A Phase I/II Study of the Combination of Temozolomide and Pazopanib in Advanced Pancreatic Neuroendocrine Tumors (PNET)

PRINCIPAL INVESTIGATOR: Sheetal M.Kircher, MD
Robert H. Lurie Comprehensive Cancer Center
Northwestern University
676 North Saint Clair, Suite 850
Chicago, IL-60611
Ph: 312-695-6180
Fax: 312-695-6189
Email: skircher@nm.org

SUB-INVESTIGATORS:

Northwestern University
Al B. Benson, III, MD
Mary F. Mulcahy, MD
Vahid Yaghmai, MD
Michael J. Avram, PhD

University of Michigan
Mark Zalupski, MD
U of M Comprehensive Cancer Center
1500 E. Medical Center Dr, Rm 3219
Ann Arbor, MI 48109-5934
734-615-3969 (phone)
734-647-9647 (fax)
zalupski@med.umich.edu

Fox Chase Cancer Center
Crystal Denlinger, MD
Fox Chase Cancer Center
333 Cottman Avenue
Philadelphia, PA 19111
215-214-1676 (phone)
crystal.denlinger@fccc.edu

Vanderbilt University
Jordan D. Berlin, MD
2220 Pierce Avenue
777 Preston Building
Nashville, TN 37232
615-936-8422 (phone)
jordan.berlin@Vanderbilt.edu

University of Washington
E. Gabriela Chiorean, MD
Fred Hutchinson Cancer Research Center
825 Eastlake Ave East, G4830
Seattle, WA 98109
Phone: 206-288-6248
gchiorea@seattlecca.org

STATISTICIAN: Alfred Rademaker, PhD
Northwestern University

FUNDING AGENCY: NCCN

IND STATUS: EXEMPT

Robert H. Lurie Comprehensive Cancer Center
Clinical Research Office
676 N. St. Clair Street, Suite 1200
Chicago, IL 60611

SYNOPSIS

Title	A Phase I/II Study of the Combination of Temozolomide and Pazopanib in Advanced Pancreatic Neuroendocrine Tumors (PNET)
Version Date	January 24, 2018
Study Duration	3 Years
Study Center(s)	Northwestern University, University of Michigan, Vanderbilt University, Fox Chase Cancer Center, University of Washington
Objectives	**Phase I Primary Objective:** Determine the maximum tolerated dose (MTD) of temozolomide and pazopanib combination in patients with advanced PNET. **Phase I Secondary Objectives:** 1. Determine safety and toxicity profile. 2. Describe the pharmacokinetics of temozolomide alone and in combination with pazopanib. 3. Observe the ORR. **Phase II Primary Objective:** Determine the ORR. **Phase II Secondary Objectives** 1. Determine PFS and OS, DCR, and DOR. 2. Determine the safety and toxicity profile of the combination in a larger cohort of patients. **Exploratory/Correlative Objectives:** 1. Correlate the expression of tissue methyl–guanine methyl transferase (MGMT) as measured by immunohistochemistry (IHC) with ORR and PFS.
Number of Subjects	**Phase I:** 9-18 patients + an additional 6 enrolled at the MTD to form a PK cohort **Phase II:** 11-27 patients (includes the 6 from the PK cohort)

Diagnosis and Main Inclusion Criteria	Inclusion Criteria: • Histologically confirmed islet cell carcinoma not amenable to surgical resection, with measurable disease (as defined by RECIST version 1.1 criteria) • Age 18 years or older • 0-4 prior therapies allowed • ECOG performance status ≤ 2 • Life expectancy > 3 months • Controlled blood pressure • LVEF ≥ 50% • Adequate baseline organ and marrow function Exclusion Criteria • Known HIV infection • Uncontrolled hypertension (≥ 140/90 mm Hg) • Symptomatic brain or bone metastasis • History of seizure disorder requiring antiepileptic medication • Active second malignancy other than non-melanoma skin cancer or cervical carcinoma in situ. • Clinically significant GI abnormalities that may increase the risk for gastrointestinal bleeding or absorption • Cardiovascular conditions within the past 6 months • Corrected QT interval (QTc) > 480 msecs. • Cerebrovascular accident including TIA, untreated PE or deep DVT within past 6 months. • Recent hemoptysis
Treatment Summary	**Phase I:** One cycle = 28 days. Starting doses (cohort 1) will be temozolomide 150 mg/m^2 orally on Days 1-7 and 15-21, and pazopanib 400 mg orally once daily continuously throughout cycle. Dose escalation and de-escalation will be conducted following a standard "3+3" design. DLT period = 1st cycle (28 days) **Phase II:** Once MTD established, will proceed to the phase II portion. Response will be assessed after every 2 cycles. (Note: The MTD has been identified at dose level -2 (75 mg/m2 per day p.o. days 1-7 and 15-21 of Temozolomide and 400 mg per day p.o. days 1-28 of Pazopanib. As of 12.15.15 , all patients moving forward will be treated at this dose)

Analysis Summary	The study design is a multicenter, phase I/II, open-label, non-randomized study. Phase I will be a dose-escalation study to determine the MTD and the safety profile of the combination of temozolomide and pazopanib in patients with advanced pancreatic neuroendocrine tumors. Pharmacokinetic sampling for temozolomide and pazopanib will be performed in an additional 6 patients enrolled at the MTD. The MTD will be the recommended Phase II dose. Once the MTD is determined, the study will proceed to a single-arm, open-label phase II to evaluate efficacy endpoints. Phase II analyses will include patients treated at the MTD in the PK cohort from phase I. This protocol describes the phase I/II trial. Data will be pooled from patients enrolled at all study sites.

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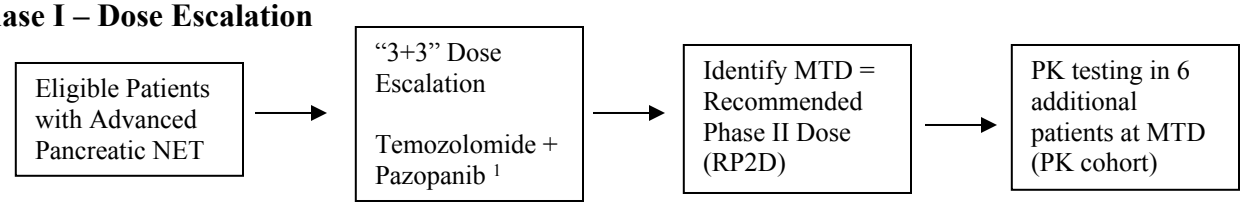
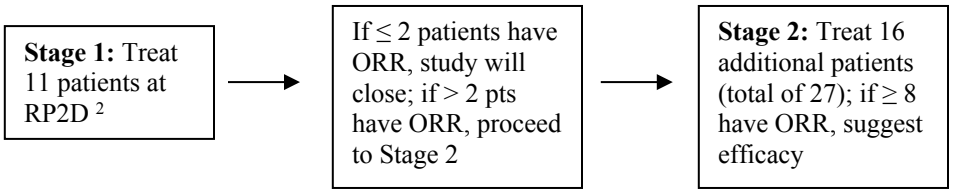
SCHEMA

Phase I – Dose Escalation



Phase II – Simon Two-Stage



[1] Starting doses for Cohort 1: temozolomide 150 mg/m^2 orally – Days 1-7 and 15-21 of each cycle, pazopanib 400 mg orally daily continuously throughout each cycle (1 cycle = 28 days).

[2] The sample size for Stage 1 of the phase II portion will include the 6 patients from the PK cohort treated at the MTD.

(Note: The MTD has been identified at dose level -2 (75 mg/m2 per day p.o. days 1-7 and 15-21 of Temozolomide and 400 mg per day p.o. days 1-28 of Pazopanib.
As of 12.15.15, all patients moving forward will be treated at this dose.)

1.0 INTRODUCTION – BACKGROUND AND RATIONALE

1.1 Pancreatic Neuroendocrine Tumors: Background and Standard Therapies

Pancreatic neuroendocrine tumors (NETs), also known as pancreatic endocrine tumors or islet cell carcinomas, are rare malignancies with a reported annual incidence of 0.32 cases per 100,000 in the Surveillance, Epidemiology, and End Results (SEER) Program registries.[1] Advanced pancreatic NETs have a reputation for being more indolent than other pancreatic malignancies. However, they can be aggressive and are most often diagnosed at an advanced stage (14% localized, 22% regional, and 64% distant). Analyses from the SEER data from 2000 to 2004 showed a median survival time of only 27 months among patients with advanced disease.[2] Pancreatic NETs are sometimes divided into functioning and nonfunctioning tumors based on whether they cause clinical hormonal symptoms. However, the functional status of these tumors may change over time or with treatment. The introduction of somatostatin analogs has resulted in major advances in the management of hormonal syndromes from NETs and has recently been shown to prolong time to tumor progression in patients with advanced midgut NETs.[3]

Pancreatic NETs are responsive to cytotoxic chemotherapy. Streptozocin- based combination therapy has been an historical treatment standard for patients with advanced pancreatic NET. In an early randomized trial, streptozocin plus doxorubicin had a combined biochemical and radiologic response rate of 69% and a median survival of 2.2 years.[4] A retrospective analysis of 84 patients with either locally advanced or metastatic pancreatic NETs treated with streptozocin, 5-FU, and doxorubicin reported a 39% objective radiographic response rate and a median survival duration of 37 months.[5] The widespread adoption of streptozocin-based regimens has been limited by a relatively cumbersome administration schedule and by concerns about toxicity, including nausea, hair loss, and renal dysfunction. More recently, novel approaches including vascular endothelial growth factor (VEGF) pathway inhibitors (including bevacizumab[6], sorafenib[7], sunitinib[8], and pazopanib[9]) have shown preliminary evidence of activity in pancreatic NETs.

1.2 Temozolomide in Pancreatic NETs

1.2.1 Clinical activity in Pancreatic NETs

Temozolomide is a cytotoxic alkalyting agent that has been specifically developed as an oral and less toxic alternative to dacarbazine.[10] Temozolomide and dacarbazine have similar mechanisms of action: both agents are metabolized to the active agent 5-(3-methyl-triazeno)

imidazole-4-carboxamide (MTIC), an inhibitor of nucleoside incorporation. Temozolomide is currently FDA approved for refractory anaplastic astrocytoma and newly diagnosed and recurrent glioblastoma multiforme (GBM).

Both temozolomide and dacarbazine have demonstrated activity in treatment of metastatic pancreatic NETs. The Eastern Oncology Group (ECOG) evaluated the efficacy of dacarbazine in a phase II study in patients with advanced pancreatic NETs and reported an ORR of 33% and a median overall survival (OS) of 19.3 months.[11] A combination of dacarbazine, vincristine, and cyclophosphamide in patients with pheochromocytoma was reported to result in a biochemical responses but was also associated with significant toxicity.[12-14] The potential toxicity of dacarbazine precludes its use in treatment for advanced pancreatic NET. The efficacy of temozolomide monotherapy was reported in a phase II trial in patients with advanced pancreatic NETs, only one of 12 (8%) patients with pancreatic NET had a PR, while SD lasting at least 4 weeks was noted in 8 (67%) patients.[15] A phase II study of 30 patients with metastatic pancreatic NETs investigated the combination of capecitabine plus temozolomide and reported ORR 70%. Among these patients, 21 (70%) achieved a PR, 8 (27%) had SD, and 1 (3%) had disease progression.[16]

1.2.2 Safety of temozolomide

In the phase II study of temozolomide monotherapy, toxicities were mainly hematologic, and dose reduction due to hematologic toxicity was necessary in 4 patients. There were 2 patients with grade 3/4 fatigue.[15] In the phase II study of temozolomide combined with capcitabine, Four patients (4%) experienced grade 3 or 4 adverse events (fatigue n=1, elevated AST n=1, anemia n=1, thrombocytopenia n=1).[16]

1.3 Role of VEGF Pathway in Pancreatic NETs

Neuroendocrine tumors are characterized by abundant vasculature and high levels of VEGF expression, and therefore are potentially susceptible to therapeutic strategies targeting pathways involved in angiogenesis.[17]

1.3.1 Preclinical studies of VEGF inhibition in Pancreatic NETs

Overexpression of VEGF and its receptor subtypes has been observed in preclinical models in both carcinoid and pancreatic endocrine tumors. This suggests that autocrine activation of the VEGF pathway may promote tumor growth.[17-19] Casanovas et al showed that inhibition of VEGFR with antibodies disrupted tumor growth in a mouse pancreatic neuroendocrine tumor model, providing further support for this hypothesis.[20]

1.3.2 Clinical experience with VEGF inhibition in Pancreatic NETs
Recently, agents targeting VEGF pathway have shown promising results in phase II/III clinical trials in patients with advanced pancreatic NET. Sunitinib, a small molecule tyrosine kinase inhibitor targeting the VEGF receptor has been evaluated in a phase II study in patients with advanced NET. Among 66 pancreatic NET enrolled patients, the overall response rate (ORR) was 16.7%, 68% had stable disease (SD), and the median time to progression was 7.7 months.[8] Sunitinib was subsequently evaluated in a phase III randomized trial of sunitinib versus placebo in patients with pancreatic NET. The primary end point was progression-free survival (PFS). The trial was stopped early at the recommendation of the data safety and monitoring board. The median PFS was 11.4 months in the sunitinib arm versus 5.5 months in the placebo arm ($p = 0.0001$); ORR with sunitinib was 9.3% (2 complete and 6 partial responses).[21] Another phase II study of 93 patients with advanced NET evaluated the efficacy of sorafenib, a potent small molecule inhibitor of multiple tyrosine kinases including VEGFR 2, as well as FLT3, PDGFR, and fibroblast growth factor receptor-1 (FGFR1). In a preliminary report, among the 43 pancreatic NET patients enrolled, ORR was 11% with 32% exhibiting partial or minor response; the 6 month PFS was 60% .[7]

1.4 Pazopanib in Pancreatic NETs

1.4.1 Clinical activity in Pancreatic NETs

Pazopanib is an oral, selective, small molecule inhibitor of the VEGFR-1, -2, and -3, PDGF-α, PDGFR-β, and c-kit tyrosine kinases. Pazopanib selectively inhibits VEGF-mediated endothelial cell proliferation and is active in in vivo angiogenesis assays.[22] In 2009, pazopanib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with advanced RCC [Votrient PI, 2012]. In 2012, pazopanib was FDA-approved for the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy. However, the efficacy of pazopanib for the treatment of patients with adipocytic soft tissue sarcoma or gastrointestinal stromal tumors has not been demonstrated [Votrient PI, 2012]. This approval was based on a phase III randomized, double-blind trial in which 435 patients with locally advanced or metastatic RCC were randomly assigned 2:1 to receive oral pazopanib or placebo. The primary end point was PFS. PFS was significantly prolonged with pazopanib compared with placebo in the overall study population (median PFS of 9.2 versus 4.2 months with a hazard ratio of 0.46, 95% confidence interval of 0.34 to 0.62 and $p = 0.0001$) and the ORR was 30% in the pazopanib group compared to 0% in placebo.[23]

In a phase II study, pazopanib was evaluated in two parallel cohorts of patients with carcinoid and pancreatic NET. Pazopanib was administered at a dose of 800 mg p.o. daily in combination with octreotide LAR. There

were no responses in the 20 carcinoid patients. The study opened to a second stage of accrual for the pancreatic NET cohort only. Of the 31 evaluable pancreatic NET patients, there were 6 (19%) partial responses (PR), 5 (16%) minor responses (MR), and 21 (68%) SD; the 6-month PFS was 81%7. A phase III trial evaluating pazopanib in patients with advanced pancreatic NET after progression from everolimus is currently underway.[24]

1.4.2 Safety of pazopanib

In the hallmark article leading to the approval of pazopanib in the treatment of metastatic RCC, the most common grade 3/4 adverse events (AEs) in the pazopanib arm were hypertension (4%) and diarrhea (4%). Arterial thrombotic events occurred in 3% of pazopanib-treated patients [myocardial infarction/ischemia (2%), cerebrovascular accident (1%), and transient ischemic attack (1%)] compared with none in the placebo arm. The incidence of hemorrhagic events (all grades) in the pazopanib arm was 13% compared with 5% in the placebo arm.[23] In the study of pazopanib in patients with neuroendocrine tumors, Grade 3/4 toxicities were relatively rare and included: anemia (n=1), neutropenia (n=3), hypertriglyceridemia (n=2), transaminitis (n=3), fatigue (n=3), hypertension (n=6), nausea (n=1), diarrhea (n=3), pain (n=1), rash (n=1), syncope (n=1), and confusion (n=1).[9]

(Note: please refer to updated IB version 14 dated 01.07.16 for more information.)

1.5 Rationale for Current Study: Combination of Temozolomide and Pazopanib

1.5.1 Preclinical evidence of temozolomide in combination with anti-angiogenesis therapy

As seen in the above data, there is evidence to support the use of both anti-angiogenesis therapy as well as cytotoxic therapy. There is preclinical data to support that the combination of the two is promising. Fisher and colleagues reported that 14 target genes of hypoxia-inducible factor (HIF-1), were found to be up-regulated after temozolomide treatment to GBM cell lines, including VEGF.[25] Sandström and colleagues reported ZD6474, a potent inhibitor of VEGFR-2, was evaluated in combination with either radiotherapy or temozolomide in an orthotopic glioma model; combination with temozolomide decreased tumor area by 74%. Morphologically, these tumors had a much lower cellular density and they found that the proliferation index was decreased in tumors treated with ZD6474.[26] Zhou and colleagues evaluated the combination of sunitinib with temozolomide in an orthotopic human glioma mouse model to investigate how sunitinib at different dose levels affects brain distribution of temozolomide. In this study, they found that the effect of sunitinib on the brain tumor distribution of temozolomide was dose dependent. Optimal tumor

exposure was achieved at the lower dose and was associated with a higher ratio of functioning vessels to normal vessels. This research suggests that antiangiogenic therapy with sunitinib at an appropriate dose can positively alter the vasculature to improve penetration of temozolomide into the tumor.[27] The results of these preclinical studies justify further investigation using combination therapy.

