having experienced symptoms suggesting mild to moderate study drug administration-related reactions may be premedicated

with standard measures (eg, acetaminophen, diphenhydramine, H2-blockers, and/or dexamethasone), as clinically indicated.

4.3.1.3 Mandatory premedication will be recommended for all patients treated on this study should a pattern of mild to moderate study drug administration-related reactions begin to emerge.

4.3.1.4 Any medications administered for either prophylaxis or therapy of symptoms considered to be associated with study drug will be documented and reported.

Subjects should avoid agents known to be weak Cytochrome P450 (CYP3A4) inducers or inhibitors for the duration of study treatment. See Appendix B for further information on Cytochrome P450 (CYP3A4**)** inducers and inhibitors.

4.3.2 Concomitant Medications

The following medications/treatments are prohibited during study treatment:

4.3.2.1 Chemotherapy, biological therapy (including cytokines, signal transduction inhibitors, monoclonal antibodies), immunotherapy or any other systemic therapy for ovarian, fallopian tube or primary peritoneal cancer.

4.3.2.2 Treatment with radiotherapy (including palliative)

4.3.2.3 Strong/moderate Cytochrome P450 (CYP3A4) inducers or inhibitors for the duration of study treatment. All CYP3A4 inducers and inhibitors should be used with caution (See Appendix B for further information).

Note: As this list is constantly evolving, if a medication is incorrectly documented as prohibited in this protocol, documentation from the site pharmacist to the contrary will be acceptable for the purposes of registration.

4.3.2.4 Subjects will NOT receive prophylactic growth factors [filgrastim (G-CSF), sargramostim (GM-CSF), pegfilgrastim (Neulasta)] unless they experience recurrent neutropenic complications after treatment modifications specified below.

4.3.2.5 Subjects will NOT receive prophylactic thrombopoietic agents.

4.3.2.6 Subjects may not receive erythropoietin (EPO) but may receive iron supplements, and/or transfusions as clinically indicated for management of anemia.

4.3.3 The following medications/treatments are permitted during the study treatment:

4.3.3.1 Full dose oral anticoagulants and/or anticoagulation with low molecular weight heparin or unfractionated heparin administered subcutaneously. Subjects taking anticoagulants should have their coagulation panels monitored as scheduled during the study and as clinically indicated.

4.3.3.2 Subjects are permitted to receive supportive care throughout the study including transfusions (blood, blood products), antibiotics, anti-emetics, anti-diarrheal agents, analgesics, or bisphosphonates, when appropriate, with the exception of any prohibited medications/treatments.

4.3.4 Other medications/treatments that should be avoided during the study treatment:

4.3.4.1 Herbal remedies should be avoided; however, if herbal remedies are used, they should be documented as a concomitant medication.

4.3.4.2 Medications/agents known to prolong QT interval.

4.3.5 Systemic hormonal therapy, with the exception of:

4.3.5.1 Hormonal therapy for appetite stimulation or contraception;

4.3.5.2 Nasal, ophthalmic, inhaled and topical steroid preparations;

4.3.5.3 Hormone replacement therapy for conditions such as adrenal insufficiency, hypothyroidism, etc.;

4.3.5.4 Low dose maintenance steroid therapy (equivalent of prednisone ≤ 10 mg/day) for other conditions.

4.4 Duration of Therapy

Patients may continue to receive cycles of treatment until any of the following occur:

- Disease progression
- Development of an inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from either study treatment or the study as a whole
- The treating investigator determines that the patient should be taken off treatment for any reason (i.e. changes in condition, inability to comply with study treatment or procedures)

4.5 Duration of Follow Up

Patients will return for an end of treatment visit within ±14 days of the decision to discontinue treatment.

Subjects will be followed approximately 30 days after discontinuation of treatment and then approximately every 3 months for 2 years and then approximately every 6 months for 3 years after removal from study or until death, whichever occurs first. Subjects will be monitored for survival for this 5-year period. Subjects removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

4.6 Removal of Subjects from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted)
- Patient withdraws consent (no follow-up permitted)
- Patient is unable to comply with protocol requirements
- Patient demonstrates disease progression
- Patient experiences unacceptable toxicity

- Treating physician determines that continuation on the study would not be in the patient's best interest
- Patient becomes pregnant
- Patient develops a second malignancy that requires treatment which would interfere with this study
- Patient becomes lost to follow-up (LTF)

4.7 Dose Delays/Dose Modification

Comprehensive assessments of any toxicity experienced by the patient will be performed throughout the course of this study. Anticipated toxicities that may be experienced are detailed in the section on adverse events in prior studies of tivozanib. 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 patient experiencing any adverse event while participating in this study. Any adverse event, whether observed by the investigator, or observed or experienced by the patient, will be reported. All clinical and laboratory adverse events must be carefully evaluated for severity, duration and relationship to tivozanib.

4.7.1 Tivozanib Hydrochloride Dose Modification

Clinical judgment will be used to determine appropriate management of the subject experiencing any adverse event (AE). The suggested criteria for dose modification for tivozanib hydrochloride drug-related AEs (excluding hypertension) are summarized in the table below.

Tivozanib Hydrochloride Dose Modification Guidelines for Drug-Related Adverse Events

Drug-Related Adverse Events (excluding Hypertension[1])	Action Taken	Subsequent Dosing Modification
Grade 1	No dose interruption, or reduction required; adverse event management is at the discretion of the Investigator	None required; Dosing may continue at the same dose
Grade 2	No dose interruption, or reduction required; adverse event management is at the discretion of the Investigator	None required; Dosing may continue at the same dose
Grade 3[2]	Interrupt dosing[3] until toxicity resolves to ≤ grade 1.	Dosing may resume at same dose or reduced dose at the discretion of the Investigator (see below for dose reduction guidelines).
Grade 4	Interrupt dosing until toxicity resolves to ≤ grade 1.	Dosing may resume at same dose or reduced dose at the discretion of the investigator (see below for dose reduction guidelines).

1. Hypertension must be treated as described in Appendix C prior to any dose modification
2. Referring to toxicity that persists despite appropriate medical care.
3. Tivozanib may be interrupted for up to 2 weeks. If a subject is able to resume treatment after an interruption of ≤ 2 weeks, missed doses will not be made up (i.e. the cycle duration will remain unchanged). If any drug related toxicity results in interruption of >2 weeks, the subject should be discontinued from study treatment unless there is clear benefit.

Patients should be followed for assessment of the toxicities until the AEs resolve or are deemed irreversible. The maximum delay of drug administration by the treating investigator or the patients' own decision for any reason, including toxicities, is 2 weeks. If the drug is withheld for more than 2 continuous weeks due to a treatment-related toxicity that does not resolve, the patient will be withdrawn from study treatment. The exception is HTN, which must first be treated as described in Appendix C prior to any dose modification.

Patients will be withdrawn from the study if they fail to recover to grade ≤ 1 or tolerable grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a treatment-related toxicity within 2 weeks OR if they experience agent related adverse events requiring dose modification despite previous dose reductions (i.e. would require a 2nd dose reduction) unless the investigator agrees that the subject should remain in the study because of evidence that the patient is/may continue deriving benefit from continuing study treatment. The appropriate reduced dose will be determined after discussion with the principal investigator and approval of the Data Monitoring Committee. Patients requiring dose reductions should not have the dose re-escalated with subsequent treatments. If treatment was interrupted for < 1 week, the patient will resume dosing on the current treatment cycle. If treatment was interrupted for ≥ 1 week, the patient will start a new cycle of treatment.