1.5.2 Clinical evidence for temozolomide combination with anti-aniogenesis therapy

This preclinical data has translated into clinical success with the combination of temozolomide and anti-angiogenesis therapy. Thalidomide is postulated to have anti-angiogenesis activity through its ability to interfere with VEGF and basic fibroblast growth factor (bFGF) pathways.[28] A phase II study evaluated the combination of temozolomide and thalidomide in 29 patients with metastatic NET. The results demonstrated an ORR of 45% in pancreatic NET versus only 7% in metastatic carcinoid; the median duration of response of 13.5 months and 1 year survival was 79%.[29] Another phase II study investigated the combination of temozolomide and bevacizumab in patients with advanced NET. In a preliminary report, among 17 enrolled pancreatic NET patients, there were 4 (24%) PR, and 12 (70%) SD.[30]

The combination of temozolomide with full dose anti-angiogenesis therapy has been successfully administered in multiple phase II trials. In a phase II trial of temozolomide and sorafenib in advanced melanoma patients, standard dosing of temozolomide (150mg/m^2 daily for 5 of every 28 days) was given with sorafenib 400 mg orally twice per day.[31]

1.5.3 Safety of temozolomide combination with anti-antiogenesis therapy

In the phase II study of temozolomide and thalidomide, a total of 16 (55%) patients discontinued treatment because of treatment related toxicity. Neuropathy, a known toxicity of thalidomide, developed in 11 patients (38%). Grade 2 or 3 thrombocytopenia occured in 4 patients (14%), resulting in treatment discontinuation. Other toxicity resulting in study discontinuation included rash (n=1), neutropenia (n=1), and infection (n=4). A total of 11 patients developed infections while receiving study treatment, including 3 opportunistic infections (1 case of Pnemocystis carinii pneumonia, 1 case of disseminated varicella zoster virus, and 1 case of cutaneous herpes zoster). Of these 3 patients, all had received more than 6 months of therapy and developed grade 3 or 4 lymphopenia; the study treatment did not include prophylactic antibiotics.[29]

In the phase II study combining temozolomide and bevacizumab, grade 3/4 toxicities included: lymphopenia (n=21, 62%), leukopenia (n=2, 6%), thrombocytopenia (n=7, 21%), neutropenia (n=2, 6%), hyponatremia (n=1, 3%), vomiting (n=3, 9%), nausea (n=2, 6%), dehydration (n=1, 3%),

fatigue (n=2, 6%), constipation (n=1, 3%), and hypertension (n=1, 3%). Due to anticipated lymphopenia, patients received prophylaxis with trimethoprim/sulfamethoxazole (1 DS tablet every MWF) and acyclovir (400 mg p.o. TID).[30]

In the phase I portion of another study (a phase I/II combining temozolomide and everolimus in metastatic pancreatic NET) 1 patient experienced dose-limiting toxicity (DLT) consisting of grade 4 thrombocytopenia, and the cohort was expanded to 6 patients with no further observed DLTs. A total of 24 patients were enrolled at the time of the analysis and the most common observed grade 3 or 4 toxicities were anticipated hematologic effects and included thrombocytopenia (n = 4), lymphopenia (n = 5), and neutropenia (n = 2). Grade 3 or 4 non-hematologic toxicities included hyperglycemia (n = 1), elevated transaminases (n = 1), elevated triglycerides (n = 1) and rash (n = 1).[32]

The phase II study combining temozolomide with full-dose sorafenib was generally well tolerated, with grade 3/4 toxicity including lymphopenia (15%), hypertension (13%), hand-foot syndrome (13%), and fatigue (13%).[31] A phase II study of sorafenib and temozolomide in patients with recurrent glioblastoma showed similar tolerability of full dose anti-angiogenic therapy. In this study, sorafenib 400 mg p.o. twice daily was given with continuous daily temozolomide 50mg/m^2/day, and these doses were well tolerated with the most common grade 3 toxicities including an increase in amylase/lipase (13%), erythrodysesthesia (19%), and hypophosphatemia (9%). Only 3 patients ultimately required any dose modification of sorafenib to 400 mg p.o. daily.[33]

1.5.4 Rationale for current study design

Given the overexpression and activation of the VEGF pathway in pancreatic NET, and the established activity of temozolomide in PNET, we believe that the combination of temzolomide with a molecular-targeted therapy offers potential for additive or synergistic inhibition of shared targets. We have chosen pazopanib as the anti-angiogenic agent for this trial, given the promising phase II data from Phan et al demonstrating both partial responses and stabilization of disease with pazopanib as monotherapy[9]. We propose to conduct a phase I/II clinical trial of the combination of temozolomide and pazopanib in patients with advanced PNETs. Phase I of the study will be an open-label dose escalation trial to determine maximum tolerated dose (MTD) and safety profile of the combination in this population. The MTD will be the recommended Phase II dose. Once the MTD is determined, that cohort will be expanded to 6 additional patients to establish the pharmacokinetics (PK).The study will then proceed to a single-arm, open-label phase II trial to evaluate efficacy endpoints. The phase II analyses will include the 6 patients treated at MTD for a PK cohort who will have MGMT expression and function CT

evaluation similar to the other phase II participants. Please refer to Section 5 for a detailed description of the study design for both phases. Our hypothesis for this study is that the combination of temozolomide and pazopanib is safe and may be effective in patients with advanced PNET. This is backed by clinical and preclinical evidence as outlined above.

(Note: The MTD has now been identified at dose level -2 (75 mg/m2 per day p.o. days 1-7 and 15-21 of Temozolomide and 400 mg per day p.o. days 1-28 of Pazopanib. As of12.15.15, all patients moving forward will be treated at this dose.)

1.5.5 Rationale for current study treatment doses

In the above phase II studies, studies, temozolomide was administered orally at 150 mg/m^2 daily for 7 consecutive days every other week.[30] The phase I/ II study of the combination of everolimus and temozolomide in metastatic PNET patients used a similar dose and schedule of temozolomide administration.[32] Given that the activity and safety of this regimen has been rigorously evaluated in previous studies in PNET (as outlined above) we propose to use a similar dosage and schedule for temozolomide in our phase I/II trial of the combination of temozolomide and pazopanib. The starting dose for the first cohort of the phase I portion will be temozolomide 150 mg/m^2 orally on days 1-7 and 15-21 of each cycle (1 cycle = 28 days).

The starting dose of pazopanib in our study is 400 mg orally on a daily basis throughout each cycle. The rationale for this starting dose is based on the known metabolism of both of these drugs and the low likelihood of interactions. Pazopanib metabolism is primary mediated by CYP3A4. In contrast, the cytochrome P450 enzymes play only a minor role in metabolism of temozolomide or its metabolites, and therefore should not affect the metabolism of the pazopanib.

1.5.6 Phase 1 summary:

Eighteen patients have been treated with the Combination of Temozolomide and Pazopanib in the phase I portion of this trial. As per study design, once the MTD is determined, that cohort will be expanded to 6 additional patients to establish the pharmacokinetics (PK). MTD has now been identified at dose level -2 (75 mg/m2 per day p.o. days 1-7 and 15-21 of Temozolomide and 400 mg per day p.o. days 1-28 of Pazopanib). Hence, all patients moving forward will be treated at this dose. (i.e. as of 12.15.15)

1.6 Background and Rationale for Correlative Studies

1.6.1 O6-methylguanine DNA methyltransferase (MGMT) Expression

In this study we will examine the predicitive role of MGMT expression in pancreatic NET to temozolomide therapy. O6-methylguanine DNA methyltransferase (MGMT) is a DNA repair enzyme believed to induce cancer cell resistance to O6-alkylating agents such as temozolomide. Inactivation of the MGMT gene by promoter methylation is associated with longer survival in patients with GBM treated with temozolomide.[37, 38] Low MGMT expression, detected by immunohistochemistry (IHC), correlates with response to temozolomide treatment in low-grade oligodendroglioma, and MGMT immunostaining has been suggested as a marker for predicting tumor chemosensitivity.[39] MGMT promoter hypermethylation has been described in small groups of NET including pancreatic NET and carcinoid.[40] Ekeblad et al examined the role of MGMT expression in 27 patients with a variety of NET (12 PNET) treated with temozolomide monotherapy. They found a low percentage of MGMT-positive tumor cell nuclei in 43% of tumors. Four out of five patients with a radiologic response had tumors with low MGMT expressions. This suggests a possible predictive value of MGMT IHC in NET and needs to be further investigated.[15]

2.0 STUDY OBJECTIVES

This will be a phase I/II study evaluating the combination of temozolomide and pazopanib in advanced PNET. There will be separate objectives for the phase I and II portions, as outlined below, in addition to exploratory objectives.

2.1 Phase I

2.1.1 Phase I Primary Objective

Determine the maximum tolerated dose (MTD) of temozolomide and pazopanib combination in patients with advanced PNET.

2.1.2 Phase I Secondary Objectives

2.1.2.1 Determine safety and toxicity profile of the combination of temozolomide and pazopanib in this population.

2.1.2.2 Describe the pharmacokinetics of temozolomide alone and in combination with pazopanib.

2.1.2.3 Observe the ORR.

2.2 Phase II

2.2.1 Phase II Primary Objective

The primary objective for the phase II portion of this trial will be to determine the ORR.

2.2.2 Phase II Secondary Objectives

2.2.2.1 Determine PFS and OS, disease control rate (DCR), and duration of response (DOR).

2.2.2.2 Determine the safety and toxicity profile of the combination in a larger cohort of patients.

2.2.3 Exploratory/Correlative Objectives

2.2.3.1 Correlate the expression of tissue methyl–guanine methyl transferase (MGMT) as measured by immunohistochemistry (IHC) with ORR and PFS.

3.0 PATIENT SELECTION AND ELIGIBILITY CRITERIA

3.1 Population and Accrual Overview

The target population for this phase I/II trial is patients with advanced, unresectable pancreatic neuroendocrine tumor (PNET) with adequate performance status and organ function. This will be a multicenter trial with the lead site being the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. Participating sites will include the University of Michigan Comprehensive Cancer Center, Vanderbilt-Ingram Cancer Center, University of Washington and Fox Chase Cancer Center. Patients from Northwestern University will be recruited from the Hematology-Oncology outpatient clinic of the Northwestern Medical Group. Patients may be referred to the Principal Investigator, Dr.Sheetal Kircher, at 312-695-0990. Patients from the University of Michigan will be recruited from Hematology-Oncology outpatient clinic of the University of Michigan Comprehensive Cancer Center and may be referred to Dr. Mark Zalupski at 734-615-3969. Patients from Vanderbilt University will be recruited from the Hematology-Oncology outpatient clinic and may be referred to Dr. Jordan Berlin at 615-936-8422. Patients from Fox Chase will be recruited from the Hematology-Oncology outpatient clinic and may be referred to Dr. Crystal Denlinger at 215-214-1676. Patients from University of Washington will be recruited from the Hematology-Oncology outpatient clinic and may be referred to Dr. E. Gabriela Chiorean at (206) 288-6248.

We anticipate an accrual rate of approximately 3 patients per month combined between the 5 study sites. Based upon this rate of accrual and a DLT window of 28 days, we anticipate completion of the phase I portion of this study in 6 to 14 months, depending upon determination of the MTD. Assuming a similar rate of accrual, we anticipate completion of stage I of the phase II portion in an additional 7 months. If the study proceeds to stage II of the phase II, we anticipate completion of accrual within an additional 8 months, with assessment of the primary endpoint after 6 additional months (14 months total). Accrual to both phases of the study and assessment of the primary endpoint for the phase II portion is estimated to be completed within approximately 3-4 years.

3.2 Inclusion Criteria

3.2.1 Patients must have histologically confirmed well –differentiated islet cell carcinoma (PNET) not amenable to surgical resection.

3.2.2 Patients must be age 18 years or older.

3.2.3 Patients may have had 0-4 prior therapies.
- **3.2.3.1** Prior chemoembolization or local ablative therapies are permitted if completed ≥ 6 weeks prior to study enrollment.
- **3.2.3.2** Prior temozolomide is permitted.

3.2.4 Patients must have an ECOG performance status ≤ 2 (refer to Appendix I).

3.2.5 Patients must have a life expectancy > 3 months.

3.2.6 Patients must have radiographically measurable disease as defined by RECIST version 1.1 criteria.

3.2.7 Patients' baseline blood pressure must be adequately controlled with or without antihypertensive medications prior to enrollment (systolic < 140 mmHg, diastolic < 90 mmHg).

3.2.8 Patients must have LVEF ≥ 50 as measured by echocardiogram or MUGA.

3.2.9 Patients must have adequate baseline organ and marrow function as defined below:
- **3.2.9.1** Absolute neutrophil count (ANC) ≥ 1,500/μL
- **3.2.9.2** Platelets ≥ 100,000/μL
- **3.2.9.3** Hemoglobin ≥ 9.0 g/dL
- **3.2.9.4** Total bilirubin ≤ 2 mg/dL or ≤ 1.5 times upper limit of normal (ULN)
- **3.2.9.5** AST (SGOT) and ALT (SGPT) ≤ 2.5 times ULN
- **3.2.9.6** INR ≤ 1.2 times ULN. Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.
- **3.2.9.7** Activated partial thromboplastin time (aPTT) ≤ 1.2 x ULN
- **3.2.9.8** Albumin ≥ 2.8 g/dL
- **3.2.9.9** Serum creatinine ≤ 1.5 times ULN OR if serum creatinine ≥ 1.5 mg/dL, calculated creatinine clearance ≥ 30 mL/min
- **3.2.9.10** Urine protein to creatinine ratio < 1 OR 24-hour urine protein < 1 g

3.2.10 Patients must be able to tolerate oral medications.

3.2.11 Females of child-bearing potential must have a negative pregnancy test within 14 days of study enrollment and must agree to use an effective method of birth control during treatment and for three months after receiving their last dose of study drug. Males must agree to use an effective method of birth control during treatment and for three months after receiving their last dose of study drug. All patients must notify treating provider immediately if any suspicion of pregnancy or conception.
- **3.2.11.1** Child-bearing potential is defined as any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:
  - **3.2.11.1.1** Has NOT undergone a hysterectomy or bilateral oophorectomy; OR
  - **3.2.11.1.2** Has NOT been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in

the preceding 12 consecutive months).

3.2.12 The eligibility of patients receiving any medications or substances known or with potential to affect the activity or pharmacokinetics of temozolomide and/or pazopanib will be determined following review of the case by the Principal Investigator. Efforts should be made to switch patients who are taking enzyme-inducing agents to other medications. A list of medications and substances known or with the potential to interact with selected relevant CYP450 isoenzymes is provided in Appendix II.

3.2.13 Patients must have given signed, informed consent prior to registration on study.

3.3 Exclusion Criteria

3.3.1 Patients with known HIV infection are NOT eligible for participation.

3.3.2 Patients with uncontrolled hypertension (≥ 140/90 mmHg) are NOT eligible for participation.

3.3.3 Patients who have had a transfusion within 7 days of screening are NOT eligible for participation.

3.3.4 Patients with symptomatic brain or bone metastasis are NOT eligible for participation. Prior radiation and/or steroid therapy for brain or bone mets must be completed ≥ 2 weeks prior to study enrollment.

3.3.5 Patients with a history of seizure disorder requiring antiepileptic medication or brain metastases with seizures are NOT eligible for participation.

3.3.6 Patients with an active second malignancy (other than non-melanoma skin cancer or cervical carcinoma in situ) are NOT eligible for participation. Patients who have a history of malignancy are not considered to have a currently active malignancy if they have completed therapy and are now considered by their physician to be at < 30% risk for relapse.

3.3.7 Patients with clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding are NOT eligible for participation. These may include (but are not limited to):

3.3.7.1 Active peptic ulcer disease

3.3.7.2 Known intraluminal metastatic lesion/s with risk of bleeding

3.3.7.3 Inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease)

3.3.7.4 Other gastrointestinal conditions with increased risk of perforation

3.3.8 Patients with a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment are NOT eligible for participation.

3.3.9 Patients with clinically significant gastrointestinal abnormalities that may affect absorption of the investigational product including are NOT eligible for participation. These may include (but are not limited to):

3.3.9.1 Malabsorption syndrome

3.3.9.2 Major resection of the stomach or small bowel

3.3.10 Patients with a history of any one or more of the following cardiovascular conditions within the past 6 months prior to study enrollment are NOT eligible for participation:
- **3.3.10.1** Cardiac angioplasty or stenting
- **3.3.10.2** Myocardial infarction
- **3.3.10.3** Unstable angina
- **3.3.10.4** Coronary artery bypass graft surgery
- **3.3.10.5** Symptomatic peripheral vascular disease
- **3.3.10.6** Class III or IV congestive heart failure, as defined by the New York Heart Association (refer to Appendix III)

3.3.11 Patients with a corrected QT interval (QTc) > 480 msecs are NOT eligible for participation.

3.3.12 Patients with a history of transient ischemic attack (TIA) or cerebrovascular accident (CVA) within the past 6 months prior to study enrollment are NOT eligible for participation.

3.3.13 Patients with a history of any one or more of the following thromboembolic events within the past 6 months prior to study enrollment are NOT eligible for participation:
- **3.3.13.1** Pulmonary embolism
- **3.3.13.2** Untreated deep venous thrombosis (DVT)
  Subjects with recent DVT who have been therapeutically coagulated for at least 6 weeks ARE eligible.

3.3.14 Patients who have undergone major surgery or trauma within 28 days prior to the first dose of investigational product and/or present with any non-healing wound, fracture, or ulcer are NOT eligible for participation. Procedures such as catheter placement not considered to be major surgery.

3.3.15 Patients with known endobronchial lesions and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage are NOT eligible for participation.
- **3.3.15.1** Lesions infiltrating major pulmonary vessels (contiguous tumor and vessels) are excluded; however, the presence of a tumor that is touching, but not infiltrating, the vessels is acceptable. CT with contrast is strongly recommended to evaluate such lesions.
- **3.3.15.2** Large protruding endobronchial lesions in the main or lobar bronchi are excluded; however, endobronchial lesions in the segmented bronchi are allowed.
- **3.3.15.3** Lesions extensively infiltrating the main or lobar bronchi are excluded; however, minor infiltrations in the wall of the bronchi are allowed.

3.3.16 Patients who have had recent hemoptysis (≥ ½ teaspoon of red blood within 8 weeks before first dose of study drug) are NOT eligible for participation.

3.3.17 Patients who have any history of allergic reaction(s) attributed to compounds of similar composition to temozolomide, pazopanib, their metabolites, or any component of their formulation are NOT eligible for

participation.

3.3.18 Females who are pregnant or lactating, fertile males, or females of child-bearing potential who are not willing to comply with an effective double method of birth control are NOT eligible for participation.

3.3.19 Patients with a psychiatric illness, other condition or significant medical illness, or social situation which, in the investigator's opinion, would limit compliance or ability to comply with study requirements are NOT eligible for participation.

3.3.20 Patients who have taken medications that are known strong inducers or inhibitors of CYP3A4 within 28 days prior to registration are NOT eligible for participation.

3.4 Policy on Eligibility Waivers

The eligibility criteria listed above are interpreted literally and CANNOT be waived.

4.0 PATIENT REGISTRATION

Patients may not begin protocol treatment prior to registration.

4.1 Overview

Eligible patients will be registered to the study via the Northwestern Oncology Trial Information System (NOTIS) using the web-based application, which can be found at: https://notis.nubic.northwestern.edu. Please note that a password is required to use this program. One will be provided at the time of site activation, prior to training on the NOTIS system. Please contact the assigned Quality Assurance Monitor (QAM) or the QA Department (croqualityassurance@northwestern.edu) for questions regarding the registration process. In order for registrations to be processed efficiently, study teams are asked to inform the QAM of the date and time that potential patients will need to be registered.

4.2 Registration procedures:

4.2.1 Registering a Patient for the Phase I Portion of the Study

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.