4.7.2 Tivozanib Hydrochloride Dose Reduction

Dose reductions of tivozanib hydrochloride to 1.0 mg/day will be allowed for subjects with ≥ Grade 3 drug-related adverse events. The exception is hypertension, which must be treated with anti-hypertensive drugs prior to dose reduction. Once a subject's dose of tivozanib hydrochloride is reduced, it may not be re-escalated through the remainder of the subject's participation in the study. If a subject is unable to tolerate a reduced dose due to toxicities thought to be related to treatment, treatment should be discontinued.

5 RESPONSE ASSESSMENT

The measures used to determine the objective overall response rate will be those that are already in place for determining treatment efficacy. Specifically, we will utilize physical exam findings performed at the commencement of each 4-week cycle of treatment during a clinician visit. Additionally, serum CA-125 levels will be checked at the commencement of each 4 week cycle of treatment to determine disease status. If otherwise indicated by disease state, we will obtain CT scan or MRI or chest x-ray and utilize index target lesions and RECIST 1.1 criteria to

determine treatment efficacy and response rate.

5.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [16]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

5.2 Disease Parameters

5.2.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >10 mm with CT scan, as >20 mm by chest x-ray, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Lymph nodes are considered measurable in RECIST 1.1 if their short diameter exceeds 15 mm. Lymph nodes are considered normal if they have a short axis of less than 10 mm; this applies to determination of response as well.

Lesions that are previously irradiated must show clear evidence of progression over a minimum of 3 months to include as measurable. This period of time is used to discount tumor edema in an irradiated field as a false sign of disease progression.

5.2.2 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with >10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (specifically abdominal masses that cannot be followed by CT or MRI), and cystic lesions are all non-measurable.

> ***Note****: Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by 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 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 non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.*

5.2.3 Target lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

5.2.4 Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

5.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

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

5.3.1 Clinical lesions

Clinical lesions will only be considered measurable when they are >= 10 mm diameter. For superficial lesions measured by caliper, documentation by color photography including a ruler in the field of view is strongly recommended.

5.3.2 Chest x-ray

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

5.3.3 Conventional CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If 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 (e.g. for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables

involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, subsequent image acquisitions should use the same type of scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

5.3.4 PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. PET-CT scans are not always done with oral and IV contrast. In addition, the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed. For these reasons, we will not allow PET-CT use for RECIST 1.1 response criteria.

5.3.5 FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible “new” disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

  Note: A “positive” FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

5.3.6 Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their

entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. 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.

5.3.7 Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

5.3.8 CA-125 (Ovarian, fallopian tube and primary peritoneal cancer trials)

If CA125 is initially above the upper normal limit then it may be used as a marker of treatment efficacy. It must normalize for a patient to be considered in complete clinical response. Specific guidelines for CA-125 response (in recurrent ovarian cancer) have been published [15]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria that are to be integrated with objective tumor assessment for use only in first-line trials in ovarian cancer [17]. See section 5.4.3 for explanation of clinical response.

5.3.9 Cytology, Histology

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

It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when measurable disease has met criteria for response or stable disease. This confirmation is necessary to differentiate response or stable disease versus progressive disease, as an effusion may be a side effect of the treatment.

5.4 Response Criteria

Determination of response should take into consideration all target and non-target lesions and, if appropriate, biomarkers.

5.4.1 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 the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the 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 progressions).

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.

5.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s)

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Not evaluable (NE): When at least one non-target lesion is not evaluated at a particular time point.

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

5.4.3 Evaluation of Biomarkers

If serum CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response. A partial response according to CA 125 has occurred if there is at least a 50% reduction in CA 125 levels from a pretreatment sample but the value remains above the normal range. The response must be confirmed and maintained for at least 28 days. A complete response has occurred if the CA-125 level decreases into the normal range. Progressive disease will be defined as a doubling of CA-125 levels. Stable disease will be any CA-125 level that falls within the range of progressive disease and partial response.

5.5 Duration of Response

5.5.1 Duration of overall response

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

progressive disease the smallest measurements recorded since the treatment started).

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

5.5.2 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 measurements recorded since date of study entry, including the baseline measurements.

5.6 Progression-Free Survival
Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first.

5.7 Survival
Survival is defined as the duration of time from study entry to time of death or the date of last contact.

6 DRUG INFORMATION

6.1 Tivozanib Hydrochloride
6.1.1 Other Names
AV-951

6.1.2 Classification
VEGFR tyrosine kinase inhibitor

6.1.3 Molecular Formula and Weight
$C_{22}H_{19}ClN_4O_5$ HCl H_2O 509.34 (hydrochloride monohydrate) 454.86 (free base)

6.1.4 Chemical Name
N-{2-Chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl) urea hydrochloride monohydrate

6.1.5 Mechanism of Action:
Tivozanib is a highly potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases (VEGFR1, VEGFR2, and VEGFR3). Vascular endothelial growth factor receptor inhibition may block VEGF driven angiogenesis and, as a consequence, constrain tumor growth.

6.1.6 Drug Storage and Stability
Tivozanib hydrochloride drug product should be stored at room temperature (15°–25°C) in a controlled access room that can be entered only by authorized pharmacy or investigative personnel.

Long-term stability studies conducted according to ICH guidelines support an expiration dating of 36 months for dose strengths ranging from 0.5 mg to 2.0 mg when stored at 15-25ºC with allowable excursions up to 30ºC. Tivozanib hydrochloride drug product is an investigational new drug. Accordingly, all drug handling and disposal procedures for orally administered investigational drugs should be performed by qualified personnel as documented by the American Hospital Formulary Service or other recognized formulary requirements.

6.1.7 Protocol Dose

The following dosage strengths will be made available:

1.5 mg

1.0 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 hydrochloride. Dosing compliance will be monitored at each clinic visit.

6.1.8 Route of Administration

Tivozanib hydrochloride is formulated for oral administration as a white opaque number 4 gelatin capsule.

6.1.9 Availability

Provided at free of charge by AVEO Pharmaceuticals, Inc.

6.1.10 Approximate Solubility

Practically insoluble in water, slightly soluble in methanol, very slightly soluble in ethanol, and freely soluble in dimethyl sulfoxide.

Complete study drug information (including packaging, labeling, storage and disposition) is provided in the Tivozanib Hydrochloride Investigator's Brochure (IB).