4.2.2 Registering a Patient to the Phase II Portion of the Study

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

• Eligibility eCRF (complete in NOTIS)
• Eligibility checklist (signed and dated by the treating physician – upload in NOTIS)
• Signed and dated informed consent document (upload in NOTIS)
• Pathology Report (upload in NOTIS)

The QAM will review the registration, register the patient, assign an identification number, and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

4.3 Notifying NCCN

This trial is supported by the National Comprehensive Cancer Network (NCCN), and as such, the NCCN requires notification of participant registration at the time of accrual. Accrual is defined as the point at which the informed consent is obtained and the participant has received the first dose of study treatment. At the time that registration is complete and the patient begins treatment, the Notification of Participant Registration form will be completed by the QAM. The QAM will then send completed forms to NCCN at the following email address: ORPRegistration@nccn.org.

5.0 TREATMENT PLAN

5.1 Overview

This will be a phase I/II multicenter trial of the combination of temozolomide and pazopanib in patients with advanced PNETs. The phase I portion will employ a standard 3+3 dose escalation schema. The starting dose of temozolomide for cohort 1 will be 150 mg/m^2 per day on days 1-7 and 15-21 of each 28-day cycle. The starting dose for cohort 1 of pazopanib will be 400 mg per day, taken continuously throughout each cycle. Patients will be assessed for DLT during the

first 28-day cycle. The frequency of DLTs observed in each cohort will determine whether and how the doses are adjusted (either up or down) in the next cohort. Dose escalation rules and definitions are outlined below. Once the MTD has been determined, that will be the recommended dose for the phase II portion of the trial. In the phase I portion of the trial, once the MTD is reached, the cohort will be expanded to an additional 6 additional patients to perform PK studies. MTD has now been identified at dose level -2 (75 mg/m2 per day p.o. days 1-7 and 15-21 of Temozolomide and 400 mg per day p.o. days 1-28 of Pazopanib). The phase II portion will be a Simon 2-stage design, with anywhere from 11 to 27 patients being enrolled to the phase II portion. The 6 patients in the PK cohort treated at MTD in the phase I portion will be included in the phase II analysis.

5.2 Study Drug Administration

Both study drugs will be orally self-administered. Patients will be provided a drug diary to record the date and time of each dose of temozolomide and pazopanib, as well as any skipped doses or doses intentionally held per the treating physician's instructions. The study team will instruct patients on completing the diary, and will collect the completed diaries for the previous cycle on Day 1 of the subsequent cycle.

5.2.1 Temozolomide

Patients will be instructed to take temozolomide orally once a day starting on Cycle 1 Day 1 of treatment. The dose of temozolomide will depend on the phase and cohort onto which the patient is enrolled (refer to Section 5.3 for dose escalation rules). For phase I, the starting dose of temozolomide will be 150 mg/m^2 per day. Patients will continue temozolomide for 7 consecutive days at a time, every other week (Days 1-7 and 15-21 of the cycle). One cycle equals 28 days. Patients will continue to take temozolomide every other week until study discontinuation (refer to Section 5.8 for duration of treatment and discontinuation rules).

Temozolomide tablets will be swallowed whole. Patients will be instructed to fast at least 1 hour before and 1 hour after administration of temozolomide. Water is allowed during the fasting period. Temozolomide may be taken before or after pazopanib (on days when both drugs are taken), but it is recommended that they be taken around the same time. If a dose is missed, the patient should take the dose as soon as possible, but only if there are 12 or more hours remaining before the next dose is due. If the next dose is due in less than 12 hours, the subject should skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking temozolomide, the patient should not take a replacement dose on that day. The patient should resume taking temozolomide at the next scheduled dose on the following day.

(Note: For patients in the PK cohort, please refer to the Study Parameters Table for PK Cohort for information regarding temozolomide doses on Cycle 1, Days 1-3.)

5.2.2 Pazopanib

Patients will be instructed to take pazopanib orally once a day starting on Cycle 1 Day 1 of study treatment. The dose of pazopanib will depend on the phase and cohort onto which the patient is enrolled (refer to Section 5.3 for dose escalation rules). For phase I, the starting dose of pazopanib will be 400 mg per day. Pazopanib will be taken daily continuously study discontinuation (refer to Section 5.8 for duration of treatment and discontinuation rules).

Pazopanib should be taken orally without food at least 1 hour before or 2 hours after a meal. The tablets should be swallowed whole and must not be crushed or broken. The time of day the tablets are taken should be relatively constant. Pazopanib may be taken before or after temozolomide (on days when both drugs are taken), but it is recommended that they be taken around the same time. If a dose is missed, the patient should take the dose as soon as possible, but only if there are 12 or more hours remaining before the next dose is due. If the next dose is due in less than 12 hours, the subject should skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking pazopanib, the patient should not take a replacement dose on that day. The patient should resume taking pazopanib at the next scheduled dose on the following day. If vomiting persists, the patient should be instructed to notify the investigator.

(Note: For patients in the PK cohort, please refer to the Study Parameters Table for PK Cohort for information regarding pazopanib doses on Cycle 1, Days 1-3.)

5.3 Phase I Dose Escalation

5.3.1 Dose escalation schema

For cohort Level 1, starting doses will be temozolomide 150 mg/m^2 per day (Days 1-7 and 15-21 of each cycle) and pazopanib 400 mg daily. Cycle length will be 28 days. All patients in a given cohort must complete 28 days (1 cycle) of therapy prior to proceeding with enrollment on the next cohort/dose level. Dose escalation will be conducted according to the schema below starting at cohort Level 1 with dose escalation following the standard “3+3” design.

Table 1: Phase I Dose Escalation Schema

Cohort	Temozolomide	Pazopanib
Level -4[1]	50 mg/m^2 per day p.o. Days 1-7 & 15-21	200 mg per day p.o. Days 1-28
Level -3[1]	50 mg/m^2 per day p.o. Days 1-7 & 15-21	400 mg per day p.o. Days 1-28
Level -2[1]	75 mg/m^2 per day p.o. Days 1-7 & 15-21	400 mg per day p.o. Days 1-28
Level -1	100 mg/m^2 per day p.o. Days 1-7 & 15-21	400 mg per day p.o. Days 1-28
Level 1 (starting dose)	150 mg/m^2 per day p.o. Days 1-7 & 15-21	400 mg per day p.o. Days 1-28
Level 2[2]	150 mg/m^2 per day p.o. Days 1-7 & 15-21	800 mg per day p.o. Days 1-28

[1] If DLTs occur at cohort Level -1, then a cohort Level -2 may be opened as above. If DLTs occur at cohort Level -2, then a cohort Level -3 may be opened as above. If DLTs occur at dose Level -3, then a cohort Level -4 may be opened as above. Such decisions will be made after DMC review of the data and approval.
[2] If DLTs occur at cohort Level 2, then an additional cohort may be added with a pazopanib dose of 600 mg and temozolomide 150 mg/m^2. This decision will be made following DMC review of the data and approval.

5.3.2 Dose escalation rules

If a DLT is encountered, the following rules in the table below will be applied (refer to Section 5.4.2 for definitions of DLT). All patients on a given cohort must complete at least 28 days of treatment, and toxicity data must be available for review in order to determine whether accrual should proceed to the next cohort. All toxicity data will be reviewed and dose level changes approved by the DMC prior to enrolling patients to subsequent cohorts.

Table 2: Phase I Dose Escalation Rules

# of Patients with DLT at a Given Cohort Level	Escalation Decision Rules
0 out of 3	Dose escalate to the next higher cohort level.
≥ 2 out of 3	Dose escalation will be stopped. This dose level will be declared the maximum administered dose (MAD). The next lower cohort will be expanded to 6 patients. If no DLTs are observed, an intermediate dose level between this dose and the MAD dose may be considered. The DMC must approve the creation of this intermediate dose level, and the protocol will be amended accordingly.
1 out of 3	Enter 3 more patients at this dose level. If 0 of these 3 patients experience a DLT, proceed to the next dose level.

	If 1 or more of these 3 patients experience a DLT, then dose escalation is stopped and this will be declared the MAD.
≤ 1 out of 6 at the highest dose level below the MAD	This is the MTD and the recommended phase II dose (RP2D).

If ≥ 2 patients in cohort Level -4 demonstrate DLT, the study will close. If 0 out of 3 patients in cohort Level 2 demonstrate DLT, an additional 3 patients will be enrolled at this level. If ≤ 1 out of 6 patients in cohort Level 2 demonstrate DLT, this will be considered the MTD and the RP2D without further dose escalation. A dose level must have 6 evaluable patients to be defined as the MTD.

(Note: The MTD has been identified at dose level -2 (75 mg/m2 per day p.o. days 1-7 and 15-21 of Temozolomide and 400 mg per day p.o. days 1-28 of Pazopanib. As of 12.15.15, all patients moving forward will be treated at this dose.)

5.4 Dose Limiting Toxicity

5.4.1 DLT evaluation

Toxicities will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A DLT will be defined as any of the following events (described below in 5.4.2), which are attributable to protocol treatment, occurring during the DLT window. The DLT window is defined as the first 28 days of therapy (or completion of 1 cycle of therapy). Any exclusions from these are described in 5.4.3.

5.4.2 DLT definitions

DLT will be defined as the occurrence of any of the following felt to be related to study treatment during Cycle 1:

5.4.2.1 Grade 3 or higher non-hematologic toxicity (see exceptions below in 5.4.3).

5.4.2.2 Grade 4 thrombocytopenia or anemia.

5.4.2.3 Grade 4 neutropenia or Grade 3 febrile neutropenia associated with temperature > 38°C.

5.4.2.4 Inability to complete Cycle 1 due to toxicity related to study drug.

5.4.2.5 Delay in administration of scheduled doses of study drug greater than 2 weeks due to *drug related* toxicity of any grade.

5.4.3 DLT exclusions

5.4.3.1 Fatigue, nausea, and/or vomiting (any grade) will NOT be

considered DLTs.

5.4.3.2 Lymphopenia not associated with active infection or clinical disease will NOT be considered a DLT.

5.4.3.3 Any grade non-hematologic toxicity will NOT be considered a DLT unless continued despite maximum supportive care beyond the 2 week delay allowed in section 5.4.2.5. (see 5.5.8).

5.4.3.4 Grade 3 or higher non-hematologic toxicity will be considered a DLT EXCEPT in cases where the event existed at baseline. In these cases, toxicity needs to increase in severity by 2 grades per CTCAE v. 4.03 before it is considered a DLT.

5.4.4 DLT Terminology Clarifications

5.4.4.1 Unless otherwise noted, "clinically relevant" is defined as placing the patient at risk for other toxicity by the judgment of the treating investigator.

5.4.4.2 "Optimal supportive care" is defined as standard of care measures that the treating physician deems appropriate and sustainable over multiple cycles of therapy. Specific supportive care guidelines are given below in 5.5. This definition relies upon the clinical judgment of the treating investigator. This may include (but is not limited to) the following:

5.4.4.2.1 Intravenous fluid hydration for dehydration
5.4.4.2.2 Electrolyte supplementation for low electrolytes
5.4.4.2.3 Loperamide for diarrhea
5.4.4.2.4 Antiemetics for nausea
5.4.4.2.5 Skin care for rash
5.4.4.2.6 Printed information as used in standard clinical care)

5.5 Supportive Care Guidelines

Supportive medications to alleviate or mitigate adverse effects of protocol therapy may include the following agents at the discretion of the treating investigator and according to institutional standards of care.

5.5.1 Antidiarrheal Agents

Patients should be instructed to begin loperamide at the earliest signs of a poorly formed or loose stool. Oral loperamide should be prescribed in the following manner: 4 mg at first onset of diarrhea then 2 mg every 2 hours until diarrhea-free for at least 12 hours up to 16 mg daily.

5.5.2 Antiemetic Agents

Drugs such as lorazepam, prochlorperazine, or serotonin antagonists may be used if clinically indicated.

5.5.3 Antihistamines

An antihistamine such as diphenhydramine may be used to manage dermatitis associated with therapy at the discretion of the treating physician.

5.5.4 Anti-diabetic Agents

For patients who develop clinically significant hyperglycemia on study protocol, anti-diabetic therapy and dietary modification are required. The oral anti-diabetic agents, glyburide or metformin, may be instituted at the discretion of the treating physician, assuming no contraindication.

Insulin may be instituted at the discretion of the treating physician to optimize glycemic control. Management of complications of hyperglycemia should be performed by treating physician according to institutional standard practices. All patients who develop clinically significant hyperglycemia on study protocol must receive diabetic teaching and education materials.

(Note: Metformin must be temporarily discontinued for ≥ 48 hours before and after iodinated contrast imaging, with confirmation of stable renal function prior to resuming this agent after contrast exposure.)

5.5.5 Antihyperlipidemic Agents

Patients who develop serum cholesterol > 350 mg/dL and/or triglycerides > 300 mg/dL while on therapy will require medication (assuming no contraindications and with standard precautions as appropriate for the class of agents chosen) and/or dietary modifications at the discretion of the treating investigator.

Concomitant use of pazopanib and simvastatin (Zocor) increases the risk of ALT elevations and should be undertaken with caution and close monitoring. If a subject receiving concomitant simvastatin develops ALT elevations, follow the Guidelines for Management of Treatment Emergent Hepatotoxicity and discontinue simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.

Pravastatin or rosuvastatin is recommended if LDL and/or total cholesterol are elevated, with or without elevated triglycerides, because these agents are not CYP 3A4 substrates. Atorvastatin may also be used with caution. If tryglycerides alone are elevated, fenofibrate may be considered.

5.5.6 Antihypertensive Agents

Patients who develop blood pressures ≥ 140/90 mm Hg on at least 2 occasions should be managed with oral antihypertensives including amlodipine, hydrochlorothiazide, or metoprolol by their treating physician.

5.5.7 Diuretics

Diuretics such as furosemide may be used for the management of

periorbital or lower extremity edema at the discretion of the treating physician. Severe episodes of edema, such as congestive heart failure, pleural effusion, ascites, pericardial effusion, or pulmonary edema may require additional measures such as percutaneous drainage or hospitalization.

5.5.8 Electrolyte Supplementation

Electrolytes should be repleted according to standard institutional protocols.

5.5.9 Growth Factors

Erythropoietin or darbopoietin are permitted at the discretion of the treating physician. Filgrastim and PEG-filgrastim (Neulasta) should not be used in place of protocol-specified dose reductions or delays for myelosuppression, nor should they be used prophylactically because of concern for myelosuppression from a prior cycle of chemotherapy.

For treatment of febrile neutropenia, the use of colony-stimulating factors should not be routinely instituted as an adjunct to appropriate antibiotic therapy. The use of granulocyte colony-stimulating factors may be indicated, however, in subjects who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction, sepsis syndrome, or fungal infection. Investigators should use discretion in initiating colony-stimulating factors in these settings.

5.5.10 Topical Agents

Topical steroid creams may be used to manage pruritic skin toxicity at the discretion of the treating physician. Non-alcohol-based topical emollients such as Aquaphor may be used for hand-foot syndrome or desquamating rashes. Non-alcohol-based moisturizers may be used for dry skin.

5.5.11 Anti-viral Agents

It is recommended that patients be treated with prophylactic Valtrex (valacyclovir hydrochloride) 500 mg daily, however final decisions regarding this will be up to treating physician discretion.

5.6 Concomitant Medications

Concomitant medications are any prescription medications or over-the-counter preparations used by the patient within 28 days of initiating study treatment, during study treatment, and up to 28 days following study termination.

All patients will receive prophylaxis with trimethoprim-sulfamethaxazole double strength (sulfamethoxazole 800 mg and trimethoprim 160 mg) by mouth 3 times a week. If a patient is allergic to this antibiotic it can be substituted per physician recommendation. The details of all concurrent medications including vitamins

and alternative therapies will be recorded on the electronic case report forms (eCRFs).

All medications must be reviewed for potential interaction with study drug therapy. All concomitant medications and blood products, as well as supportive interventions (such as analgesic use, paracentesis, etc.) received by patients from screening until the end of study visit will also be recorded on the appropriate eCRFs.

Concomitant use of pazopanib and simvastatin (Zocor) increases the risk of ALT elevations and should be undertaken with caution and close monitoring. If a subject receiving concomitant simvastatin develops ALT elevations, follow the Guidelines for Management of Treatment Emergent Hepatotoxicity and discontinue simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib (see section 8.2.8 and Appendix II).

Concomitant use of any of the following is PROHIBITED while on this study:

5.6.1 Subjects may not receive other anti-cancer therapy [cytotoxic, biologic, radiation, or hormonal (other than leuprolide or other GnRH agonists)] while on treatment in this study.

5.6.2 Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations; therefore, co-administration of strong CYP3A4 inhibitors is PROHIBITED beginning 28 days prior to the first dose of study drug until discontinuation from the study. Strong CYP3A4 inhibitors include (but are not limited to):

5.6.2.1 Antibiotics: clarithromycin, telithromycin, troleandomycin

5.6.2.2 HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)

5.6.2.3 Antifungals: itraconzaole, ketoconazole, voriconazole

5.6.2.4 Antidepressants: nefazodone.

Please refer to Appendix II for a more complete listing of these agents. Those who have taken medications that are known strong inducers or inhibitors of CYP3A4 within 28 days before registration will be excluded from the study. Please refer to Section 8 for details regarding drug interactions for temozolomide and pazopanib.

5.7 Toxicity Management and Dose Modifications

5.7.1 Assessing toxicity

Toxicity will be graded according to the NCI CTCAE version 4.03. Toxicity will be formally assessed at scheduled clinic follow up appointments every one to two weeks, as well as by investigator review of weekly laboratory testing; in the interim, toxicity may be assessed via patient contact with the study coordinator and/or clinical staff should new symptoms arise between visits.

5.7.2 Treatment rules for toxicity for phase I AFTER the DLT period

Protocol therapy will be delayed, dose-reduced, or discontinued based upon the most severe toxicity encountered in the previous cycle and/or laboratory parameters on the scheduled day of treatment. For *treatment-related* delays in protocol therapy, the longest permitted interval of treatment interruption is 28 days to remain on study. For *non-treatment-related* delays, the maximum permitted interval is 8 weeks to remain on study. General principles of toxicity management are as follows:

5.7.2.1 Temozolomide and pazopanib will be dose-adjusted according to attribution of toxicity. In equivocal cases, the decision may be made by treating investigator with approval from the DMC.

5.7.2.2 Individual dose modifications will be made according to the system showing greatest degree of toxicity using NCI CTCAE version 4.03.

5.7.2.3 Asymptomatic changes in laboratory values require dose modification only if assessed to be treatment-related, clinically relevant, and represent a change of ≥ 2 grades from baseline.

5.7.2.4 If toxicity occurs, supportive care medications should be applied to ameliorate signs and symptoms (refer to Section 5.5) before toxicity grade is determined.