7 CLINICAL AND LABORATORY EVALUATIONS

7.1 Schedule of Assessments

Parameter	Pre-Therapy	Weekly (-1 Day)	Prior to Each Cycle (-4 Days)	Every Odd Cycle (-7 Days)	End of Treatment Visit (±14 Days)[12]	Follow Up
History and Physical Exam	X[2]		X			
Vital signs (Blood Pressure, Heart Rate and Temperature)	X[2]	X	X			
ECOG Performance Status	X[2]		X			
Toxicity Assessment[5]	X[2]	X[4]	X		X	
CBC/Differential/Platelets	X[2]	X[3]	X[6]			
PT/INR and PTT	X[2,7]					
CMP + electrolytes[14]	X[2]	X[3]	X[6]			
Total bilirubin, AST, ALT, Alkaline Phosphatase	X[2]	X[3]	X[6]			
Urine Pregnancy Test (if childbearing potential exists)	X[2]					
X-ray or CT or MR imaging (chest/abdomen/pelvis)	X[1]			X[11]	X[11]	
Radiographic tumor measurement	X[1]			X[11]	X[11]	
CA-125	X[1]		X[15]			
Electrocardiogram (ECG)	X[1]		X[15]			
Echocardiogram (ECHO) / MUGA	X[1]					
Urinalysis to evaluate for proteinuria	X[8]			X[9, 10]		
Patient Tablet Calendar			X			
Follow-up Phone Call		X[4]				
Review Con Meds[16]	X[2]		X		X	X[16]
Survival Status						X[13]

One cycle = 28 days

1. Must be obtained within 28 days prior to study registration.
2. Must be obtained within 7 days prior to study registration.
3. During the first two cycles of therapy patients should have CBC and CMP performed weekly while taking study medication. Magnesium and Phosphorus are only required weekly during the first two cycles if clinically indicated. Thereafter the patient can be seen prior to each cycle.
4. Weekly toxicity assessment performed during for cycle 1 only. Assessment can be done at a clinic visit, by phone or by email.
5. Report all adverse events that occur within 30 days of last protocol treatment of therapy administered.

6. Must be obtained within 4 days of treatment with protocol therapy.
7. Patients on prophylactic or therapeutic anticoagulation with warfarin should have PT/INR monitored after starting and stopping tivozanib (e.g., weekly for the first cycle and weekly for a minimum of 2 weeks following discontinuation of tivozanib) and weekly for the first cycle of treatment following a warfarin or tivozanib dose modification.
8. Urinalysis to evaluate for proteinuria must be obtained 14 days prior to initiating protocol therapy.
9. If protein is 3+ or higher (≥ 300 mg/dL), 24-hour urine protein should be obtained and the level must be <1000 mg (<1g/24hrs) for patient to continue on study.
10. Urinalysis to evaluate for proteinuria should be performed prior to every odd cycle (for example, prior to cycles 1, 3, 5, 7, ETC).
11. CT scan or MRI or x-ray of chest-abdomen-pelvis every other cycle (or equivalent time frame for patients off treatment prior to disease progression) for the first 6 months; then every 3 months thereafter until disease progression; also repeat at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease; also complete at the end of treatment if clinically indicated. Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation (see section 8).
12. End of treatment visit will occur within ±14 days of the decision to discontinue study treatment.
13. Follow-up approximately 30 days after the last dose of Tivozanib and then approximately every 3 months for 2 years and then every 6 months for 3 years.
14. CMP + electrolytes includes: Sodium, potassium, chloride, bicarbonate, BUN, Glucose, Albumin, Creatinine, Calcium, Magnesium, Phosphorus, total protein. Magnesium and Phosphorus are only required if clinically indicated
15. Must be completed within 14 days prior to each cycle. Exceptions include treatment delays, in which case they would be allowed within 21 days prior to the delayed cycle.
16. Record all reported concomitant medications from the time of consent until 30 days after the last dose of Tivozanib (or until initiating the next line of anti-cancer therapy, whichever is first).

8 STATISTICAL METHODS

Statistical analyses will focus on estimation of overall response rates in patients with platinum-resistant ovarian cancer as stated in the Primary Objective. Specific definitions for complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) are defined in the Primary Endpoint section according to physical exam findings, serum CA-125 levels and imaging studies. Response frequencies and percentages will be tabulated for all four groups and then an overall frequency of response (CR or PR) v. non-response (SD or PD) will be calculated along with a one-sided lower limit 95% confidence interval, consistent with the approach used to specify staging of accrual. For the secondary objective, the Kaplan-Meier method will be utilized to estimate the median and overall distribution of progression-free survival. Toxicity will also be evaluated as a secondary objective and grades will be summarized by counts and frequencies. For description of other continuous variables, means, standard deviations, minimum and maximum values will be used. Other categorical variables will be summarized by counts and frequencies. In addition, the extent to which treatment is completed will be monitored and tabulated according to the number of complete weeks of treatment.

Total anticipated accrual to this phase II single-arm trial is 30 patients. Recruitment will be completed in two stages with 10 patients accrued in the first stage and 20 accrued in the second stage according to Simon's two-stage design (Simon, 1989; Jung et al. 2004) with a null hypothesis that the true response rate is less than or equal to 5% and 5% type I error and 80% power when the true response rate is greater than or equal to 20%. In the first stage, if there are 0 responses (CR or PR) in the 10 patients that are accrued, the study will be stopped. Otherwise, 20 additional patients will be accrued, with rejection of the null hypothesis occurring if 4 or more responses are observed in the total 30 patients. On 10/12/16 the Northwestern DSMC reviewed the first 9 evaluable patients and approved the study to open to an additional 21 patients. Calculations were conducted using the online software at http://cancer.unc.edu/biostatistics/program/ivanova/SimonsTwoStageDesign.aspx.

With an expected response rate of 20%, if all 30 patients are accrued, a one-sided 95% lower-limit confidence interval will have a distance from the sample proportion to the lower limit of about 14%.

For ***exploratory aims*** we will proceed as follows. **The first** exploratory endpoint is the expression of proteins that play a role in VEGF signaling and other relevant oncogenic pathways. The level of expression of each protein will be correlated via ANOVA with response to treatment (CR, PR, SD, PD); **The second exploratory** endpoint is a retrospective genetic mutation burden to be correlated via ANOVA or contingency table analysis with response to treatment (CR, PR, SD, PD).

9 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires high-risk monitoring as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

9.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 7 for timepoints). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

9.2 Definitions & Descriptions

9.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests

are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

9.2.2 Severity of AEs

Note, some hematology studies may choose to grade toxicity using alternatives to the CTCAE v4.03 (e.g., iwCLL criteria). When an alternative is used, please modify this section as needed. If using the CTCAE state:

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html.

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

9.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study drug, must be reported upon discovery or occurrence.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- Results in *death*.
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- Is life-threatening.
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event.

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

9.2.4 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

9.3 Adverse Event Reporting

9.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF. Routine AEs will be reviewed by the Data and Safety Monitoring Committee (DSMC) according to the study's phase and risk level, as outlined in the DSMP.

9.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v 4.03.
3) Determine whether the adverse event is related to the protocol therapy.
   Attribution categories are as follows:
   Definite: AE is clearly related to the study treatment.
   Probable: AE is likely related to the study treatment.
   Possible: AE may be related to the study treatment.
   Unlikely: AE not likely to be related to the study treatment.
   Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event.

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for

expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current protocol
- the drug package insert
- the current Investigator's Brochure

9.3.3 Expedited Reporting of SAEs/Other Events

9.3.3.1 Reporting to the Northwestern University QAM/DSMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form, provided as a separate document, is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DSMC at their next meeting.

9.3.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment)
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 5 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

9.3.3.3 Reporting to the FDA (to be done by QAM if applicable)

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-*

threatening. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DSMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

9.3.3.4 Reporting to AVEO Pharmacovigilance/Drug Safety and NCCN

AVEO Pharmacovigilance/Drug Safety and NCCN must be informed of ALL SAE/suspected unexpected serious adverse reaction (SUSAR) reports within 24 hours of first awareness.

The Sponsor-Investigator must comply with any applicable requirements related to the reporting of SAEs involving his/her subjects to the IRB that approved the study.

All SAEs should be recorded on the CRO SAE Form and sent to AVEO and NCCN:

- AVEO SAE reports should be sent to Parexel GPPG at AVEOsafety@parexel.com. If submission via email is not possible or delayed then submission via fax (NA: +1-781-434-5957) is acceptable.

  Occasionally, AVEO Pharmacovigilance/Drug Safety may contact the reporter for additional information, clarification, or current status of the subject for whom the adverse event was reported.

- National Comprehensive Cancer Network (NCCN)
  Fax: (215)358-7699
  Email: orpreports@nccn.org

9.3.4 Safety Reporting Requirements for IND Holders

For Investigator Sponsored IND Studies there are some additional reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 312.32. Sponsor-investigators of studies conducted under an IND must comply with the following safety reporting requirements:

9.3.4.1 Expedited IND Safety Reports

The Sponsor-Investigator is required to report all serious, unexpected and related adverse events directly to the FDA on a MEDWATCH Form 3500A (Appendix E) within 7 (if fatal or life-threatening) or 15 calendar days of first awareness, as described below.

AVEO Pharmacovigilance/Drug Safety and NCCN must be informed of ALL SAEs on a MEDWATCH Form 3500A within 24 hours of first awareness, whether or not they are considered related to the investigational agent(s)/protocol intervention (21 CFR 312.64).

9.4 IND Annual Reports

In accordance with the regulation 21 CFR 312.33, the Sponsor-Investigator shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR 312.33 for a list of the elements required for the annual report. All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to AVEO. Copies of such reports should be submitted to AVEO via NCCN.

10 CORRELATIVES/SPECIAL STUDIES

Correlative Samples - Details for Lab Manual	
Correlative study (sample type) *e.g. Pharmacokinetics (blood)*	Tissue
Mandatory or Optional	Optional
Timing (+/- windows)	Retrospective
Volume Needed (blood only)	n/a
Tube type needed (blood only)	n/a
Tissue thickness and/or # slides (tissue only)	10 FFPE slides cut at 5um
Processing center (e.g. PCF-CTU)	PCF-CTU
Sample handling/processing instructions	
Shipping/delivery info	All samples will be analyzed
Storage needs	Samples can be stored at RT and batch delivered to the Matei Lab.
Analysis center	Matei Lab Lurie Medical Research Center 303 E Superior St, Suite 4-220 Chicago, IL 60611
Assay methodology	IHC

10.1 Sample Collection Guidelines

10.1.1 Tissue Samples

Archival tissue samples from all patients enrolled in the study will be requested. Ten FFPE slides with tissue cut at approximately 5um thick will be used for IHC.

10.1.2 NGS

Collection of existing reports detailing genomic testing (Tempus, Foundation One, Charis, other). No additional testing will be obtained, but where data is available, it will be collected and analyzed. Correlate presence of detectable molecular alterations (mutations, deletions, amplifications, fusion) in the VEGF/PDGF pathway with response to treatment (CR, PR, SD, PD).

10.3 Assay Methodology

Standard staining techniques will be used to measure the expression of proteins that play a role in VEGF signaling and other relevant oncogenic pathways (VEGF, VEGFR1, 2, 3, PDGFR α and β). Protein expression levels measured by IHC will be correlated with response to treatment (CR, PR, SD, PD).

11 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by Janssen Scientific Affairs. Amendments will be distributed

by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

For potential patients for the phase I portion of this study, study teams are asked to inform the QAM of the date and time that the patient will need to be registered (croqualityassurance@northwestern.edu).

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive an identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Eligibility checklist (signed and dated by the treating physician – upload to NOTIS)
- Eligibility eCRF (complete in NOTIS)
- Copy of the pathology report (upload to NOTIS)

The QAM will review all source documentation required to confirm eligibility that is readily available in the patient's electronic medical record (EMR). Any information that is not available in the EMR must be de-identified and emailed to the QAM. Once the QAM confirms the patient is eligible, he or she will register the patient, assign a subject identification number, provide a cohort assignment, and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

11.4 Data Submission

Once a subject is confirmed and registered to the study, eCRFs should be submitted according to the detailed data submission guidelines (provided in a separate document). Generally, all data for phase I patients during the time period patients are evaluated for Dose Limiting Toxicities (DLTs) must be submitted on a weekly basis. Generally, for all phase II patients, data are due at the end of every cycle.

This is a general template. Data Submission language can be revised as make sense for each protocol. A detailed data submission guideline must be included as a separate document for all NU IITs determined to require high or moderate level intensity monitoring. To develop your data submission guideline, contact croqualityassurance@northwestern.edu.

11.5 Instructions for Participating Sites

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Office at Northwestern University:

- Signed and completed Letter of Invitation to participate in the study.
- Signed copy of Northwestern University's Data Monitoring Committee policy pertaining to data submission.

- Draft informed consent form should for review/approval prior to submission to the local IRB
- A copy of the official IRB approval letter for the protocol and informed consent.
- CVs and medical licensure for the local PI and any sub-investigators who will be involved in the study at the site.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation.

Additional activities may be required prior to site activation (i.e. contract execution, study-specific training). Full requirements will be outlined in a memo upon receipt of the signed Letter of Invitation.

11.6 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires High Risk Monitoring as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to the Appendices for additional data submission instructions.

11.7 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.7.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.

- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Promptly Reportable Non-Compliance (PRNC) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

11.8 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.9 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. For trials that require high intensity monitoring, the assigned QAM will prepare a preliminary data summary (to be approved by the DSMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DSMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DSMC at their next available meeting, and a final, DSMC-approved dataset will be released along with any DSMC decisions regarding publication. The investigators are expected to use only DSMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DSMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

12.0 REFERENCES

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12 APPENDICES

12.1 Appendix A Performance Status Criteria

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

12.2 Appendix B Cytochrome P450 (CYP3A4) Strong/moderate Inducers/Inhibitors

Investigators should consult a frequently updated drug information reference (see below) for a list of strong inducers and prohibitors.