5.7.2.5 A patient will be removed from protocol therapy if either of the two study drugs is discontinued.

5.7.2.5.1 Temozolomide will be discontinued if it is not tolerated at a dose of 50 mg/m2 daily.

5.7.2.5.2 Pazopanib will be discontinued if it is not tolerated at a dose of 200 mg daily.

5.7.2.6 A patient will be removed from protocol therapy if treatment with either of the two study drugs is held for toxicity for longer than 28 days (1 cycle).

5.7.2.7 Once a dose has been reduced for toxicity, it should not be re-escalated.

5.7.2.8 In obese patients, all dosing is to be determined by the patient's actual body weight.

5.7.2.9 If there is more than one indication for dose modification, use the more strict dose modification (i.e. modify according to the most severe toxicity).

5.7.3 Patient dose level adjustments for toxicity in Phase II

For patients enrolled in the phase II portion, the following adjustments should be made in the appropriate drug (depending on attribution of toxicity) based upon the patient's starting dose and the guidelines below in Section 5.7.4. As stated above, if either study drug is discontinued, a patient will be removed from study.

Table 4: Patient Dose Level Adjustments for Toxicity: Temozolomide

Patient Temozolomide Dose Level	Temozolomide Dose Modification
Level 1: 150mg/m^2 per day p.o.	↓ 100 mg/m^2 per day p.o.
Level -1: 100 mg/m^2 per day p.o.	↓ 75 mg/m^2 per day p.o.
Level -2: 75mg/m^2 per day p.o.	↓ 50 mg/m^2 per day p.o
Level -3: 50mg/m^2 per day p.o.	Discontinue

Table 5: Patient Dose Level Adjustments for Toxicity: Pazopanib

Patient Pazopanib Dose Level	Pazopanib Dose Modification
Level 3 800 mg per day p.o.	↓ 600 mg per day p.o.
Level 2 600 mg per day p.o.	↓ 400 mg per day p.o.
Level 1 400 mg per day p.o.	↓ 200 mg per day p.o.
Level -1 200 mg per day p.o.	Discontinue

5.7.4 Dose modifications for toxicity

Held doses of either drug will be considered as omitted. For example, if pazopanib is held for one week starting cycle 2 day 8, the next dose of temozolomide the following week will still be considered cycle 2, day 15 (rather than delaying the cycle and repeating the day 8 dose).

5.7.4.1 Temozolomide dose modifications

Please refer to Table 6 below for a summary of dose modifications for temozolomide for both hematologic and non-hematologic toxicities. Toxicities that are judged to be unrelated to study drug will not require dose modifications.

Table 6: Summary of Hematologic & Non-Hematologic Dose Modifications for Temozolomide

Toxicity	Grade (NCI CTCAE v 4.03)	Temozolomide (TMZ) Adjustment
HEMATOLOGIC		
Neutropenia	Grade 1 ANC 1500 to < 2000/mm^3	No change
	Grade 2 ANC 1000 to < 1500/mm^3	No change

Toxicity	Grade (NCI CTCAE v 4.03)	Temozolomide (TMZ) Adjustment
	Grade 3 ANC 500 to < 1000/mm^3	Hold TMZ, repeat CBC weekly until ≤ grade 2, then decrease 1 level
	Grade 4 ANC < 500/mm^3	Hold TMZ, repeat CBC weekly until ≤ grade 2, then decrease 1 level
Lymphopenia	Any Grade	No dose reductions
Thrombocytopenia	Grade 1 Plts 75,000 to < LLL/mm^3	No change
	Grade 2 Plts 50,000 to 75,000/mm^3	No change
	Grade 3 Plts 25,000 to < 50,000/mm^3	Hold TMZ, repeat CBC weekly until ≤ grade 2, then decrease 1 level
	Grade 4 Plts < 25,000/mm^3	Hold TMZ, repeat CBC weekly until ≤ grade 2, then decrease 1 level
Anemia	Any Grade	No dose reductions or delays will be performed for anemia; transfusions and/or growth factor support may be used at the discretion of the investigator
ALL OTHER NON-HEMATOLOGIC TOXICITY		
Other toxicity (despite optimal care)	Grade 1	No change
	Grade 2	No change
	Grade 3	Hold TMZ until ≤ grade 2, then decrease 1 level
	Grade 4	Discontinuation of therapy and removal from study

5.7.4.2 Pazopanib dose modifications

There will be no dose modifications of pazopanib for hematologic toxicity of any grade. There will be no dose modifications for grade 1 or 2 non-hematologic toxicities. For grade 3 and/or 4 non-hematologic toxicities, please see Table 7 below.

Table 7: Summary of Hematologic & Non-Hematologic Dose Modifications for Pazopanib

Toxicity	Grade (NCI CTCAE v 4.03)	Pazopanib (PAZ) Adjustment
GASTROINTESTINAL (EXCLUDING HEPATIC DYSFUNCTION)		
Nausea/vomiting, constipation, or mucositis (despite optimal supportive care)	Grade 1	No change
	Grade 2	No change
	Grade 3	Hold PAZ and monitor until ≤ grade 2, then decrease 1 level
	Grade 4	Hold PAZ and monitor until ≤ grade 2, then decrease 1 level
Diarrhea (despite optimal supportive care)	Grade 1	No change
	Grade 2	No change
	Grade 3	Hold PAZ and monitor until ≤ grade 2, then decrease 1 level
	Grade 4	Hold PAZ and monitor until ≤ grade 2, then decrease 1 level
CARDIOVASCULAR AND VASCULAR		
Hypertension	Scenario A: Asymptomatic and persistent SBP of ≥ 140 and < 170 mmHg, or DBP ≥ 90 and < 110 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 110 mmHg)	1. Continue PAZ at the current dose. 2. Adjust current or initiate new antihypertensive medication(s). 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to Scenario B.
	Scenario B: Asymptomatic SBP ≥ 170 mmg Hg or DBP ≥ 110 mmHg, or failure to achieve well-controlled BP within 2 weeks under Scenario A.	1. Consider reducing or interrupting PAZ, as clinically indicated. 2. Adjust current or initiate new antihypertensive medication(s). 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. 4. Once BP is well-controlled, restart PAZ at 1 dose level (200 mg) lower if PAZ was interrupted.

Toxicity	Grade (NCI CTCAE v 4.03)	Pazopanib (PAZ) Adjustment
	Scenario C: Symptomatic hypertension or recurring SBP ≥ 170 mmHg or DBP ≥ 110 mmHg, despite modification of hypertensive medication(s)	Interrupt PAZ. Adjust current or initiate new antihypertensive medication(s). Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is recommended. Once BP is well-controlled, restart PAZ at 1 dose level (200 mg) lower if PAZ was interrupted.
	Scenario D: Refractory hypertension unresponsive to above interventions.	Discontinue PAZ and follow-up per protocol.
Arterial Thrombus [Cardiac ischemia/infarction, CNS ischemia (TIA, CVA), any peripheral or visceral arterial ischemia/thrombus]	≥ Grade 3	Discontinue PAZ
Venous Thrombus	Grade 3/4	Hold PAZ. If the planned duration of full-dose anticoagulation is <2 week, PAZ should be held until this is over If the planned duration of the full-dose anticoagulation is >2 weeks, PAZ can be resumed once criteria are met: Subject must have in-range INR (usually 2-3) on a stable dose of warfarin or be on a stable dose of heparin and the subject must not have pathologic conditions that carry high risk of bleeding. If thromboembolic disease worsens, discontinue PAZ
DERMATOLOGIC		
Hand-foot syndrome (despite optimal supportive care)	Grade 1	No change
	Grade 2	No change
	Grade 3	Hold PAZ until ≤ grade 2, then decrease 1 level
	Grade 4	Hold PAZ until ≤ grade 2, then decrease 1 level

RENAL AND URINARY		
Proteinuria	UPC < 3	Continue PAZ at the current dose; monitor as clinically indicated.
	UPC ≥ 3 or 24-hr urine protein ≥ 3g	1. Interrupt PAZ 2. Weekly UPC or 24-hr urine protein monitoring until UPC is < 3 or 24-hr urine protein is < 3g. Then restart PAZ at 1 dose level (200 mg) lower. 3. If UPC ≥ 3 or 24-hr urine protein ≥ 3g recurs, repeat steps 1 and 2. 4. If UPC ≥ 3 or 24-hr urine protein ≥ 3g recurs and the PAZ dose can no longer be reduced, discontinue PAZ and follow-up per protocol.
CARDIAC		
Prolongation of QTc Interval	QTc ≥ 480 < 500 msec	Continue PAZ; monitor as clinically indicated.
	QTc ≥ 500 msec	Discontinue PAZ and follow-up per protocol.
HEMORRHAGE/BLEEDING		
Hemorrhage/Bleeding	Grade 1	For hemoptysis, interrupt PAZ and contact the NOVARTIS Study Physician to discuss whether further treatment with PAZ is appropriate. For other Grade 1 hemorrhage/bleeding events, continue PAZ at the current dose; monitor as clinically indicated.
	Grade 2	1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue PAZ and continue follow-up per protocol. Otherwise, interrupt PAZ until resolved to ≤ Grade 1. 2. Restart PAZ; consider reducing dose and monitor as clinically indicated.
	Grade 3 or 4 or Recurrent ≥ Grade 2 event after dose interruption/reduction	Discontinue PAZ and follow-up per protocol.
ALL OTHER NON-HEMATOLOGIC TOXICITY		
Other toxicity (despite optimal care)	Grade 1	No change
	Grade 2	No change
	Grade 3	Hold PAZ and monitor until ≤ grade 2, then decrease 1 level
	Grade 4	Discontinue PAZ

HEPATIC DYSFUNCTION	
Event	**Dose Modification Algorithms**
(A). ALT of ≤ 3.0 x ULN	Continue pazopanib at current dose with full panel LFTs**Error! Reference source not found.** monitored as per protocol.
(B). ALT >3.0 x ULN to ≤8.0 x ULN **without** bilirubin elevation (defined as total bilirubin**Error! Reference source not found.** <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**Liver Event Monitoring Criteria:** (1) Continue pazopanib at current dose levels. (2) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.

(C). ALT >8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[b] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**1st occurrence – Liver Event Interruption Criteria Error! Reference source not found.:** (1) Interrupt pazopanib until toxicity resolves to ≤Grade 1 or baseline. Report the event to NOVARTIS as an SAE *within 24 hours* of learning of its occurrence and complete the eCRF liver event forms. Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries and liver event follow up assessments. (2) Liver imaging and other laboratory investigations should be considered as clinically appropriate. (3) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs [a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1. (4) If the potential benefit for reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose and measure serum liver tests weekly for 8 weeks..[d] Re-treatment may be considered if ALL following criteria are met: - ALT/AST reduced to Grade 1 - Total bilirubin <1.5 x ULN or direct bilirubin ≤35% - No hypersensitivity signs or symptoms - Subject is benefiting from therapy. If approval for re-treatment is granted, the subject must be re-consented (with a separate informed consent specific to hepatotoxicity). **Recurrence – Liver Event Stopping Criteria Error! Reference source not found.:** Discontinue pazopanib permanently and monitor subject closely for clinical signs and symptoms; perform full panel LFTs [a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1. At the time of the recurrence, complete the eCRF liver event forms.

(D). ALT >3.0 x ULN **with** concomitant elevation in bilirubin**Error! Reference source not found.** (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) or **with** hypersensitivity symptoms (e.g., fever, rash).	**Liver Event Stopping Criteria****Error! Reference source not found.:** (1) Discontinue pazopanib immediately, report the event to NOVARTIS as an SAE **within 24 hours** of learning of its occurrence , and complete the eCRF liver event forms. Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries and liver event follow up assessments. (2) Consult a gastroenterologist / hepatologist, collect PK sample and perform the following assessments to identify potential co-factors: - Eosinophil count - Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus (IgM antibody, heterophile antibody, or monospot testing) - Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies. - Serum creatinine phosphokinase for possible muscle injury caused LFT elevation - Liver imaging -Consider toxicological blood screen for possible contributing chemical/medical entities (3) Monitor subject closely for clinical signs and symptoms; record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form. Perform full panel LFTs [a] weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.
For isolated total bilirubin**Error! Reference source not found.** elevation without concurrent ALT increases (defined as ALT <3 X ULN).	(1) Isolated hyperbilirubinemia (i.e., in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. Pazopanib inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury. (2) If bilirubin is >1.5 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If bilirubin is >35% direct (conjugated), further evaluation for underlying cause of cholestasis should be performed.

a. Full panel LFTs include: AST, ALT, alkaline phosphatase, GGT, and total bilirubin. Coagulation tests should be performed as clinically indicated.
b. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin >1.5 x ULN, then the event should be promptly reported as an SAE.
c. When a liver chemistry event meets the Liver Event Interruption Criteria, or Liver Event Stopping Criteria, blood samples should be obtained for PK and for clinical laboratory testing by the central laboratory (Liver Event Kits will be provided for this purpose).
d. Please refer to Investigator's Brochure, Summary of Data and Guidance for Investigator, Warnings and Precautions, Hepatic Effects for information about rechallenge dose.

Abbreviations: ALT alanine aminotransferase; AST aspartate aminotransferase; eCRF electronic case report form; IP investigational product; LFT liver function tests; PK pharmacokinetics; SAE serious adverse event; ULN upper limit of normal

5.7.4.5 For any toxicity (regardless of grade), despite optimal supportive care, that is felt by the treating investigator to represent a risk to the patient's safety, additional dose reduction, treatment delay, or treatment discontinuation is permitted at the discretion of the treating investigator with approval from the Principal Investigator and DMC.

5.8 Duration of Therapy

Patients will receive 2 cycles of protocol therapy prior to radiographic assessment for response or progression. Patients with clinical signs or symptoms of rapid disease progression prior to completing 2 cycles of protocol therapy may be removed from the study by the treating physician. Patients without disease progression at the time of response assessment will continue on the study, with repeat assessments after every 2 cycles (8 weeks +/- 7 days) until one of the criteria for treatment discontinuation is met. It is recommended that temozolomide treatment be discontinued after 1 year, due to risk of Myelodysplastic syndrome (MDS) . Patients can continue on Pazopanib. If patient is receiving benefit from combination treatment after one year, it is up to the treating physician's discretion whether or not the patient continues Temozolomide.

5.8.1 Criteria for discontinuing study treatment

When a patient is discontinued from treatment, the reason(s) for discontinuation will be documented on the appropriate eCRFs. Individual patients will continue on study therapy until any of the following occurs:

5.8.1.1 Unacceptable toxicity despite optimal supportive care and dose modifications (refer to Sections 5.6 and 5.7),

5.8.1.2 Disease progression by RECIST (version 1.1),

5.8.1.3 The patient or his/her legally authorized representative requests to discontinue protocol therapy or withdraws consent.

5.8.1.4 The decision is made by the treating physician to discontinue treatment due to one of the following:

5.8.1.4.1 Patient non-compliance or lack of follow-up.

5.8.1.4.2 Patient requires exclusionary concurrent treatment.

5.8.1.4.3 Physician assessment that continuation of protocol therapy would be detrimental to the patient.

5.8.1.5 Death

5.8.2 Unacceptable toxicity

Patients must be removed from the study and protocol therapy discontinued for toxicities deemed by the treating investigator as unacceptable. These toxicities include but are not limited to:

5.8.2.2 Recurrent grade 3 or any grade 4 hemorrhage.

5.8.2.3 Gastrointestinal perforation requiring medical or surgical therapy.

5.8.2.4 Wound dehiscence requiring medical or surgical therapy.

5.8.2.5 Grade 4 hypertension despite optimal medical management

5.8.2.6 Grade 4 hypersensitivity reaction to either study drug, or Grade 3 reaction that recurs despite optimal supportive care.

5.8.2.7 Any Grade 3 or 4 toxicity that is deemed serious and/or life-threatening by the treating investigator after review with the Principal Investigator.

5.8.2.8 Any irreversible (lasting ≥ 2 weeks despite optimal supportive care) Grade 3 or 4 toxicity (excluding nausea, vomiting, asymptomatic Grade 3 hypophosphatemia or Grade 3 hyponatremia, anemia, lymphopenia, or fatigue)

5.8.2.9 Any toxicity requiring treatment delay for > 28 days or discontinuation of either study drug.

5.9 Follow-Up

After treatment discontinuation, patients will be followed every 6 months for 1 year in clinic and/or via phone for survival follow-up. The study will end 30 days after the last patient discontinues therapy and completes the protocol-defined follow-up period.

6.0 ENDPOINT ASSESSMENT

6.1 Phase I

6.1.1 Primary Endpoint

The primary objective for the phase I portion of this trial will be to determine the MTD of temozolomide and pazopanib combination in patients with advanced PNET. The primary endpoint will be toxicity, as assessed after 28 days of treatment (or completion of 1 cycle of therapy). Toxicity will be assessed at scheduled clinic follow up appointments every one to two weeks, as well as by investigator review of weekly laboratory testing; in the interim, toxicity may be assessed via patient contact with the study coordinator and/or clinical staff should new symptoms arise between visits. The MTD will be the level at which ≤ 1 out of 6 patients experience a DLT (the highest dose level below the MAD). This will be the dose for the phase II portion of the study. Toxicity will be assessed according to the NCI CTCAE version 4.03.

6.1.2 Secondary Endpoints

6.1.2.1 Determine the safety and toxicity profile

One secondary objective for the phase I portion of this trial will be to determine safety and toxicity profile of the combination of temozolomide and pazopanib in this population. The endpoint for this objective will be toxicity, which will be assessed at scheduled clinic follow up appointments every one to two weeks, as well as by investigator review of weekly laboratory testing; in the interim, toxicity may be assessed via patient contact with the study coordinator and/or clinical staff should new symptoms arise between visits. Toxicity will be graded according to the NCI CTCAE version 4.03.

6.1.2.2 Describe the pharmacokinetics (PK) of the combination of temozolomide and pazopanib

Once the MTD is reached in the phase I portion of the study, this cohort will be expanded to include an 6 additional patients who will have PK studies performed. We will examine the effect of pazopanib on the pharmacokinetics of temozolomide. Full PK profiles will be taken after a single dose of temozolomide on Day 1 and again on Day 2 after administration of the combination of temozolomide and pazopanib. On Day 1, Cycle 1, the patient will have a time = 0 sample, take their dose of temozolomide, and then have samples drawn at the following times:

6.1.2.2.1 Day 1, Cycle 1

Time = 0 (prior to temozolomide dose) 10 min (+/- 5 minutes), 30 min (+/- 5 min), 1 hour (+/- 5 min), 2 hours(+/- 5 min), 3 hours(+/- 5 min), 4 hours (+/- 30 min) , 6 hours(+/- 30 min), 8 hours(+/- 30 min), and 24 hours(+/- 1 hour) post-dose.(drawn on Day 2.This will be the same sample as the pre-dose PK sample of Day 2 provided Day 2 drug administration is done within 1 hour of sample collection. One 3 ml sample is needed).