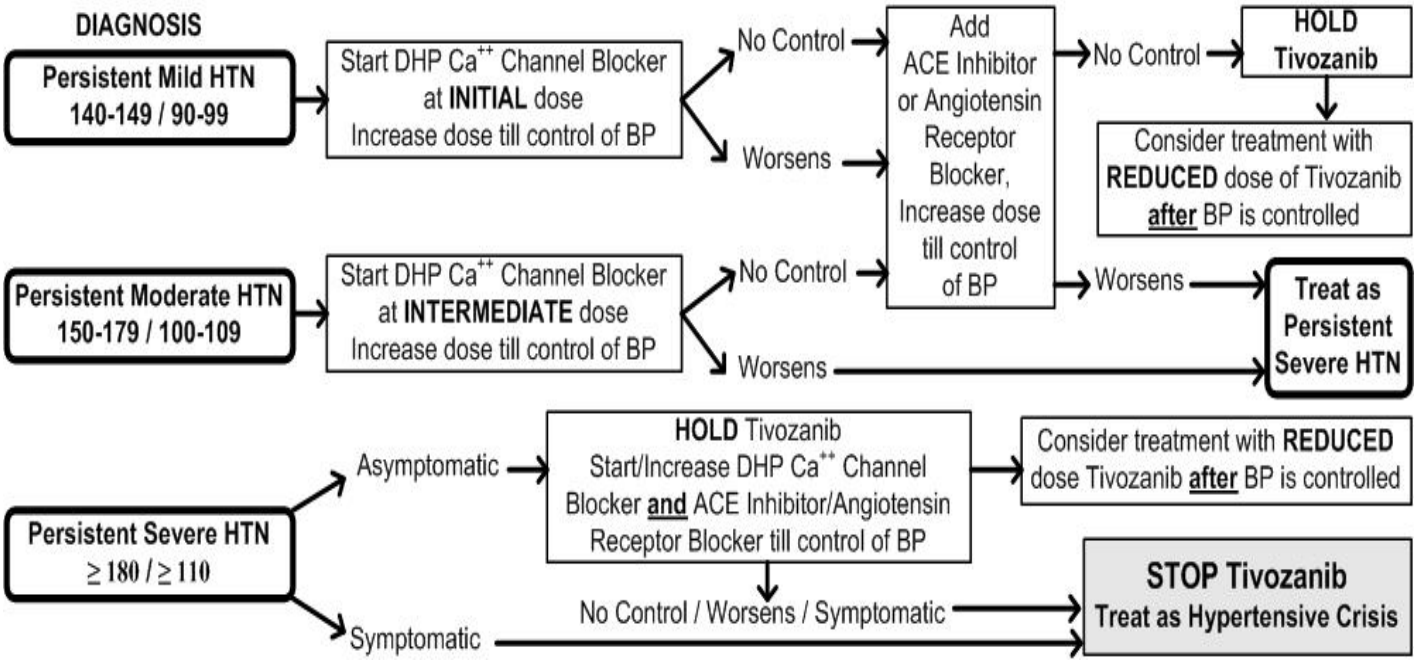
Flockhard DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp.

As this list is constantly evolving, if a medication is incorrectly documented as prohibited in this protocol, documentation from the site pharmacist to the contrary will be acceptable for the purposes of registration.

12.3 Appendix C: Management of Hypertension

RECOMMENDED MANAGEMENT FOR TIVOZANIB HYDROCHLORIDE-RELATED HYPERTENSION

Figure 1 provides a guideline for treatment of hypertension (HTN); however, changes may be made at the discretion of the treating physician.



RECOMMENDED ANTI_HYPERTENSIVE MEDICATIONS

Agent	Initial Dose	Intermediate Dose	Maximum Dose
Dihydropyridine (DHP) Calcium Channel Blockers			
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
Angiotensin Converting Enzyme (ACE) Inhibitors			
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
Angiotensin II Receptor Blockers			
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.

Hypertension (HTN) that occurs during study treatment must be treated with anti-hypertensive drugs prior to any dose reduction. Recommended management of HTN for subjects receiving study drug is presented in Figure 1 (Appendix C).

Persistent HTN is defined as 2 consecutive elevated blood pressure (BP) measurements preferably taken in the clinic and obtained at least 1 hour apart. It is recommended that 24-48 hours should elapse between the decision steps. For a listing of recommended DHP (dihydropyridine) calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers, see Appendix C, Recommended Anti-hypertensive Medications.

> **Note:** If a subject has controlled HTN on an anti-hypertensive regimen at baseline and then develops a worsening of HTN requiring more intensive therapy then the previous regimen, this would be considered Grade 3 HTN.

Hypertension will be considered controlled if the following criteria are met: Diastolic blood pressure is reduced to less than 100 mmHg within 2 weeks of the initiation of anti-hypertensive treatment, confirmed by two consecutive blood pressure measurements at least 24 hours apart. Diastolic blood pressure does not increase by more than 20 mmHg subsequent to the start of anti-hypertensive treatment.

If subjects require a delay of >2 weeks for management of hypertension, discontinue protocol therapy. Subjects may have up to 2 drugs for management of hypertension prior to any dose reduction in tivozanib. 24-48 hours should elapse between modifications of antihypertensive therapy.

12.4 Appendix D CTCAE v.4.03

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

12.5 Appendix E: Summary of Changes

Amendment 5 – February 21, 2017			
Section(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Cover Page	Emily Berry, MD, Kristina Mori, MD & Abigail Winder, MD listed as Sub-Investigators	Removed Emily Berry, MD, Kristina Mori, MD and Abigail Winder, MD as Sub-Investigators and replaced with Wilberto Nieves-Neira, MD, Shohreh Shahabi, MD, Margaux Kanis, MD, Anna Strohl, MD, Brandon Seagle, MD, Valerie Nelson, MD, Barbara Buttin MD, and LaToya Perry, MD	Administrative
	Study Drug Intervention(s): Tivozanib Hydrochloride, IND#: 117703	IND Number and IND Holder listed as their own categories.	To adhere to NU protocol template
	"Protocol"	Removed "Protocol" from cover page	To adhere to NU protocol template
	Co-Investigator	**Sub-**Investigator	To adhere to NU protocol template
	Statistician	**Bio**statistician	To adhere to NU protocol template
	Funding **Organization**	Funding **Source**	To adhere to NU protocol template
Table of Contents	N/A	"Table of Contents" title added	To adhere to NU protocol template
List of Abbreviations	N/A	Added "List of Abbreviations"	To adhere to NU protocol template
Study Schema	N/A	Study Schema was added	To adhere to NU protocol template
Study Summary	"Synopsis" title	"Study Summary" title	To adhere to NU protocol template
	Diagnosis and **Main Inclusion** Criteria	Diagnosis and **Key Eligibility** Criteria	To adhere to NU protocol template
	"Analysis Summary" Title	"Statistical Methodology" title	To adhere to NU protocol template

Section 1.0 Introduction – Background & Rationale	Title "Background & Rationale"	Title "**Introduction** – Background & Rationale"	To adhere to NU protocol template
Section 1.2.2 Clinical Studies	"…pharmacodynamics **(PD)** studies were also performed…"	"…pharmacodynamics studies were also performed…"	Abbreviation of "PD" indicates "progressive disease", not pharmacodynamics.
Section 3.0 Patient Selection	N/A	NU Template language inserted for clarification of target population, recruitment approximation, PI contact information.	To adhere to NU protocol template
	Single-site study	Multi-site study including Northwestern Medicine Cancer Center Warrenville and the Northwestern Medicine Cancer Center Delnor and Northwestern Lake Forest Hospital.	Study will include additional sites.
3.1.1 Inclusion Criteria	"Patients must have recurrent or persistent, platinum resistant…." "…within 6 months of completing **adjuvant**, platinum-based chemotherapy. "	"Patients must have recurrent or persistent platinum resistant **or refractory**…" "…within 6 months of completing platinum-based chemotherapy. "	"Refractory" was included in criteria to clarify the patient population allowed. "Adjuvant" was removed from inclusion criteria to clarify that any prior platinum-based chemotherapy is included.
3.1.3 Inclusion Criteria	"Patients with measurable disease must have at least one **"**target lesion**"** to be used to assess response	"Patients with measurable disease must have at least one target lesion **as defined by RECIST**	Updated text to use RECIST 1.1 and clarified sentence.

	on this protocol **as defined by RECIST**."	**1.1** to be used to assess response on this protocol."	
3.1.5 Inclusion Criteria	N/A	Added: "Note: Use of bevacizumab as maintenance therapy after initial adjuvant platinum-based chemotherapy is allowed so long as platinum-resistant recurrence occurred subsequent to a separate platinum-based regimen AND more than 6 months after completion of bevacizumab maintenance."	Clarification of bevacizumab as prior therapy for patient eligibility
3.1.7 Inclusion Criteria	"Patients must meet pre-entry requirements as specified in section 8.2"	Removed criteria	Section 8.2 was removed.
	N/A	Added criteria "Patients must be willing and able to complete all study procedures"	To adhere to NU protocol template
3.1.8 Inclusion Criteria	List of organ and bone marrow function requirements for eligibility	Converted list of organ and bone marrow function requirements into a table	To adhere to NU protocol template
	List of organ and bone marrow function requirements listed in exclusion criteria	List of organ and bone marrow function requirements moved to inclusion criteria All criteria was altered to define adequate function	To adhere to NU protocol template
	BOTH total bilirubin > ULN AND AST or ALT > ULN	Also excluded are patients with elevations in BOTH total bilirubin > ULN	For clarification

		AND AST or ALT > ULN	
3.1.10 Inclusion Criteria	Language regarding adequate contraception.	Replaced with NU template language regarding females of child-bearing potential (FCOBP) and males to agree to use adequate contraception	To adhere to NU protocol template
3.1.11 Inclusion Criteria	N/A	FOCBP must have a negative pregnancy test within 7 days prior to registration on study.	Confirm pregnancy before study therapy.
3.1.12 Inclusion Criteria	N/A	Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.	To adhere to NU protocol template
3.2.1 Exclusion Criteria	"Age Patients < 18 years of age are excluded"	Removed	Patient age requirements already stated in Inclusion Criteria 3.1.9
	"Patients who have had previous treatment with tivozanib"	"Patients who have had previous treatment with tivozanib **are excluded**."	Clarification
3.2.2 Exclusion Criteria	Previously listed under 3.2.4 "symptomatic left ventricular dysfunction or baseline left ventricular ejection fraction (LVEF) by multigated acquisition scan (MUGA) or echocardiogram (ECHO) of ≤ lower limit of institutional normal (LLN)"	Made a standalone criteria: "Patients with symptomatic left ventricular dysfunction or baseline left ventricular ejection fraction (LVEF) my multigated acquisition scan (MUGA) or echocardiogram (ECHO) of ≤ 50% are not eligible."	LVEF drop is a known side effect of tivozanib. Standalone criteria was added so that there is documentation of LVEF for eligibility.
3.2.3 Exclusion Criteria	Previously listed under 3.2.4 "Uncontrolled	Made a standalone criteria: "Patients with	Because patient must meet certain

	hypertension: systolic blood pressure of >140mmHg or diastolic blood pressure of >90mmHg documented on 2 consecutive measurements taken at least 24 hours apart"	uncontrolled hypertension as defined as Systolic blood pressure of >140mmHg or diastolic blood pressure of >90mmHg documented on 2 consecutive measurements taken at least 24 hours apart are not eligible."	criteria for eligibility, hypertension is made a standalone criteria.
3.2.4 Exclusion Criteria	"Significant cardiovascular disease, including:"	"**Patients with** significant cardiovascular disease **are excluded**, including:"	For clarification
3.2.5 Exclusion Criteria	"Central nervous system metastases"	"**Patients with** central nervous system metastases **are excluded**"	For clarification
3.2.6 Exclusion Criteria	"Non-healing wound, bone fracture, or skin ulcer"	"**Any patient with a current** non-healing wound, bone fracture, or skin ulcer **is excluded**"	For clarification
3.2.7 Exclusion Criteria	N/A	Added exclusion criteria restricting treatment with drugs known to be strong inhibitors or inducers of isoenzyme CYP3A4 including herbal medications	Drugs known to be strong inhibitors or inducers of CYP3A4 are restricted on this study therapy.
3.2.10 Exclusion Criteria	"Corrected QT interval (QTc) of > 480 msec using Bazett's formula."	"**Patients must not have a** corrected QT interval (QTc) of > 480 msec using Bazett's formula."	For clarification
3.2.11 Exclusion Criteria	"Radiotherapy or minor surgical procedure within **2 weeks**, or major surgical procedure within **4 weeks** prior to administration of first	**"Patients who have had** radiotherapy or minor surgical procedure within **14 days**, or major surgical procedure within **28 days** prior	For clarification and adherence to NU template.

	dose of study drug; inadequate recovery from prior surgical procedure."	to administration of first dose of study drug **are not eligible; patients with** inadequate recovery from prior surgical procedure **are also not eligible**."	
3.2.12 Exclusion Criteria	N/A	Added criteria excluding: "Patients with active infection requiring antibiotics are not eligible (with the exception of uncomplicated UTI and uncomplicated respiratory tract infections)."	Patients with infections are not eligible for the study treatment.
3.2.13 Exclusion Criteria	N/A	Added criteria excluding: "Patients may not have had any prior systemic therapy ≤ 21 days prior to registration for treatment of ovarian cancer."	A 21 day washout period is necessary before beginning this study therapy.
3.2.14 Exclusion Criteria	N/A	Addition of criteria excluding: "Patients who have received investigational or licensed drugs that target vascular endothelial growth factor [VEGF] or VEGF receptors/pathways (such as bevacizumab, sorafenib, pazopanib, sunitinib, axitinib, cabozantinib, etc.) for the treatment of recurrent cancer are not eligible. Exceptions: prior treatment with bevacizumab in the	Clarify patients who are excluded from study due to previous investigational or licensed therapy.

		up-front or maintenance setting is allowed, provided the patient had a favorable response to bevacizumab. Favorable response is defined as having had a disease free interval of >6 months following completion of a bevacizumab-containing regimen. If questions, contact the PI."	
3.2.15 Exclusion Criteria	Referenced CTCAE Version 4.0	Updated to reference CTCAE Version 4.03	Updated to utilize current version of CTCAE (Version 4.03)
3.2.16 Exclusion Criteria	Referenced CTCAE Version 4.0	Updated to reference CTCAE Version 4.03	Updated to utilize current version of CTCAE (Version 4.03)
3.2.17 Exclusion Criteria	Non metastatic prostate cancer listed in restriction of currently active primary malignancy	Non metastatic prostate cancer removed from list of currently active primary malignancy	Patient population is female and would not have non metastatic prostate cancer
3.2.18 Exclusion Criteria	"Pregnant or lactating females"	"Pregnant or lactating females **are excluded**"	For clarification
4.0 Patient Registration	Instructions outlining patient registration procedures.	Section was replaced with NU template language found in section 10.	To adhere to NU protocol template
4.1 Overview	N/A	Included an overview of treatment plan that is outlined in the NU template.	To adhere to NU protocol template
4.2 Study Drug Administration: Tivozanib	Details on study drug administration (other names, classification, mechanisms of action, molecular formula and weight, chemical name, approximate solubility,	Information was moved to Section 6 Drug Information to adhere to NU template format	To adhere to NU protocol template

	route of administration, dose to be administered)		
4.2.4 Dosing Parameters	Previously listed under management of hematologic toxicity	Moved to Study drug administration section	Management of hematologic toxicity section was removed. This information was retained and moved to Study Drug Administration section.
4.3.1.4 Premedications for Study Drug-Related Toxicities	N/A	Clarified that **weak** CYP3A4 inducers or inhibitors are to be used with caution	For clarification
4.3.2.3 General Concomitant Medication and Supportive Care Guidelines	N/A	Added note: "As this list is constantly evolving, if a medication is incorrectly documented as prohibited in this protocol, documentation from the site pharmacist to the contrary will be acceptable for the purposes of registration."	Addition of note to clarify use of CYP3A4 inducers of inhibitors.
4.3.2.4 Premedications for Study Drug-Related Toxicities	Previously listed under 4.3.3 The following medications/treatments are permitted during the study treatment	Moved to list under prohibited medications	For clarification – so all information on prohibited medications is in one place.
4.3.2.6 Premedications for Study Drug-Related Toxicities	Previously listed under 4.7.3 Management of Hematologic Toxicity	Moved to list under prohibited medications	For clarification – so all information on prohibited medications is in one place.
4.3.2.7 Premedications for Study Drug-Related Toxicities	Previously listed under 4.7.3 Management of Hematologic Toxicity	Moved to list under prohibited medications	For clarification – so all information on prohibited medications is in one place.