6.1.2.2.2 Day 2, Cycle 1

Time = 0 (prior to both pazopanib and temozolomide. This will be the same sample as the 24 hour post-dose PK sample of Day 1, provided Day 2 drug administration is done within 1 hour of sample collection. If this drug administration is delayed beyond one hour, then another 3 ml PK sample has to be collected for the pre-dose PK of Day 2), 10 min(+/- 5 minutes), 30 min(+/- 5 min), 1 hour(+/- 5 min), 2 hours(+/- 5 min), 3 hours(+/- 5 min), 4 hours(+/- 30 min), 6 hours(+/- 30 min), 8 hours(+/- 30 min), and 24 hours(+/- 1 hour) (done on Day 3) post dose.

Plasma temozolomide concentrations will be measured using our triple quadruple API3000 LC-MS/MS after sample preparation by solid-phase extraction. The plasma temoxolamide concentration versus time relationships will be modeled using the SAAM II software system (SAAM Institute, Seattle, WA) implemented on a Windows™-based PC as described by Argiris et al. Cmax and Tmax will be taken as the observed values.

These 6 patients in the PK cohort will be included in the phase II analysis. These patients will have correlative studies including MGMT. These 6 patients will be evaluated for phase II endpoints.

6.1.2.3 Observe the ORR

For all patients enrolled in the phase I portion of the study, we will describe the ORR as the best overall response recorded from the start of the study treatment until the end of treatment based on RECIST (version 1.1) criteria.

6.2 Phase II

6.2.1 Primary Endpoint

The primary objective for the phase II portion of this trial will be to determine the ORR. All enrolled patients will undergo contrast-enhanced CT or MRI imaging at baseline and after every 2 cycles of protocol therapy until study discontinuation. Patients will be assessed radiographically for response or progression after 2 cycles (8 weeks ± 7 days) of study treatment. After 1 year of protocol therapy, patients may switch to imaging every 12 weeks (+/- 7 days) per treating physician discretion. Centralized RECIST measurements may be performed for some sites, depending upon feasibility. The schedule and methods of radiographic evaluation are described in Section 7.0.

6.2.2 Secondary Endpoints

6.2.2.1 Determine PFS, OS, DCR, and DOR.

For these endpoints, all enrolled patients will undergo contrast-enhanced CT or MRI imaging at baseline and after every 2 cycles of protocol therapy until study discontinuation. Please see Section 6.3 for definitions.

6.2.2.1.1 PFS will be defined as will be defined as the time from the first study treatment to the first occurrence of progression or death.

6.2.2.1.2 OS will be defined as the time from first study treatment until death from any cause.

6.2.2.1.3 DCR will be defined as CR + PR +SD

6.2.2.1.4 DOR will be defined as the time from documented overall response to time of documented disease progression.

6.2.2.2 Determine the safety and toxicity profile of the combination in a larger cohort of patients.

All patients enrolled in the phase II portion of the trial will be evaluated for toxicity throughout the course of their participation on study and through 30 days after the last dose of study treatment.

6.2.3 Exploratory/Correlative Endpoints

Exploratory objectives of this study will look at different types of correlations. We will examine the relationship between tumor blood flow (as measured by perfusion functional computed tomography) and overall response. We will also correlate the expression of tissue MGMT as measured by immunohistochemistry with PFS.

6.2.3.1 Correlate the expression of tissue MGMT with PFS.

Immunohistochemistry for MGMT expression will be performed on all patients enrolled in the phase II portion of the study (the 6 patients in the PK cohort will also be included in these exploratory studies).

MGMT expression will be measured in a blinded fashion utilizing mouse monoclonal antibodies to MGMT. Nuclear MGMT will be scored as either present or absent in tumor cells and correlated with treatment outcome (PFS).

6.3 Definitions

Target and non-target lesions will be defined by RECIST guidelines (version 1.1).

6.3.1 Measureable disease

Measurable lesions are defined as measurable in at least one dimension with clearly defined margins; at least one diameter must be greater than 0.5 cm. Bone lesions are excluded.

6.3.2 Non-measureable disease

All other lesions (or sites of disease), including small lesions and bone lesions, are considered non-measurable disease.

6.3.3 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 diameters. The baseline sum diameters will be used as reference by which

to characterize the objective tumor. Pathological lymph nodes: nodes with a short axis of ≥ 15 mm are considered measurable and assessable as target lesions. The short axis measurement should be included in the sum of lesions in calculation of tumor response. Nodes that shrink to < 10 mm short axis are considered normal.

6.3.4 Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.4 Evaluation of response to therapy

The following criteria (RECIST version 1.1) will be used to define disease response to therapy based upon radiographic measurements using contrast-enhanced CT or MRI imaging with contiguous cuts of 10 mm or less in slice thickness:[41]

Table 8: Definitions & Evaluation of Response

Evaluation of Target Lesions	
Complete Response (CR)	Disappearance of all target lesions.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded on study AND an absolute increase in the sum of at least 5 mm OR the appearance of one or more new lesions.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study
Evaluation of Non-Target Lesions	
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level.
Incomplete Response/ Stable Disease (SD)	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal[1] progression of existing non-target lesions[2].

[1] For unequivocal progression on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. The designation of overall

progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will be extremely rare.[42]

[2] In the uncommon scenario of a mixed response with response or stable disease in target lesion(s) but progression in non-target lesions only, assessment of overall response will be made by the treating investigator and confirmed with the Principal Investigator and DMC.

6.5 Evaluation of best overall response

At study completion, each patient's case will be reviewed to determine a best overall response to therapy. Based on RECIST, the best overall response is the best response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation.[41, 42] In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document objective tumor progression even after discontinuation of treatment. The best overall response will be defined as follows:

Table 9: Best Overall Response Definitions

Best Overall Response			
Target Lesion	Non-Target Lesion	New Lesion	Overall Response
CR	CR	No	CR
CR	Non CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

6.6 Confirmation of disease response or progression

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. The Principal Investigator will confirm the objective response for each patient, and the confirmed responses will be reviewed by the DMC prior to reporting the results.

In cases where confirmation of response is not feasible, it will be made clear when reporting the outcome that the responses are not confirmed. To be assigned a status of PR or CR by RECIST, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.[41, 42] In the case of SD, follow-up

measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (± 7 days).

6.7 Criteria for study completion

6.7.1 Phase I

The phase I portion of the study will close to accrual when the MTD is confirmed in a cohort of at least 6 patients and the additional 6 patients for the PK cohort have been enrolled. The study may also be closed prematurely if more than 1 of 3 patients at cohort Level -3 experience a DLT so that the MTD cannot be determined. At the discretion of the Principal Investigator and the DMC, the study may be terminated early for failure to enroll an adequate number of patients or for significant, unexpected toxicities.

6.7.2 Phase II

The phase II portion of the trial will be completed when all patients have been enrolled and all data for the study endpoints have been collected. At the discretion of the Principal Investigator and the DMC, the study may be terminated early for failure to enroll an adequate number of patients or for significant, unexpected toxicities.

7.0 STUDY PARAMETERS

Table 10: Schedule of Events

	Screening	Cycle 1 [20]				Cycles 2 & 3[20,]		Cycle 4+ [11,20]		Follow-Up [12]	
Assessments	**Baseline [1]**	**D1 [17]**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**D15[21]**	**Off Treatment**	**Post-Treatment**
Informed Consent	X										
History and physical [2]	X	X	X	X	X	X	X	X		X	
Toxicity assessment [3]	X	X	X	X	X	X	X	X		X	
WBC, ANC, hemoglobin, platelet	X	X	X	X	X	X	X	X	X[23]	X	
Electrolytes & renal function tests (Na, K, Cl, CO2, BUN, Creatinine, Mg, Phos)	X	X	X	X	X	X	X	X	X[23]	X	
Liver function tests (AST, ALT, alk phos, total bilirubin)	X	X	X	X	X	X	X	X	X[23]	X	
Albumin, INR, PTT	X										
Serum chromogranin A		X[18]				X		X			
Serum creatinine [4]	X										
Urine protein/creatinine [5]	X	X				X		X			
Serum pregnancy test [6]	X										
EKG [19]	X					X		X			
Echocardiogram or MUGA	X										
Pathology review [15]	X										
Imaging [7]	X							X		X	X
Temozolomide [8]		X (D1-7)		X (D15-21)		X (D1-7)	X (D15-21)	X (D1-7)	X (D15-21)		
Pazopanib [9]		*Continuous daily administration beginning Cycle 1 Day 1*									
Sulfamethoxazole prophylaxis [10]		*Administered 3 times per week while on treatment*									
Drug Diary collection [22]						X		X			
Survival Follow-up										X	X
Correlative Studies [14]											
PK sampling (PK cohort only) [13]		X (D1-3)									
IHC for MGMT expression [16]	X										

[1] Baseline studies should be completed within 14 days of initiating treatment except for imaging, which must be within 28 days.

[2] A complete history and physical exam [including weight, height, vital signs (pulse, temperature, respiratory rate, blood pressure, oxygen saturation) and ECOG PS] will be

conducted at baseline. Subsequent visits require physical exam including vital signs, weight and ECOG PS.

[3] Toxicity will be assessed using the NCI CTCAE version 4.03.

[4] If serum creatinine ≥ 1.5 mg/dL, then creatinine clearance should be calculated and ≥ 30 mL/min

[5] For baseline, patients must have urine protein to creatinine ratio < 1 OR a 24-hour urine protein < 1 g. For treatment cycles, only a urine protein/creatinine ratio is required.

[6] Required for females of childbearing potential (within 14 days) – *see definition of child-bearing potential in Section 3.2.*

[7] Imaging with CT or MRI (whichever test is used for a particular patient at baseline should be the same that is used throughout for disease assessment). Response will be assessed every 2 cycles (8 weeks +/- 7 days). After 1 year of protocol therapy, patients may switch to imaging every 12 weeks (+/- 7 days) per treating physician's discretion.

[8] Temozolomide will be administered on Days 1-7(+/-1 day) and 15-21(+/-1day) of each cycle. Please refer to Section 5.2 for further details.

[9] Pazopanib will be administered continuously starting Cycle 1, Day 1 until study discontinuation. Please refer to Section 5.2 for further details.

[10] All patients will receive prophylaxis with trimethoprim-sulfamethaxazole double strength (sulfamethoxazole 800 mg and trimethoprim 160 mg) by mouth 3 times a week.

[11] Patients will continue on treatment until disease progression (or until removed from study for other reasons, as outlined in Section 5.8.1).

[12] Patients removed from the study for disease progression who have no ongoing toxicity will undergo one last off-treatment visit for response. Survival follow-up will continue every 6 months for 1 year in clinic and/or via phone ; survival follow-up may occur either in clinic or via phone contact. Additional follow-up may be required for patients experiencing toxicity at the time of treatment discontinuation. .

[13] Patients in the PK cohort only will have PK samples drawn on Days 1-3 of Cycle 1. Please refer to Sections, 6.1.2.2and 12.1 for details.

[14] Correlative studies will only be done on the 6 patients in the PK cohort, as well as all patients enrolled to the phase II portion of the study.

[15] Copy of pathology report is sufficient for registration. However a sample of tissue from a recent biopsy will be required for the 6 patients enrolled in the PK cohort and all patients in the phase II portion of the trial

[16] Please refer to Section 12 for details regarding tissue requirements. Tissue from the most recent biopsy will be obtained for study purposes – patients will not undergo repeat biopsy for correlative studies. This applies to both PK cohort and Phase II patients

[17] If baseline labs (chemistries, Mg, Phos, and CBC) were completed within 48 hours prior to start of treatment, they do not need to be repeated for Cycle 1 Day 1.

[18] If serum chromogranin is completed within 14 days of treatment, it does not need to be repeated for Cycle 1 Day 1.

[19] EKG will be performed at baseline (within 14 days of initiating study treatment) and then Day 1 of every cycle beginning with Cycle 2 – EKG does NOT need to be repeated at Cycle 1 Day 1.

[20] Assessments will be completed +/- 3 day from treatment Days 1, 8, 15, and 22 unless otherwise noted. Imaging will be assessed every 2 cycles (8 weeks +/- 7 days).

[21] For Cycle 4 and beyond, Day 15 labs may be completed at a local facility if more convenient for patients, per treating investigator's discretion.

[22] The drug diary (completed by the patient during each cycle) should be collected on Day 1 of the next cycle. Patients should be instructed to complete the drug diary every day and bring it to their visit on Day 1 of the next cycle.

[23]For patients who discontinue Temozolamide after 1 year of treatment, D15 laboratory tests (WBC, ANC, hemoglobin, platelet, Electrolytes & renal function tests [Na, K, Cl, CO2, BUN, Creatinine, Mg, Phos] and AST, ALT, alk phos, total bilirubin) are not required to be done.

8.0 DRUG FORMULATION AND PROCUREMENT

8.1 Temozolomide

8.1.1 Other Names

Temodar®, TMZ, Temodal®, methazolastone

8.1.2 Classification – type of agent

Temozolomide is a cytotoxic alkalyting agent.

8.1.3 Mode of Action

Temozolomide is not directly active but undergoes rapid non-enzymatic conversion at physiologic pH to the reactive compound MTIC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O6 and N7 positions at guanine.

8.1.4 Storage and Stability

Temozolomide capusles are packaged in amber glass bottles and should be stored at 25°C (temperature excursions between 15-30°C are permitted). Refer to the product label for storage and stability information.

8.1.5 Protocol Dose

The starting dose for the phase I portion of this trial will be 150 mg/m^2 taken orally on days 1-7 and 15-21 of each cycle (1 cycle = 28 days). The dose will be escalated (or de-escalated) according to the toxicities observed in each cohort of patients. The MTD, once determined in the phase I portion, will be the recommended dose for the phase II portion of the trial. The MTD has been identified at dose level -2: Temozolomide 75 mg/m2 per day p.o. days 1-7 and 15-21. As of 12.15.15, all patients moving forward will be treated at this dose.

8.1.6 Preparation

Temozolomide is supplied in white opaque, preservative-free capsules in a variety of dosage strengths.

8.1.7 Protocol Administration

Temozolomide will be administered orally on days 1-7 and 15-21 of each 28-day cycle. Capsules should be swallowed whole with a glass of water. Absorption is affected by food. Temozolomide may be administered on an empty stomach or at bedtime to reduce nausea and vomiting. A dose should not be repeated if vomiting occurs after administration. Capsules should not be opened or chewed. Contact with skin should be avoided if capsules are accidentally opened or damaged.

8.1.8 Incompatibilities

Administration of valproic acid decreases oral clearance of temozolomide by about 5%. The clinical implication of this effect is not known.

8.1.9 Availability

Temozolomide is FDA-approved for the treatment of anaplastic astrocytoma and GBM. Locally-obtained, commercial supplies of temozolomide will be prescribed for this study.

8.1.10 Side Effects

The most common grade 3 or 4 toxicities reported with standard dosing include:

8.1.10.1 Lymphopenia < 5%
8.1.10.2 Thrombocytopenia < 5%
8.1.10.3 Nausea/vomiting < 10%
8.1.10.4 Elevated liver enzymes < 10%
8.1.10.5 Elevated BUN/Cr < 10%
8.1.10.6 Constipation < 10%
8.1.10.7 Rash 5%
8.1.10.8 Headache < 5%
8.1.10.9 Alopecia < 5%
8.1.10.10 Lethargy < 1%

8.1.11 Nursing Implications

8.1.11.1 Monitor CBC carefully and report any significant changes to the treating physician. Instruct patients to report signs/symptoms of infection, unusual bruising and bleeding to health care team.
8.1.11.2 Instruct patients to report any fever, cough, chest pain, or other signs of infection to the health care team.
8.1.11.3 Advise patients that a mild-moderate rash may be experienced.
8.1.11.4 Work with patients in energy conserving lifestyle methods to combat fatigue.
8.1.11.5 Encourage patients to increase fluid intake. Administer stool softeners or laxatives as ordered and monitor for their effectiveness.

8.2 Pazopanib

8.2.1 Other Names

None

8.2.2 Classification – type of agent

Pazopanib is an ATP-competitive tyrosine kinase inhibitor of VEGFR.

8.2.3 Mode of Action

Pazopanib is an orally-bioavailable, ATP-competitive tyrosine kinase inhibitor of VEGFR (-1, -2, and -3), PDGFR (-α and -β) –Kit.

8.2.4 Storage and Stability

Keep in tightly closed containers or packages away from moisture and away from sources of ignition. Avoid direct sunlight.

8.2.5 Protocol Dose

The starting dose for the phase I portion of this trial was 400 mg taken orally on a daily basis for each cycle (1 cycle = 28 days). The dose was escalated (or de-escalated) according to the toxicities observed in each cohort of patients. The MTD has been identified at dose level -2; Pazopanib 400 mg per day p.o. days 1-28.
As of 12.15.15, all patients moving forward will be treated at this dose.

8.2.6 Preparation

For clinical supply, Pazopanib is supplied as a series of aqueous film-coated tablets containing 200 mg or 400 mg of the freebase:

8.2.6.1 200 mg, oval-shaped, white, packaged in bottles containing 34 tablets each

8.2.6.2 400 mg, oval-shaped, white, packaged in bottles containing 68 tablets each.

For commercial supply,

8.2.6.3 200mg, gray, oblong-shaped tablets, packaged in bottles containing 120 tablets each.
Votrient (Pazopanib) commercial available supply with auxiliary label will also be provided by Novartis. The study drug should be administrated and stored according to the instructions specified on the drug labels.

(Note: Sites will start using the commercial supply when they finish the previous clinical supply).

8.2.7 Protocol Administration

Pazopanib should be taken orally without food at least 1 hour before or 2 hours after a meal. The tablets should be swallowed whole and must not be crushed or broken. The time of day the tablets are taken should be relatively constant. If a dose is missed, the patient should take the dose as soon as possible, but not if there are less than 12 hours before the next dose is due. If the next dose is due in less than 12 hours, the patient should skip the missed dose and take the next dose as scheduled. If vomiting occurs after taking pazopanib another dose is not permitted on that day. The patient should resume taking pazopanib at the next scheduled dose. If vomiting persists, the subject should be instructed to notify the investigator.

8.2.8 Incompatibilities

Results from drug-drug interaction studies conducted in cancer patients suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D2 in vivo, but had no effect on CYP1A2, CYP2C9, or CYP2C19.

The concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations and should be avoided. Grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib. A list of CYP3A4 inhibitors is provided in Appendix II.

The concomitant use of strong CYP3A4 inducers (e.g., rifampin) may decrease pazopanib concentrations and should be avoided. Pazopanib should not be used in patients who cannot avoid chronic use of strong CYP3A4 inducers. A list of CYP3A4 inducers is provided in Appendix II.

Concomitant use of pazopanib with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. A list of these agents is provided in the Appendix II.

Concomitant use of pazopanib and simvastatin (Zocor) increases the risk of ALT elevations and should be undertaken with caution and close monitoring. If a subject receiving concomitant simvastatin develops ALT elevations, follow the Guidelines for Management of Treatment Emergent Hepatotoxicity and discontinue simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.