4.3.2.8 General Concomitant Medication and Supportive Care Guidelines	Previously listed under 4.7.3 Management of Hematologic Toxicity	Moved to list under prohibited medications	For clarification – so all information on prohibited medications is in one place.
4.3.3.1 The following medications/treatments are permitted during the study treatment	"Full dose oral anticoagulants **(such as warfarin, and other similar agents; with target INR 2-3)** and/or anticoagulation with low molecular weight heparin or unfractionated heparin administered subcutaneously…"	"Full dose oral anticoagulants and/or anticoagulation with low molecular weight heparin or unfractionated heparin administered subcutaneously…"	Removed outdated examples in order to include all current anticoagulants
4.4 Duration of Therapy	Section title: "Duration of Treatment and Follow Up"	Section Title: "Duration of Therapy"	Split up explanation of duration of treatment and follow up to adhere to NU template.
	"In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies: • Disease progression, • Intercurrent illness that prevents further administration of treatment, • Unacceptable adverse event(s), • Patient decides to withdraw from the study, or • General or specific changes in the patient's condition render the patient unacceptable for further treatment in	"Patients may continue to receive cycles of treatment until any of the following occur: • Disease progression • Development of an inter-current illness that prevents further administration of treatment • Unacceptable adverse event(s) • Patient decides to withdraw from either study treatment or the as a whole study • The treating investigator determines that the patient should be taken off treatment	Replaced description of duration of therapy with NU template language.

	the judgment of the investigator."	for any reason (i.e. changes in condition, inability to comply with study treatment or procedures)"	
4.5 Duration of Follow Up	"Subjects will be followed for every 3 months for 2 years and then every 6 months for 3 years after removal from study or until death, whichever occurs first**.** Subjects removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event."	"**Patients will return for an end of treatment visit within 30 days (±3 days) of the last dose of study treatment.** Subjects will be followed for every 3 months for 2 years and then every 6 months for 3 years after removal from study or until death, whichever occurs first**. Subjects will be monitored for survival for this 5-year period.** Subjects removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event."	For clarification and to adhere to NU template format.
4.6 Removal of Subjects from Study Treatment and/or Study as a Whole	Section title: "Patient Discontinuation"	Section Title: Removal of Subjects from Study Treatment and/or Study as a Whole"	To adhere to NU template
	List of criteria for discontinuing patients from study treatment.	NU Template criteria for patients discontinuing from study treatment.	Replaced description of removal of subjects with NU template language.
4.7 Dose Delays/Dose Modification	Referenced CTCAE Version 4.0	Updated to reference CTCAE Version 4.03	Updated to utilize current version of CTCAE (Version 4.03)

	Any **significant clinical** adverse event, whether observed by the investigator, or observed or experienced by the patient, 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 severity, duration and relationship to tivozanib.	Any adverse event, whether observed by the investigator, or observed or experienced by the patient, will be reported. All clinical and laboratory adverse events must be carefully evaluated for severity, duration and relationship to tivozanib.	To adhere to NU template language. All AEs (not just clinically significant) will be reported.
4.7.1 Tivozanib Hydrochloride Dose Modification	Footnote #1 directing to Section 5.5.5 and 6.1.4	Footnote #1 directing to Appendix C	Formatting
	N/A	Added footnote: "Referring to toxicity that persists despite appropriate medical care."	For clarification
	N/A	Added: "Tivozanib may be interrupted for up to 2 weeks. If a subject is able to resume treatment after an interruption of ≤ 2 weeks, missed doses will not be made up (i.e. the cycle duration will remain unchanged). If any drug related toxicity results in interruption of >2 weeks, the subject should be discontinued from study treatment unless there is clear benefit."	For clarification
	Description of Tivozanib dose delay/modification	Replaced original text with standard language used in	Replaced original text to clarify instructions.

		previous tivozanib study	
4.7.2 Tivozanib Hydrochloride Dose Reduction	The dose of tivozanib hydrochloride may be reduced to 1.0 mg/day.	Removed redundant sentence on dose reduction.	Repeated text from previous paragraph.
4.7.1 Management of Hematologic Toxicity	Explanation on dose modifications due to hematologic toxicity	Information is included in Section 4.7.1 under Tivozanib Hydrochloride Dose Modification.	
4.7.1 Management of Hypertension	Explanation on treatment for hypertension	This section was moved to Appendix C that contains further information on treatment for hypertension.	Section was moved to keep information on hypertension all in one place – Appendix C
5.2.1 Measurable Disease	"…All tumor measurements must be recorded in decimal fractions of centimeters."	Further explanation of tumor measurement specifics as well as incorporating lymph node measurement.	For clarification.
5.2.2 Non-measureable disease	"… Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, and inflammatory breast disease are considered as non-measurable."	"…**Bone lesions**, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, **inflammatory breast disease, abdominal masses (specifically abdominal masses that cannot be followed by CT or MRI),** and cystic lesions are all non-measurable."	Expanded on non-measurable disease types to have a more current list.
5.2.3 Target Lesions	Instructions for evaluating target lesions	Replaced with identical instruction in a more concise manner	For clarification
5.3 Methods for Evaluation of Measurable Disease	N/A	Added text "Imaging-based evaluation is preferred to evaluation by clinical examination when	For clarification

		both methods have been used to assess the antitumor effect of a treatment."	
5.3.1 Clinical Lesions	N/A	Added text "For superficial lesions measured by caliper, documentation by color photography including a ruler in the field of view is strongly recommended."	For clarification
5.3.8 CA-125	"A response according to CA 125 has occurred if there is at least a 50% reduction in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. A complete response has occurred if the CA-125 level decreases into the normal range."	Replaced with "See section 5.4.3 for explanation of clinical response."	Portion of the text is already stated in section 5.4.3. Removed to avoid repetition.
7.1 Schedule of Assessments	Numbers identifying scheduled activity	Numbers replaced with Xs	For clarification and to adhere to NU template.
	N/A	Windows added to cycle activities	For clarification, to avoid scheduling deviations
	History and Physical	History and Physical **Exam**	For clarification
	"Electrolytes, BUN, Glucose, Albumin, Creatinine, Ca14, Mg, PO4"	CMP + electrolytes	For clarification. Specific tests are footnoted (14)
	N/A	Direct and indirect bilirubin	For clarification
	Chest imaging (X ray or CT imaging)	X-ray or CT imaging (chest/abdomen/pelvis)	For clarification

	N/A	Echocardiogram (ECHO)/MUGA added	Added because LVEF drop is a known side effect of tivozanib.
	N/A	Added "Survival Status"	For clarification
	Weekly toxicity assessment throughout the study	Weekly toxicity assessment during cycle 1 only by clinic visit, phone or email.	Weekly toxicity assessment not needed weekly (performed at each cycle visit) beyond cycle 1.
	N/A	In footnote #8, included "absolute or estimated via complete urinalysis" as methods for urinalysis.	Expand methods of capturing urinalysis. In some clinics dipstick is not available.
	"If protein is 2+ or higher, 24-hour urine protein should be obtained and the level must be <1000 mg (<1g/24hrs) for patient **enrollment**."	"If protein is 3+ or higher, 24-hour urine protein should be obtained and the level must be <1000 mg (<1g/24hrs) for patient to **continue on study**."	Patient eligibility requires urine protein <2, once patient is enrolled in study, if protein is 2+, 24hr urine protein should be obtained.
	N/A	For X-Ray/CT imaging "If abnormal at baseline, repeat every other cycle (or the equivalent timeframe for patient off treatment prior to disease progression) for the first 6 months."	For patient safety
	Footnote: "See the guidelines provided in Section 6.0 regarding treatment with tivozanib and proteinuria. Each value should be recorded on the D2R form, for the appropriate cycle."	Text removed.	Sections referenced in text were not included in protocol. Proteinuria management should be performed according to section 4.7.

Pretreatment evaluations	Description of pretreatment evaluations	Text was removed	Text no longer required in the NU Template. Repetitive from schedule of assessment table.
Evaluations during Treatment	Description of evaluations during treatment	Text was removed	Text no longer required in the NU Template. Repetitive from schedule of assessment table.
Evaluations post treatment	Description of follow up activities	Text was removed	Text no longer required in the NU Template. Repetitive from schedule of assessment table.
8. Statistical Methods	N/A	"On 10/12/16 the Northwestern DMC reviewed the first 9 evaluable patients and approved the study to open to an additional 21 patients. "	Interim analysis was performed after the first 9 evaluable patients.
9. Adverse Events	N/A	All AE description was replaced with NU Template language	To adhere to NU Template
9.3.3.4 Reporting to AVEO Pharmacovigilance/ Drug Safety and NCCN	AVEO reporting to "Pharmacovigilance/Drug Safety AVEO Pharmaceuticals, Inc 650 E Kendall Street, Cambridge, MA 02142 Phone: 617-299-5800, Ext 2 Fax: 1-800-376-8513 E-mail: Aveo_gds@synowledge.com"	AVEO reporting to Parexel GPPG at AVEOsafety@parexel.com or by fax 1-781-434-5957	Per memo received from AVEO, reporting is now through Parexel.
10. Study Management	Section title "Administrative Requirements"	Study title "Study Management"	To adhere to NU Template
	N/A	All study management description was	To adhere to NU Template

		replaced with NU template language	
11.2 Appendix B	Table of CYP3A4 inducers or inhibitors	List was replaced with a link to the master list of CYP3A4 inducers and inhibitors. Note to contact pharmacy with questions was also included.	Like to master list replaced table to ensure a current list of CYP3A4 inducers or inhibitors is used.
11.3 Appendix C	N/A	Added descriptive title: "Management of Hypertension"	For clarification of appendix contents
	N/A	Description of management of hypertension moved from section 4.7.1 to Appendix C.	To provide all information of management of hypertension in one place.
Appendix E	Medwatch Form 3500A	Removed	Form was removed. QA has access to this form.
Appendix H	Pill calendar	Removed	Pill calendar will be submitted as a separate document.
Appendix I	Data Collection and Submission	Removed.	Data collection and submission is outlined in Section 10 Study Management
Amendment 6 – June 5, 2017			
Section(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
Cover Page	Principal Investigator: Mario Javier Pineda, MD, PhD	Principal Investigator: Daniela Matei, MD	Administrative
	IND Holder: Mario Javier Pineda, MD, PhD	IND Holder: Daniela Matei, MD	Administrative
Amendment 7 – October 5, 2018			
Section(s) Affected	***Prior Version***	***Amendment 7 Changes***	***Rationale***
Cover Page	Daniela Matei, MD listed as Sub-Investigator	Removed Daniela Matei as Sub-Investigator	Dr. Matei is PI of study and was listed as a Sub-I in error.

	Margaux Kanis and Brandon Seagle listed as Sub-Investigators	Removed Margaux Kanis and Brandon Seagle as Sub Investigators	Administrative. No longer at institution
	N/a	Emma Barber listed as Sub-Investigator	Administrative
Section 2.3 (Exploratory Objectives); Section 8 (Statistical Methods); Section 10 (Correlatives/Special Studies)	n/a	Two additional exploratory endpoints were added: The first exploratory endpoint is a retrospective analysis of archival tissue from all patients who have enrolled to measure the expression of proteins that play a role in VEGF signaling and other relevant oncogenic pathways. The level of expression will be correlated with the best response to treatment (CR, PR, SD, PD). The second exploratory endpoint is a retrospective analysis of genetic reports from all patients who have enrolled, if available. This analysis will be used to correlate genetic mutation burden with response to treatment.	Exploratory objectives have been added to identify novel molecular markers that can predict response to Tivozanib. Additional statistical and correlative sections have been added to further explain analysis of exploratory endpoints.
Section 3 (Patient Selection)	Contact information for Dr. Mario Pineda	Removed contact information for Dr. Pineda and replaced with Dr. Daniela Matei.	Administrative. Correction of error.

Section 4.5 (Duration of Follow Up); Section 7.1 (Schedule of Assessments)	"Patients will return for an end of treatment visit **within 30 days (±3 days) of the last dose of study treatment**."	"Patients will return for an end of treatment visit **within ±14 days of the decision to discontinue treatment**."	Timing of the End of Treatment visit has been corrected to reflect that the end of treatment visit occurs at the time of progression or decision to discontinue treatment
	"Subjects will be followed for every 3 months for 2 years and then every 6 months for 3 years after removal from study or until death, whichever occurs first."	"Subjects will be followed **approximately 30 days after discontinuation of treatment and then approximately** every 3 months for 2 years and then **approximately** every 6 months for 3 years after removal from study or until death, whichever occurs first."	Clarification of timing of follow up.
Section 7.1 (Schedule of Assessment)	n/a	Addition of MR as imaging option in the table and including x-ray in footnote #11	Clarification to align the table and footnote information.
	Footnotes 1 & 2: procedures obtained prior to "initiating protocol therapy"	Footnotes 1 & 2: procedures obtained prior to "study registration"	Corrected to
	n/a	Footnote # 14 added "Magnesium and Phosphorus are only required if clinically indicated"	Added to align with footnote #3 that says only if clinically indicated.
	n/a	Footnote #15 was added "Must be completed within 14 days prior to of each cycle. Exceptions include treatment delays, in which case they would be allowed	Added so we don't have to repeat CA-125 or EKG in the case of a 1-3 week dose delay, as insurance may not cover repeat testing

		within 21 days prior to the delayed cycle."	
Section 8 (Statistical Methods); Section 9.3.1 (Routine Reporting); Section 9.3.3.1 (Reporting to the NU QAM/DSMC); Section 11.9 (Publication Policy)	Data Monitoring Committee "DMC"	Data and Safety Monitoring Committee "DSMC"	Administrative. Name of committee has been updated.
Amendment 8 – January 3, 2019			
Section(s) Affected	***Prior Version***	***Amendment 8 Changes***	***Rationale***
Cover page	Biostatistician listed as Borko Jovanovic	Biostatistician listed as Masha Kocherginsky	Administrative