Please refer to the development core safety information in the current Investigator's Brochure for detailed information about interactions with simvastatin, CYP3A4 inhibitors, impact on drugs eliminated through UGT1A1 and OATP1B1, and the use of pazopanib with drugs known to increase the gastric pH. Please also refer to Appendix II of this protocol.

8.2.9 Availability

Votrient (Pazopanib) commercial available supply with auxiliary label will be provided by Novartis. The study drug should be administrated and stored according to the instructions specified on the drug label.

Pazopanib will be provided by study supporters Novartis and NCCN. All requests for study drug should be submitted via email to Desiree Hiraman (desiree.hiraman@novartis.com), Quincy Chau (quincy.chau@novartis.com), and Donna Scharff (Scharff@nccn.org) and should include the following information:

8.2.9.1 Quantities needed
8.2.9.2 Protocol number
8.2.9.3 PI's name and shipping address

8.2.10 Side Effects

8.2.10.1 Very common (≥ 1 in 10): anorexia, headache,

hypertension, diarrhea, nausea, vomiting, abdominal pain, increases in ALT, AST, hair depigmentation, fatigue, asthenia.

8.2.10.2 Common (≥ 1 in 100 and < 1 in 10): thrombocytopenia, neutropenia, hypothyroidism, decreased weight, dysgeusia, transient ischemic attack, myocardial ischemia, QT prolongation, epistaxis, hematuria, dyspepsia, hepatic function abnormalities, hyperbilirubinemia, rash, alopecia, skin depigmentation, Palmar-plantar erythrodysaesthesia syndrome, proteinuria, chest pain

8.2.10.3 Uncommon (≥ 1 in 1000 and < 1 in 100): ischemic stroke, Torsade de Pointes, atrial fibrillation, pulmonary hemorrhage, GI hemorrhage,
cerebral hemorrhage, GI perforation, GI fistula
(Note: please refer to updated IB version 14 dated 01.07.16 for more information.)

8.2.11 Nursing Implications

8.2.11.1 Take without food.

8.2.11.2 Monitor liver function tests at baseline while on treatment.

8.2.11.3 Monitor blood pressure.

9.0 STATISTICAL CONSIDERATIONS

The study design is a phase I/II, open-label, non-randomized dose-escalation study to determine the MTD, safety profile, pharmacokinetics, response rate, and overall survival with the combination of temozolomide and pazopanib in patients with advanced pancreatic neuroendocrine tumor.

The MTD determined in phase I will be the recommended Phase II dose. Once the MTD is determined, the study will proceed to a single-arm, open-label Phase II to evaluate efficacy endpoints. Data will be pooled from patients enrolled at both study sites.

9.1 Phase I Endpoints

The primary endpoint in Phase I is MTD and RP2D determination for the combination of temazolamide and pazopanib in patients with advanced pancreatic neuroendocrine tumor. This will be achieved using a standard "3+3" dose escalation as detailed in Section 5.2. Secondary endpoints in Phase I include determining the safety and toxicity profile of the combination of temozolomide and pazopanib, describing the pharmacokinetics, and observing the ORR. Patients who are removed from study for reasons other than disease progression (i.e. for toxicity or patient preference) will be censored for measurement of secondary endpoints at the time of their latest objective tumor assessment.

9.1.1 Sample Size of Phase I

Between 9 and 12 patients will be accrued in phase I. The MTD of the regimen will be determined using standard "3+3" phase I methodology.

9.1.2 Phase I Statistics

Safety will be assessed through a summary of adverse events and laboratory test results. Safety analyses will include all patients who receive at least one dose of study regimen. Verbatim description of treatment-related adverse events will be mapped to thesaurus terms. Adverse events assessed as related to study drug and serious adverse events will be summarized similarly. Adverse events leading to treatment discontinuation will also be summarized. The safety analysis will include a tabulation of all toxicities by grade. The frequency of toxicities will be tabulated separately for each treatment dose level. Treatment safety and toxicity will be evaluated using NCI CTCAE v 4.0 with scheduled assessments every week for the first cycle and then biweekly thereafter.

The statistical analysis for the secondary objectives of phase I will be descriptive in nature. The pharmacokinetics of temozolomide alone (Cycle 1 Day 1) and in combination with pazopanib (Cycle 1 Day 2) will be described in a population of 6 patients enrolled at the MTD. C_{max} and T_{max} will be taken as the observed values. At a minimum, for temozolomide, the following PK parameters will be determined: maximal serum concentration (C_{max}); observed time to achieve Cmax (T_{max}); minimum (trough) serum concentration (C_{min}); elimination half-life (t1/2); elimination clearance (CL_E); volume of distribution at steady-state (V_{SS}), and area under the concentration-time curve extrapolated to infinity (AUCinf). These parameters will be summarized for each person and each day, and each constant will be compared between Day 1 and Day 2 using a Wilcoxon signed rank test. The plasma temozolomide concentration versus time relationships will be modeled using the SAAM II software system. The 6 patients enrolled at the MTD to form the PK cohort will be included in the phase II analysis for all other endpoints.

9.2 Phase II Endpoints

9.2.1 Sample Size of Phase II

The sample size estimate for phase II is based upon a two-stage Simon's optimal design. The primary efficacy endpoint will be the objective response rate (partial or complete response). A Simon (1989), optimum two-stage design will be employed. A 19% response rate precludes further study whereas a 39% response rate would indicate that further investigation of the treatment is warranted (i.e., P0=0.19 and P1=0.39 in the Simon terminology). Using α and β errors of 0.10 and 0.20, respectively, 11 patients will be enrolled in the first stage and this will include the 6 patients in the PK cohort. If 2 or fewer responses are observed, the trial will be terminated. Otherwise, an additional 16 patients will be enrolled in the second stage and if ≤ 7 responses are observed among the 27 patients, the agents will not be considered worthy of further testing; whereas, if 8 or more responses are observed the drugs will be

considered sufficiently active to justify further study. This design has 80% power under the alternative hypothesis and provides a 65% probability of early stopping if the true response rate is only 19%. Therefore, a maximum of 27 patients will be accrued to the phase II portion of the study.

9.2.2 Response Rate Statistics

Radiological response will be analyzed using an intent-to-treat approach of including all enrolled patients. After every 2 cycles of protocol therapy, patients will undergo imaging studies to assess for response to therapy using RECIST. At study termination, each patient's case will be reviewed to determine a best overall response to therapy by RECIST. A descriptive analysis of evidence of antitumor activity will be provided based on radiographic assessments of activity. The proportion with PFS at 6 months will also be calculated based on RECIST criteria.

9.2.3 Toxicity Profile Statistics

Safety will be assessed through a summary of adverse events and laboratory test results. Safety analyses will include all patients who receive at least one dose of study regimen. Verbatim description of treatment-related adverse events will be mapped to thesaurus terms. Adverse events assessed as related to study drug and serious adverse events will be summarized similarly. Adverse events leading to treatment discontinuation will also be summarized. The safety analysis will include a tabulation of all toxicities by grade. The frequency of toxicities will be tabulated separately for each treatment dose level. Treatment safety and toxicity will be evaluated using NCI CTCAE v 4.03 with scheduled assessments every week for the first cycle and then biweekly thereafter.

9.3 Exploratory Endpoints

Exploratory endpoints in this phase I/II trial will be assessed in all patients enrolled in the phase II portion of this study. As noted above, patients who are removed from study for reasons other than disease progression (i.e. for toxicity or patient preference) will be censored for measurement of secondary endpoint, PFS at 6 months, at the time of their latest objective tumor assessment. Exploratory endpoints include:

- Correlate the expression of tissue MGMT as measured by IHC with PFS.

9.3.1 Exploratory Study Statistical Analyses

9.3.1.1 MGMT expression

Changes in MGMT over time will be assessed using repeated measures analysis of variance; pre-treatment levels and changes in levels from baseline to day 30 will be related to response using a Wilcoxon rank sum test, and to PFS and OS using a proportional hazards regression model.

9.4 Replacement Policy

A patient may be replaced if protocol therapy is discontinued due to early disease progression, defined as occurring within the first 28 days of therapy. Patients will not be replaced if taken off study due to toxicity, however, if a patient is taken off study during their DLT period for a reason unrelated to study treatment, another patient may be added to that cohort.

9.5 Statement of Feasibility

The Northwestern University GI Oncology program derives study patient populations from patients currently undergoing treatment or evaluation at the Robert H. Lurie Comprehensive Cancer Center (RHLCCC), as well as from a broad referral base in the Chicago and Midwest area. The weekly multidisciplinary GI Tumor Board at RHLCCC provides additional means to identify potential study subjects. Based upon these resources, we anticipate monthly accrual of approximately 2-3 patients with advanced PNET. Estimated time of study completion is 2.5 years. Dr. Halla Nimeiri, the Principal Investigator of this proposal, has experience leading and designing clinical trials in GI oncology. She is also an active member of the ECOG GI committee. She has received an NCCN grant in the past for evaluating temsirolimus and sorafenib in HCC. As of June2017, she is being replaced by Dr.Sheetal Kircher as Principal Investigator of this study. The co-investigators on this study proposal are all members of the RHLCCC with strong clinical research backgrounds in the development and implementation of clinical trials in gastrointestinal malignancies. Dr. Benson is the director of the GI oncology program and the chair of the ECOG Gastrointestinal and Data Monitoring Committees. The group includes well developed research infrastructure including research nurses and nurse practitioners, data managers, biostatisticians, and research pharmacists. Safety monitoring and oversight will be provided by the RHLCCC Data Monitoring Committee (DMC) in accordance with the Data Safety Monitoring Plan (DSMP) of the RHLCCC. Additional details regarding how this study will be monitored can be referenced in Appendix IV.

10.0 ADVERSE EVENT MONITORING & REPORTING

This trial will be conducted in accordance with the DSMP of the RHLCCC ((http://cancer.northwestern.edu/CRO/data/Data andSafetyMonitoringPlanMay2014.pdf). The level of risk attributed to this study requires High Intensity Monitoring, as outlined in the DSMP.

10.1 Adverse Event Monitoring

Collection and reporting of adverse event (AE) data is required as part of every clinical trial, and is done to ensure the safety of patients enrolled in this study as well as those who will enroll in future studies using similar agents. Toxicity will be assessed daily during treatment, and at least twice weekly (if not more frequently) after treatment until count recovery (as described in Section 7.0). All adverse events will be reported on the appropriate eCRF (as outlined in

Appendices V and VI). Additionally, certain serious adverse events (SAEs) will be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an AE, regardless of its relationship to study drug, will be monitored until one of the following occurs:

10.1.1 The AE resolves or the symptoms or signs that constitute the AE return to baseline.

10.1.2 Any abnormal laboratory values have returned to baseline.

10.1.3 There is a satisfactory explanation other than the study drug for the changes observed.

10.1.4 Death.

10.2 Definitions & Descriptions

10.2.1 Adverse Event

An 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 temporarily 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).

10.2.2 Severity of AEs

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 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:

10.2.2.1 Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

10.2.2.2 Moderate (grade 2): the event causes discomfort that affects normal daily activities.

10.2.2.3 Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

10.2.2.4 Life-threatening (grade 4): the patient was at risk of death at the time of the event.

10.2.2.5 Fatal (grade 5): the event caused death.

10.2.3 Serious Adverse Event

An SAE is any untoward medical occurrence i.e. an undesirable sign or symptom or medical condition that at any dose results in one of the following outcomes:

10.2.3.1 ***Death***; if death results from progression of the disease, the disease progression should be reported as an SAE itself.

10.2.3.2 ***A life-threatening adverse event***; the patient was at risk of death at the time of the event (this does not refer to an event that hypothetically might have caused death if it were more severe).

10.2.3.3 ***A congenital anomaly/birth defect.***

10.2.3.4 ***A persistent or significant incapacity*** or substantial disruption of the ability to conduct normal life functions.

10.2.3.5 An adverse event that ***requires inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours,*** unless hospitalization is for:

10.2.3.5.1 Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes).

10.2.3.5.2 Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug.

10.2.3.5.3 Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.

10.2.3.5.4 Social reasons and respite care in the absence of any deterioration in the patient's general condition.

10.2.3.6 ***Is medically significant or is an important medical event***,

Important medical events are those that may not meet any of the above criteria, but that are clearly of major clinical significance in the judgment of the investigator. They may jeopardize the subject, and/or may require intervention to prevent one of the other serious outcomes noted above. Examples might include: allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that may not result in hospitalization, or development of drug abuse or drug dependency.

10.2.5 Exceptions to AE & SAE Definitions

Generally speaking, any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE, as described above. Likewise, any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE. However, for the purposes of this study, neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as AEs or SAEs under the following circumstances:

10.2.5.1 Hospitalization or prolonged hospitalization is for a diagnostic or elective surgical procedure for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

10.2.5.2 Hospitalization or prolonged hospitalization is required to allow efficacy measurement for the study.

10.2.5.3 Hospitalization or prolonged hospitalization is required for study-directed therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the principal investigator.

10.2.5.4 Hospitalization or prolonged hospitalization is due to social reasons (i.e. awaiting transport home).

10.2.6 Unanticipated Problem Involving Risk to Subject or Others (UPIRSO)

In order for an adverse event to be reported to the Northwestern University IRB, it must qualify as a UPIRSO. In order to qualify as a UPIRSO, the event must meet *all three* of the following criteria:

10.2.5.1 The event must be unanticipated in terms of nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.).

10.2.5.2 The event must place the research subject or others at a different or greater risk of harm (including physical, psychological, economic, or social harm).

10.2.5.3 The event must be *at least possibly* related to participation in the study.

10.3 Reporting of SAEs

All SAEs, regardless of attribution, occurring during the study or within 30 days of the last administration of temozolomide and/or pazopanib must be reported to the principal investigator upon discovery or occurrence. Additional expedited or routine reporting may be required, depending on the nature of the SAE (as outlined below). Please also refer to Table 7 – Summary of Hematologic & Non-Hematologic Dose Modifications for Pazopanib – for additional information regarding toxicities that should be reported as SAEs.

10.3.1 Reporting to the QAM/DMC

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 is required (available as stand-alone document).

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

10.3.1.1 Protocol description and number

10.3.1.2 The patient's identification number

10.3.1.3 A description of the event, severity, treatment, and outcome (if known)

10.3.1.4 Supportive laboratory results and diagnostics

10.3.1.5 The hospital discharge summary (if available/applicable)

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

10.3.2 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.

10.3.2.1 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 Northwestern University IRB within 24 hours of notification.

10.3.2.2 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)

10.3.2.3 The following SAEs will be reported to the NU IRB within 5 working days of notification:

10.3.2.2.1 Death of a *non-NU subject* that is *unanticipated* in nature and at least *possibly related* to study participation

10.3.2.2.2 Other UPIRSOs

10.3.2.4 The following SAEs will be reported to the NU IRB at the time of annual continuing review:

10.2.3.4.1 All deaths of NU subjects that were not previously reported.

10.2.3.4.2 All deaths of non-NU subjects that are deemed to be unanticipated in nature *and unrelated* to participation.

10.2.3.4.3 All other SAEs not previously reported to the IRB as UPIRSOs

10.3.3 Reporting to Novartis

The principal investigator has the obligation to report all serious adverse events to Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E).

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

To ensure patient safety, every SAE, regardless of suspected causality, occurring:

10.3.3.1 After the patient has provided informed consent and until atleast 30 days after the patient has stopped study treatment/participation.

10.3.3.2 After protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and 30 days after the patient has stopped study treatment.

10.3.3.3 After the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant. medication) and until 30 days after the patient has stopped study treatment.

All events must be reported to Novartis within 24 hours of learning of its occurrence. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form (NU SAE form); all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form (NU SAE form) in English, and **send the completed, signed form by fax to (fax: 877-778-9739) within 24 hours to the oncology Novartis DS&E department with the provided FAX cover sheets** (available as stand-alone documents).

This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 24 hours.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. The end date of the first event must be provided.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, stating that this is a follow-up to the previously reported SAE, and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Pazopanib Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence.
The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.
Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology (DS&E) department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form (NU SAE form).

10.3.4 Reporting to NCCN

10.3.4.1 All SAEs must also be reported to NCCN via fax at 215-358-7699 or e-mailed to ORPReports@nccn.org

10.3.4.2 The NU CRO SAE form will be used to report SAEs to NCCN. This form will include a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included.

10.3.4.3 In addition, the Investigators will adhere to the safety reporting requirements and timelines described in the Clinical Trial Agreement with National Comprehensive Cancer Network (NCCN).

11.0 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

The items detailed in section 4.2.1 (for phase I patients) and 4.2.2 (for phase II patients) must be submitted in order for the patient to be registered and an identification number assigned.

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.

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 level of monitoring as outlined in the DSMP(http://cancer.northwestern.edu/CRO/data/Data andSafetyMonitoringPlanMay2014.pdf). 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 Reportable New Information (RNI) 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 DMC) 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 DMC-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 DMC at their next available meeting, and a final, DMC-approved dataset will be released along with any DMC decisions regarding publication. The investigators are expected to use only DMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

12.0 PATHOLOGY REQUIREMENTS – CORRELATIVE STUDIES

12.1 Pharmacokinetics (PKs)

12.1.1 Timing

After determination of the MTD, the last cohort of the phase I portion will be expanded to include an additional 6 patients who will undergo PK testing to evaluate the effect of pazopanib on the pharmacokinetics of temozolomide. The MTD has now been identified at dose level -2 (75 mg/m2 per day p.o. days 1-7 and 15-21 of Temozolomide and 400 mg per day p.o. days 1-28 of Pazopanib). As of 12.15.15,all patients moving forward will be treated at this dose. As stated above, the PKs are mandatory for this cohort.

The schedule and dosing for these 6 patients will be as follows:

12.1.1.1 Day 1, Cycle 1

Patients will not take either study drug prior to arriving to the clinic. Patients will have a time = 0 sample drawn, and then be instructed to take their dose of temozolomide. Patients will then have PK samples drawn at 10 min (+/-5 min), 30 min (+/-5 min), 1 hour (+/-5 min), 2 hours (+/-5 min),, 3 hours (+/-5 min),4 hours(+/-30 min), 6 hours (+/-30 min), 8 hours(+/-30 min),, and

24 hours(+/-1 hour) post-dose (drawn on Day 2. This will be the same sample as the pre-dose PK sample of Day 2 provided Day 2 drug administration is done within 1 hour of sample collection. One 3 ml sample is needed).

Pazopanib will be held on this day.

12.1.1.2 Cycle 1, Day 2:

Patients will continue to take temozolomide as instructed but will not take pazopanib until instructed to do so in clinic. Patients will have a time = 0 sample drawn and then be instructed to take their dose of pazopanib. This will be the same sample as the 24-hour post-dose PK sample of Day 1, provided Day 2 drug administration is done within 1 hour of sample collection. If this drug administration is delayed beyond one hour, then another 3 ml PK sample has to be collected for the pre-dose PK of Day 2). Patients will then have PK samples drawn at 10 min(+/- 5 min), 30 min(+/- 5 min), 1 hour(+/- 5 min), 2 hours(+/- 5 min), 3 hours(+/- 5 min), 4 hours(+/- 30 min), 6 hours(+/- 30 min), 8 hours(+/- 30 min), and 24 hours(+/-1 hour) (done on Day 3) post-dose.

12.1.1.3 Cycle 1, Day 3:

Patients will not take either study drug prior to arriving to the clinic. Patients will have 1 PK sample drawn (the 24 hours[+/- 1 hour] post-pazopanib dose sample from Day 2) and then continue to take both temozolomide and pazopanib as instructed per protocol.

12.1.2 Sample collection

PK samples will be drawn in the outpatient setting. Collect each blood sample (3 mL) in an evacuated blood tube containing lithium heparin. Invert the tube gently 4 or 5 times (avoid shaking). Care must be taken to ensure that blood does not come in further contact with the stopper on the evacuated tube. Blood samples should be kept in an ice water bath from the time of collection to the time of centrifugation, which should occur within 30 minutes of sample collection. Samples at Northwestern University should be picked up by the Pathology Core Facility Clinical Trials Technician for processing and storage until they are ready to be analyzed. Samples should be labeled with the patient's study ID number and initials, as well as the date and collection time point (i.e. 30 min post-dose).

12.1.3 Processing

Centrifuge samples in a laboratory centrifuge designed for separating plasma from cells at approximately 3,000 rpm for 10 min at 4°C. Transfer the plasma to 2 polypropylene tubes (a primary and a back-up

tube, approximately 0.75 mL per tube). After aliquoting, 30 uL 8.5% phosphoric acid should be added to each mL of plasma being stored in the polypropylene tubes before freezing the samples (22.5 microL/0.75 mL). Computer-printed labels will be generated at each study site for the polypropylene (storage) tubes detailing study ID number, patient study ID, date of collection, time of collection, and protocol therapy time point. If it should be necessary to handwrite the information, only indelible ink should be used. Apply the labels along the length of the tube. Secure the labels by wrapping with clear tape.

Apply the preprinted labels to the polypropylene tubes at room temperature at least 2 hours before refrigerating or freezing. Adequate adhesion cannot be guaranteed if the labels are applied to cold tubes. Blood samples must be kept frozen at approximately -80°C after collection and until delivery/shipment is initiated.

Sample collection details (i.e., patient study ID, date of collection, time of collection, and protocol therapy time point) should be indicated on a log sheet along with the times of last study drug dose(s). A copy of the sheet should be submitted with the samples.

12.1.4 Shipment

Plasma samples for the PK portion of the study will be shipped directly from study sites to Northwestern University for bioanalysis. Samples should be stored as referenced above until shipment. All samples for all patients on study may be batched and shipped upon completion of the enrollment phase to the PK cohort.

One specimen from each pair of a sample should be included in the initial shipment. Samples will be shipped overnight along with a copy of the log sheet via FEDEX on dry ice to Northwestern University at the address provided below. The remaining set of samples will be saved at each study site until receipt of the first set of samples has been confirmed, then shipped to Northwestern University separately (in case of lost shipment or other complication).

Shipment should only be initiated on Mondays, Tuesdays, or Wednesdays to ensure arrival of samples within working hours Tuesdays through Thursday (excluding holiday dates). Dr. Michael Avram should be contacted prior to shipment to confirm shipment date and to notify of expected time and date of delivery.

The address and contact for shipments is as follows:

Michael J. Avram, Ph.D.
Northwestern University Feinberg School of Medicine
Department of Anesthesiology
Tarry Building Room 4-735

303 E. Chicago Avenue
Chicago IL 60611
Phone: 312-908-0636
mja190@northwestern.edu

Please refer to laboratory manual for further details (available as stand-alone document)

12.2 MGMT Analysis

12.2.1 Tissue requirements

From each patient, 5 unstained slides will be obtained. Paraffin-embedded sections of 4 μm from the most recent biopsy will be used for immunohistochemistry.

12.2.2 Processing

For antigen retrieval, sections will be subjected to pretreatment with 45-min pressure boiling in citrate buffer (pH 6.0). Immunohistochemistry will be done using an autostainer (Dako Cytomation). Sections will be incubated with a mouse monoclonal MGMT antibody, diluted in antibody diluent (Dako Cytomation), at room temperature for 60 min. The reaction product will be revealed using Dako kit 50087 (Dako Cytomation). Sections will be counterstained with Mayer's hematoxylin. Initial experiments will be done with omission of the primary antibody. Nuclear MGMT will be scored as either present or absent in tumor cells and correlated with treatment outcome (PFS).

All staining and analysis will take place in the Pathology Core Facility at Northwestern University.

12.2.3 Shipment

Pathology samples from biopsy will be shipped to:

Northwestern University
Pathology Core Facility
710 N. Fairbanks Ct, Olson 8421
Chicago, IL 60611
312-908-5546

APPENDIX I - ECOG Performance Status

Grade	ECOG
0	Fully active; no performance restrictions
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead
As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.	

APPENDIX II – P450 Drug Interactions: Substrates, Inhibitors, and Inducers

Please note that these lists are not exhaustive. If investigators are unsure of potential for drug-drug interaction, the Investigational Pharmacist should be consulted, along with the current version of the Investigator's Brochure. For the most up to date table of cytochrome P450-related drug interactions, please refer to the Indiana University drug interaction table at the following website: http://medicine.iupui.edu/clinpharm/ddis/ClinicalTable.aspx. Below is an abbreviated table of *clinically relevant* substrates, inhibitors, and inducers. Inhibitors are classified as *Strong, Moderate, Weak,* or *Other*. A *strong inhibitor* is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance. A *moderate inhibitor* is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance. A *weak inhibitor* is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

<table>
<tr><th colspan="8">SUBSTRATES</th></tr>
<tr><th>1A2</th><th>2B6</th><th>2C8</th><th>2C9</th><th>2C19</th><th>2D6</th><th>2E1</th><th>3A4,5,7</th></tr>
<tr><td>clozapine</td><td>bupropion</td><td>paclitaxel</td><td rowspan="5">NSAIDs:
• diclofenac
• ibuprofen
• piroxicam</td><td rowspan="5">PPIs:
• lansoprazole
• omeprazole
• pantoprazole
• rabeprazole</td><td rowspan="5">Beta blockers:
• S-metoprolol
• propafenone
• timolol</td><td rowspan="5">Anesthetics:
• enflurane
• halothane
• isoflurane
• methoxyflurane
• sevoflurane</td><td rowspan="5">Macrolide antibiotics:
• clarithromycin
• erythromycin (not 3A5)
• NOT azithromycin
• telithromycin</td></tr>
<tr><td>cyclobenzaprine</td><td>Cyclophospha-mide</td><td>torsemide</td></tr>
<tr><td>duloxetine</td><td>efavirenz</td><td>amodiaguine</td></tr>
<tr><td>fluvoxamine</td><td>ifosfamide</td><td>cerivastatin</td></tr>
<tr><td>haloperidol</td><td>methadone</td><td>repaglinide</td></tr>
<tr><td>imipramine</td><td rowspan="12" colspan="3"></td><td rowspan="6">Oral hypoglycemic:
• tolbutamide
• glipizide</td><td rowspan="6">Anti-epileptics:
• diazepam
• phenytoin
• phenobarbitone</td><td rowspan="6">Antidepressants:
• amitriptyline
• clomipramine
• desipramine
• imipramine
• paroxetine</td><td rowspan="6">Others:
• acetaminophen
• aniline
• benzene
• chloroxazone
• ethanol
• N,N-dimethyl formamide
• theophylline 8-OH</td><td rowspan="6">Anti-arrhythmics:
• quinidine 3-OH (not 3A5)</td></tr>
<tr><td>mexiletine</td></tr>
<tr><td>nabumetone</td></tr>
<tr><td>naproxen</td></tr>
<tr><td>olanzapine</td></tr>
<tr><td>riluzole</td></tr>
<tr><td>tacrine</td></tr>
<tr><td>theophylline</td><td rowspan="3">Angiotensin II blockers:
• losartan
• irbesartan</td><td rowspan="3">Others:
• amitriptyline
• clomipramine
• clopidogrel</td><td rowspan="3">Antipsychotics:
• haloperidol
• risperidone
• thioridazine</td><td rowspan="3"></td><td rowspan="3">Benzodiazepines:
• alprazolam
• diazepam 3OH
• midazolam</td></tr>
<tr><td>tizanidine</td></tr>
<tr><td>triamterene</td></tr>
</table>

zileuton			• cyclophosphamide • progesterone			• triazolam
zolmitriptan		Others: • celecoxib • fluvastatin • naproxen • phenytoin • rosiglitazone • sulfamethoxazole • tamoxifen • tolbutamide • torsemide • warfarin		Others: • aripiprazole • codeine • dextromethorphan • duloxetine • flecainide • mexiletine • ondansetron • tamoxifen • tramadol • venlafaxine		Immune modulators: • cyclosporine • tacrolimus (FK506)
						HIV antivirals: • indinavir • ritonavir • saquinavir
						Prokinetics: • cisapride
						Antihistamines: • astemizole • chlorpheniramine
						Calcium channel blockers: • amlodipine • diltiazem • felodipine • nifedipine • nisoldipine • nitrendipine • verapamil
						HMG CoA reducutase

							inhibitors: • atorvastatin • lovastatin • NOT pravastatin • NOT rosuvastatin • simvastatin
							Others: • aripiprazole • boceprevir • buspirone • gleevec • haloperidol • methadone • pimozide • quinine • sildenafil • tamoxifen • telaprevir • trazodone • vincristine
INHIBITORS							
1A2	**2B6**	**2C8**	**2C9**	**2C19**	**2D6**	**2E1**	**3A4,5,7**
Weak inhibitors: • cimetidine	thiotepa ticlopidine	Strong inhibitors: • gemfibrozil	Strong inhibitors: • fluconazole	fluoxetine fluvoxamine ketoconazole lansoprazole omeprazole ticlopidine	Strong inhibitors: • bupropion • fluoxetine • paroxetine • quinidine	disulfiram	Strong inhibitors: • indinavir • nelfinavir • ritonavir • clarithromycin • itraconazole • ketoconazole • nefazodone
Other inhibitors: • fluoroquinolones		Other inhibitors: • montelukast	Moderate inhibitors: • amiodarone		Moderate inhibitors: • duloxetine		Moderate inhibitors: • erythromycin

• fluvoxamine • ticlopidine							• grapefruit juice • verapamil • diltiazem
			Other inhibitors: • isoniazid		Weak inhibitors: • amiodarone • cimetidine		Weak inhibitors: • cimetidine
					Other inhibitors: • chlorpheniramine • clomipramine • doxepin • haloperidol • methadone • mibefradil • ritonavir		Other inhibitors: • amiodarone • NOT azithromycin • fluvoxamine • mibefradil • troleandomycin
INDUCERS							
1A2	**2B6**	**2C8**	**2C9**	**2C19**	**2D6**	**2E1**	**3A4,5,7**
tobacco	phenobarbital		rifampin			ethanol	carbamazepine
	phenytoin		secobarbital			isoniazid	phenobarbital
	rifampin						phenytoin
							pioglitazone
							rifabutin
							rifampin
							St. John's wort
							troglitazone

http://medicine.iupui.edu/clinpharm/ddis/ClinicalTable.aspx

APPENDIX III – NY Heart Association Classifications

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Appendix IV – NCI CTCAE Version 4.03

All toxicities in this protocol will be graded according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0, which can be found at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix V – History of Changes

Original Protocol as Approved by Scientific Review Committee – June 7, 2011			
Update 1 (1st version submitted to IRB) – June 28, 2011 *Scientific Review Committee Approval: June 29, 2011*			
Section (s) Affected	***Prior Version***	***Update 1 Changes***	***Rationale***
Synopsis, Schema, 1.5.5 (Rationale for current study treatment doses), 5.1 (Treatment Overview), 5.2.2 (Pazopanib administration), 5.3.1 & Table 1, (Phase I dose escalation schema), 8.2 (Drug Information: pazopanib)	Starting dose for pazopanib was to be 600 mg.	Revises starting dose for pazopanib to be 400 mg and adjusts dose escalations and de-escalations accordingly; indicates that if cohort Level 2 (pazopanib = 800 mg) is too toxic, an additional cohort (pazopanib 600 mg) may be added upon DMC review and approval.	Upon review, the study collaborators (NCCN and GSK) recommended that the starting dose for pazopanib be 400 mg.
Amendment 1 – January 10, 2012 *Scientific Review Committee Approval: February 24, 2012*			
Section (s) Affected	***Prior Version***	***Update 1 Changes***	***Rationale***
Cover-page	1. Dr. Mark Zalupski listed as the local PI for University of Michigan; Dr. Sheetal Kircher listed as a sub-investigator at Northwestern University. 2. No mention of IND status.	1. Replaces Dr. Zalupski with Dr. Kircher as the local PI for University of Michigan and removes Dr. Kircher from the list of sub-investigators at Northwestern. 2. Indicates that study is IND exempt.	Administrative
3.2.12 (Inclusion criteria)	Inclusion criterion indicated that "eligibility of patients receiving any medications or substances known or with potential to affect the activity or pharmacokinetics of temozolomide and/or pazopanib" would be determined by the PI and the Data Monitoring Committee.	Removes "and the Data Monitoring Committee" from the statement.	Although it is understood that any questions regarding eligibility may ultimately be brought to the DMC for review and confirmation, it is not necessary to state this specifically for this criterion only. Thus, it was removed for clarity.

4.0 (Patient Registration)	n/a	Adds a new section 4.4 to describe the procedures for notifying the study supporter (NCCN) when a new subject is registered to the study.	Administrative – per request from NCCN.
8.2.9 (Availability of pazopanib)	Ordering instructions not included in drug procurement section.	Adds contact information and details to be included when ordering drug supply.	Administrative
10.3 (Reporting of SAEs)	Gave timeframes and indicated that SAEs would be reported to the FDA as required for IND studies.	Removes reporting to FDA since it was determined that the study is IND exempt.	Administrative/clarity.
Amendment 2 – October 10, 2012 *Scientific Review Committee Approval – October 17, 2012* *Updated Amendment SRC approved on February 6, 2013*			
Section(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
Cover-page	n/a	Adds Dr. E. Gabriela Chiorean (University of Washington) as a sub-investigator/participating site. Adds Dr. Hidayatullah Munshi as a sub-investigator. Removes Lisa Marshall, RN as a sub-investigator.	Administrative
Section 1.4.1	Pazopanib has been approved by the FDA for treatment of metastatic renal cell carcinoma (RCC).	Adds the following: In 2009, pazopanib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with advanced RCC [Votrient PI, 2012]. In 2012, pazopanib was FDA-approved for the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy. However, the efficacy of pazopanib for the treatment of patients with adipocytic soft tissue sarcoma or gastrointestinal stromal tumors has not been demonstrated [Votrient PI, 2012].	The additional language provides more data on the FDA approval of pazopanib.
Synopsis and 3.2 (inclusion criteria)	Patients may have 0-2 prior therapies.	Patients may have 0-3 prior therapies.	Broadens the patient population.
Section 5.5.5 (Antihyperlipidemic Agents), 5.6 (Concomitant	n/a	Adds information about pazoparib standards for concomitant medications and that using it with simvastatin	Added to fully disclose all information about concomitant medications.

Medications) & 8.2.8 (Incompatibilities)		increases the risk of ALT elevations.	
5.7.2 (Treatment rules for toxicity for phase II)	Stated that "regardless of the reason for delay" the maximum permitted interval for delay was 28 days.	Revises the allowed delay timeframe to specify 28 days for *treatment related* delays and up to 8 weeks for *non-treatment-related* delays.	This clarification is necessary to allow patients who are responding to treatment to continue to receive treatment following necessary delays longer than 28 days for non-study-related issues.
Table 7 - Summary of Hematologic & Non-Hematologic Dose Modifications for Pazopanib	Hepatic Dysfunction table	Replaces the table for hepatic dysfunction provided by the NCCN.	Changes requested by the NCCN & provided more specific dose modifications related to liver enzyme changes with or without hyperbiliruinemia
Appendix II - - Substrates, Inhibitors, and Inducers of CYP3A4	CYP3A4,5,7 Substrates table	Replaces previous table with a table that includes the following: CYP3A4,5,7 Substrates CYP3A4,5,7 Inducers CYP3A4,5,7 Inhibitors Also adds table for substrates of CYP2B6, CYP2C8, and CYP2C9	The original version included only a portion of the information. The additions should have been included, but were inadvertently omitted. Also provides updated/corrected website reference.
Amendment 3 – May 15, 2013 *Scientific Review Committee Approval – May 29, 2013*			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Cover-page	Listed Dr. Sheetal Kircher as the local PI for University of Michigan.	Replaces Dr. Kircher with Dr. Mark Zapulski at U of M. Adds Dr. Kircher to the list of sub-investigators at Northwestern.	Administrative – Dr. Kircher has left U of M and is now back at Northwestern.
Cover-page	Listed Dr. Hidayatullah Munshi as a sub-investigator at Northwestern.	Removes. Dr. Munshi.	Dr. Munshi is no longer an active member of the GI research team at Northwestern.
Section 3.2 (Inclusion Criteria)	Allowed patients with 0-3 prior therapies.	Expands inclusion criteria to allow patients with **0-4** prior therapies.	Changed in order to increase accrual to the study.
Section 3.3 (Exclusion Criteria)	Excluded patients taking immunosuppressive medications (including systemic corticosteroids unless	Removes this exclusion criterion entirely.	It will be up to the discretion of the treating investigator to determine whether or not any

	used for adrenal replacement), appetite stimulants, acute therapy for asthma or acute bronchitis exacerbation, or antiemetics.		concomitant medications are a concern for interactions with study therapy.
Section 5.7.4 (Dose modifications for toxicity) – Table 7: Table 7: Summary of Hematologic & Non-Hematologic Dose Modifications for Pazopanib	In the event of a 1st occurrence of liver event interruption, protocol stated to contact GSK Medical Monitor regarding possible re-challenge. Gives criteria to be met for re-treatment.	Revises this to state: If the potential benefit for reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose and measure serum liver tests weekly for 8 weeks. Criteria to be met for re-treatment remain the same. Adds a footnote directing investigators to the IB for further information.	Changed per request from GSK and NCCN.
Sections 7.0 (Study Parameters) & 7.2.2 (Study Visits)	Perfusion CT required for all subjects.	Perfusion CT required only as feasible.	Some participating sites do not have perfusion CT capability. Since this is a secondary endpoint, this is not required to meet the study objectives.
Sections 7.0 (Study Parameters) & 7.2.2 (Study Visits)	Required labs, physical exam, and toxicity assessment on days 1 and 15 of all cycles after cycle 1 (indefinitely).	Revises schedule to require these *on both days* only for cycles 2 and 3. Starting with cycle 4 and beyond, physical exam and toxicity assessment may be done only on day 1 of each cycle. Labs will still be required on days 1 and 15, but day 15 labs may be drawn at a local facility, *per treating investigator's discretion*.	This was changed to accommodate feasibility for patients who are on treatment and tolerating it well for several cycles.
Section 8.2.8 (Pazopanib incompatibilities)	n/a	Adds language referring investigators to thecurrent IB for detailed information about interactions with simvastatin, CYP3A4 inhibitors, impact on drugs eliminated through UGT1A1 and OATP1B1, and the use of pazopanib with drugs known to increase the gastric	Administrative

		pH. Also refers them to an updated Appendix.	
Section 10.3 (Reporting of SAEs)	n/a	Adds language referring investigators to Table 7 in the protocol (Summary of Hematologic & Non-Hematologic Dose Modifications for Pazopanib) for additional information regarding toxicities that should be reported as SAEs.	Administrative
Section 11.0 (Records to Be Kept)	Stated that "Treatment and Summary eCRFs" were to be completed at the end of study therapy.	Clarifies that "Treatment eCRF" should be completed at the end of each cycle of study therapy.	Administrative
Appendix II	Outdated and incomplete list of P450 drug interactions.	Updates the entire listing to include an expanded table of inducers, inhibitors, and substrates. Updates the website link for additional/current information.	Administrative
Amendment 4 – October 16, 2013 *Scientific Review Committee Approval – October 22, 2013*			
Section (s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Throughout	n/a	Updates numbering of appendices and website links for the NU CRO & the NCI's CTCAE v. 4.0.	Administrative
Section 3.2 (Inclusion Criteria)	Baseline parameters require AST/ALT ≤ 5 x ULN.	Changed to AST/ALT ≤ 2.5 x ULN.	Changed to match grantor requirements and to
Section 4.0 (Patient Registration)	Contained old standard language for registering patients via NOTIS.	Updates language to outline new procedures and requirements for reserving slots on a cohort, registering patients in NOTIS, and confirming eligibility for phase I vs. phase II patients. Also clarifies the procedure for notifying NCCN of new enrollments.	Administrative – NU is implementing new study-specific procedures and plans.

Section 5.2 (Study Drug Administration) & Section 7.1 Table 10: Schedule of Events	n/a	Adds reference to the drug diary that patients will be asked to complete and that study teams will be required to collect each cycle.	A drug diary was already in use but procedures were not explicitly stated in the protocol.
Section 5.3.1 Table 1: Phase I Dose Escalation Schema	Cohort -1 included temozolomide at a dose of 150 mg/m^2 q day PO and pazopanib at a dose of 200 mg q day PO.	Revises dosing for ohort -1 and -2, and adds a cohort -3, as follows: **Level -1:** Temozolomide 100 mg/m^2 + pazopanib 400 mg **Level -2:** Temozolomide 75 mg/m2 + pazopanib 400 mg **Level -3:** Temozolomide 75 mg/m2 + pazopanib 200 mg	Changes made based on review of data from recent patients in conjunction with the Data Monitoring Committee.
5.4.3 (DLT Exclusions)	n/a	Adds the following as an exclusion to the definition of DLT: *Any grade of hypophosphatemia or other metabolic abnormality…unless continued despite maximum supportive care.*	Added to clarify the DLT definition.
Section 5.5 (Supportive Care Guidelines)	n/a	Adds prophylactic treatment with Valtrex 500 mg q day.	This was added given the higher incidence of herpes zoster that has been observed in recent patients (likely due to lymphopenia).
Section 5.6 (Concomitant Medications)	n/a	Adds a specific list of prohibited concomitant medications (previously only referenced in the Appendices).	Added to comply with grantor requirements.

Section 5.7 (Toxicity Management and Dose Modifications – Table 7)	Did not list specific dose modifications for proteinuria, hemorrhage, or prolongation of the QTc interval.	Added specific dose modifications for proteinuria, hemorrhage, and prolongation of the QTc interval. Also modified instructions for hypertension.	Added/revised to comply with grantor requirements and recommendations.
Section 10.3 (Reporting of SAEs), Appendices	Reporting requirements varied based on type of SAE (death of a subject vs. UPIRSO vs. other) and timeframes for reporting to the NU IRB were based on previous policy.	Updates and simplifies SAE reporting language. Requires ALL SAEs to be reported to the QAM within 24 hours of notification. Updates NU IRB reporting timeframes. Adds that the new NU CRO SAE form will be used to report all SAEs.	Administrative and to improve clarity.
Section 11.0 (Records to be Kept)	Contained old standard language.	Updates and simplifies language.	Administrative
Section 12.1 (Pharmacokineticsc)	n/a	Update some processing instructions and details (tube type, centrifugation requirements, and shipping address) for PK samples.	Administrative updates
Appendices	n/a	Adds newly implemented, study and phase-specific monitoring procedures and data submission requirements.	Administrative – NU is implementing new study-specific procedures and plans for each phase of the study to help improve compliance and patient safety.
Amendment 5 – April 15, 2015 *Scientific Review Committee Approval – April 15, 2015*			
Section (s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Study Synopsis & 3.1	n/a	University of Washington	Additional site added
3.1 (Population and Accrual overview)	"Accrual to both phases of the study and assessment of the primary endpoint for the phase II portion is estimated to be completed within approximately **2.5** years."	Revised to "Accrual to both phases of the study and assessment of the primary endpoint for the phase II portion is estimated to be completed within approximately 3-4 years."	Revised to account for Phase I enrolling 9-18 patients

3.2.1 (Inclusion Criteria)	"Patients must have histologically confirmed islet cell carcinoma (PNET) not amenable to surgical resection."	Revise to "Patients must have histologically confirmed **well – differentiated** islet cell carcinoma (PNET) not amenable to surgical resection."	Revised to clarify patient eligibility
3.2.3.2 (Inclusion Criteria)	n/a	Revised to add "Prior temozolomide is permitted."	Revised to clarify patient eligibility
5.3.1(Dose escalation schema)	Phase I Level-3 cohort at Temozolomide 75 mg/m^2 per day p.o. Days 1-7 & 15-21 and Pazopanib 200 mg per day p.o. Days 1-28	Revised to add dose level -4: Temozolomide 50 mg/m^2 per day p.o. Days 1-7 & 15-21 and Pazopanib 400 mg per day p.o. Days 1-28	Revision of dose levels after DMC review of data
5.3.1(Dose escalation schema)	n/a	Dose level -3 revised to: Temozolomide 50 mg/m2 per day p.o. Days 1-7 & 15-21 and Pazopanib 200 mg per day p.o. Days 1-28	Addition of reduced dose level after DMC review of data
5.3.1(Dose escalation schema)	n/a	Footnote 1 revised to add " If DLTs occur at dose Level -3, then a cohort Level -4 may be opened as above."	Revised to accommodate dose level -4
5.4.2 (DLT definitions)	n/a	Revised to "Inability to complete Cycle 1 due to toxicity **related to study drug**."	Clarification
5.4.3.3 (DLT Exclusions)	Any grade of hypophosphatemia, or other metabolic abnormality will NOT be considered a DLT, unless continued despite maximum supportive care."	Revised to "Any **grade non-hematologic toxicity** will NOT be considered a DLT unless continued despite maximum supportive care **beyond the 2 week delay allowed in section 5.4.2.5**. (see 5.5.8)."	Clarification
5.4.3.4 (DLT Exclusions)	n/a	Added "Grade 3 or higher non-hematologic toxicity will be considered a DLT EXCEPT in cases where the event existed at baseline. In	Clarification

		these cases, toxicity needs to increase in severity by 2 grades per CTCAE v. 4.0 before it is considered a DLT. "	
4.4.4.2.2 (DLT Terminology Clarifications)	"Electrolyte supplementation for hypophosphatemia"	Revised to "Electrolyte supplementation for low electrolytes"	Correction
5.5.11 (Anti-viral Agents)	"Patients should be treated with prophylactic Valtrex (valacyclovir hydrochloride) 500 mg daily".	Revised to "**It is recommended that patients** be treated with prophylactic Valtrex (valacyclovir hydrochloride) 500 mg daily, **however final decisions regarding this will be up to treating physician discretion."**	Clarification
5.7.2 (Treatment rules for toxicity for phase II)	Treatment rules for toxicity for phase II	Section name revised to "Treatment rules for toxicity for phase I AFTER the DLT period"	Clarification
5.7.3 (Patient dose level adjustments for toxicity)	"Discontinue"	Revised to "↓ 50 mg/m^2 per day p.o"	Addition of reduced dose level adjustment for toxicity after DMC review of data
5.7.3 (Patient dose level adjustments for toxicity)	n/a	Added additional reduced dose level adjustment for toxicity for Temozolomide. "Level (-3) ↓50mg/m2 per day p.o., Dose Modification, Discontinue"	Addition of reduced dose level adjustment for toxicity after DMC review of data
5.7.4.2 (Table 7: Summary of Hematologic & Non-Hematologic Dose Modifications for Pazopanib)	n/a	Revised to include "Diarrhea **(despite optimal supportive care)"**	Clarification
5.8 (Duration of Therapy)	n/a	Added "It is recommended that temozolomide treatment be discontinued after 1 year, due to risk of Myelodysplastic syndrome (MDS). Patients can continue on Pazopanib. If patient is receiving benefit from combination treatment after one year, it is up to the treating physician's discretion whether or not the patient continues	Clarification

		Temozolomide..”	
5.8.2 (Unacceptable toxicity)	“Thrombotic events, including cerebrovascular accident, myocardial infarction or thrombotic event requiring anticoagulation. Patients with superficial thrombophlebitis, superficial venous thrombosis, or portal venous thrombosis not requiring anticoagulation may remain on therapy at the discretion of the treating physician. “	Deleted	Anticoagulation allowed on study
5.9 (Follow-up)	After treatment discontinuation, patients will be followed every **3** months in clinic and/or via phone for survival follow-up	After treatment discontinuation, patients will be followed every **6** months **for 1 year** in clinic and/or via phone for survival follow-up.	Clarification
9.4 (Replacement Policy)	“Patients will not be replaced if taken off study due to toxicity.”	Revised to “Patients will not be replaced if taken off study due to toxicity**, however, if a patient is taken off study during their DLT period for a reason unrelated to study treatment, another patient may be added to that cohort.”**	

Amendment 6 – August 4, 2016

Section (s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
Cover page Section 3.1	Site PI for Fox Chase Center was Steven J.Cohen,MD	New Site PI for Fox Chase Center is Crystal Denlinger,MD	***.Change in site PI***
Throughout: Synopsis; Schema; Section 1.5.4; 5.3.2; 8.2.5; 12.1,8.1.5	N/A	**Language inserted:** *Note: The MTD has been identified at dose level -2 (75 mg/m2 per day p.o. days 1-7 and 15-21 of Temozolomide and 400 mg per day p.o. days 1-28 of Pazopanib.* *As of 12.15.15 , all patients moving forward will be treated at this*	***MTD has been established for this combination.***

		dose	
Section 1.4.2 Safety of pazopanib Section 8.2.10 Side effects of pazopanib	Previous safety information	**Language added:** *Note: please refer to updated IB version 14 dated 01.07.16 for more information*.	***Per updated IB***
Section 1.5.6 Phase I summary	N/A	**New Section added: Phase I summary:** language stating phase I treatment and establishment of MTD, which will serve as the dose for patients, moving forward.	***Per study design and establishment of MTD***
Throughout	Functional CT to be done for all patients, in sites where it is feasible	The functional CT has been removed completely from the study. All descriptions and language pertaining to fCT has been removed in appropriate sections. **Exploratory objective** "Examine the relationship between tumor blood flow, as measured by perfusion functional computed tomography (fCT), and overall response " has been removed	***The fCT wasn't required for Phase I. Some (3/4) affiliate sites stated they could not afford this component. Therefore, it would not be in best interest to only have this done at 1 participating site. Monetary resources saved was used towards PK analysis***
Section 3.1	Northwestern Memorial Hospital	Northwestern Medical group	***Per new NU policy***
Section 3.3.3	Patients with uncontrolled hyperlipidemia (total cholesterol >350 or	This exclusion criteria removed	***The study is not performing lipid profile tests at baseline.***

	triglycerides>300) are NOT eligible for participation		
Section4.0	Previous patient registration details	Updated with current language from NU template	***Per current NU template***
Section 5.7.3	Section heading: Patient dose level adjustments for toxicity	Section heading: Patient dose level adjustments for toxicity in **Phase II**	***For clarity***
Section 7.0 Study procedures table	Only a +/-1 day window for assessments	Appropriate windows have been inserted for treatment, assessments and imaging. Footnote 7, 8 and 21 modified to reflect this.	***Treatment windows inserted for logistical convenience and to minimize protocol deviations***
Section 6.1.2.2; 7.0,12.1,	PK sample collection time points listed without windows, for PK cohort. Two samples of 3 ml each were being drawn around the same time for Day 1 24 hour post-dose and Day 2) sample pre-dose.	Windows inserted for PK sample collection time points e.g 10mins(+/-5 min) Language inserted to state that these two samples may be clubbed into one 3ml sample provided that the study drug administration of Day 2 is done within an hour of drawing the sample. If it is delayed more than an hour then another 3 ml sample will have to be drawn. Reference has been made to this wherever appropriate. Laboratory manual updated as well.	***For logistical convenience and in order to minimize protocol deviations.***

Section 7.0 Study Procedures table	Has separate correlative studies section(PK cohort only)	Deleted "(PK cohort only)" Modified to cover both PK and Phase II Footnotes 14, 15 and 17 updated.	***For clarity***
Section 7.1 Schedule of Events Footnote 7; section 6.2.1;	Imaging with CT or MRI (whichever test is used for a particular patient at baseline should be the same that is used throughout for disease assessment). Response will be assessed every 2 cycles (8 weeks +/- 7 days).	Added: After 1 year of protocol therapy, patients may switch to imaging every 12 weeks (+/-7 days) per treating physician discretion.	*This is for patients being treated beyond 1 year, so that Temozolomide safety can be monitored and at the same time radiation exposure will be decreased. Hence, it will be done per treating physician's discretion.*
Section 7.2. Description of study procedures by visit	Each visit explained in detail	Deleted this section. All necessary details are present in the Study procedures table(section 7.0,Table 10) and accompanying footnotes. All references to this section have been removed	*This is to be in alignment with the current NU template.*

Section 8.2.9 Availability of pazopanib	Drug supply from GLAXO SMITHKINE(GSK): clinical supply	Drug supply from NOVARTIS: commercial supply with auxiliary label. Other details added	Drug supply availability changed companies.
Section 8.2.6 Preparation of pazopanib	Details about previous'clinical supply'only	Added details about 'commercial supply' that is provided by Novartis Added note: *Sites will start using the commercial supply when they finish the previous clinical supply).*	***Updated per information from Novartis***
Section 8.2.9	All requests for study drug should be submitted via email to Kamal Bhatt (kamalnaya.H.Bhatt@gsk.com) and Donna Scharff (Scharff@nccn.org) and should include the following information:	All requests for study drug should be submitted via email to Desiree Hiram (desiree.hiraman@novartis.com), Lixian Jin (lixian.jin@novartis.com), and Donna Scharff (Scharff@nccn.org) and should include the following information:	***Per Novartis updated contact information***
Section 8.2.10.3	Few uncommen side effects listed	Atrial fibrillation added	***Per memo received from sponsor stating this was thought to be 'possibly related' to pazopanib.*** (*This event occurred in a patient being treated with pazopanib, during the course of a clinical study [115210])*
Section 10.2.1 Adverse Event	AE definition	Additional language added	***Per updated NU protocol template***
Section 10.2.2	AE graded by NCT CTCAE version 4.0	Version updated to 4.03. Additional grading	***Per updated***

Severity of AEs; Section 5.7.4.2 Table 7(dose modification for pazopanib)		information inserted in case CTCAE not available	***NU protocol template***
Section 10.2.3 Serious Adverse Event	Previous standard SAE criteria	Updated with Novartis specifications/language	***Per sponsor Novartis***
Section 10.3.2	Previous NU template language Note : SAE to be reported to NU IRB within 10 working days	Updated NU template language. Note : SAE to be reported to NU IRB within 5 working days	***Per updated NU protocol template***
Section 10.3.3; 10.3.4 Reporting to Novartis and NCCN	Information regarding Reporting to GSK and NCCN	Updated to : Section 10.3.3: Reporting to Novartis Section 10.3.4: Reporting to NCCN	***Per new information from Novartis***
Section 11. Data submission	Previous NU template language	Replaced with current NU template language Removed previous data submission guidelines from appendix since it now available as stand-alone document	***Per current NU template requirements.***
Section 12.1.3 Processing of PK sample	Transfer the plasma to 2 polypropylene tubes (approximately 0.75 mL per tube).	Transfer the plasma to 2 polypropylene tubes (a primary and a back-up tube, approximately 0.75 mL per tube).	***For clarity, based on information received from laboratory personnel.***

Section 12.1.4 Shipment of PK samples	Details about shipment.	Added: ***Please refer to laboratory manual for further details (available as stand-alone document)***	***As new laboratory manual has been developed***
Appendices	Previous list of appendix	Numbering has been changed. Appendix with Data submission guidelines and Data safety Monitoring Plan and Slot reservation Procedure has been removed. These are now available as stand-alone documents.	***Per changes made to the protocol and per new NU template requirements.***
Throughout	Temozolomide spelling incorrect in some sections.Spelt as 'Temozolamide'	Spelling corrected throughout to Temozolomide	***Correction of error***
Amendment 7 – June 20, 2017			
Section (s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
Protocol title page and section 3.1	Dr.Halla Nimeri was the Principal Investigator	Dr.Nimeri is replaced by Dr.Sheetal M. Kircher as Principal Investigator	***Dr.Nimeri leaving NU and handing over study to Dr.Kircher.***
Section 9.5 Statement of feasibility	Statement of feasibility with Dr.Nimeri's details.	Added statement: "As of June 2017, she is being replaced by Dr.Sheetal Kircher as Principal Investigator of this study."	***Dr.Nimeri leaving NU and handing over study to Dr.Kircher.***

Amendment 8– January 24 , 2018			
Section 7: Study procedures table (Footnote 7)	Survival follow-up was stated as "every 3 months until death"	Updated to "every 6 months for 1 year in clinic and/or via phone"	***Correction of discrepancy. (to be in alignment with information in section 5.9)***
Section 7: Study procedures table (Footnote 23)	All patients were required to do D15 labs till end of treatment, even if they discontinued Temozolamide after 1 year of treatment.	For patients who discontinue Temozolamide after 1 year of treatmnet, for them the D15 laboratory tests (WBC, ANC, hemoglobin, platelet; Electrolytes & renal function tests [Na, K, Cl, CO2, BUN, Creatinine, Mg, Phos]; Liver function tests [AST, ALT, alk phos, total bilirubin]) are not required.	***To save patients from undergoing additional testing that is not required from a safety standpoint.***
Section 8.2.9 Pazopanib supply	One of the contact s for drug order was Lixian Jin	Update: Removed Lixian Jin and added Quincy Chau (quincy.chau@novartis.com)	***Lixian Jin is no longer part of the specific Votrient (Pazopanib) program.***

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