A Phase II Study of Pazopanib with Oral Topotecan in Patients with Metastatic and Non-resectable Soft Tissue and Bone Sarcomas

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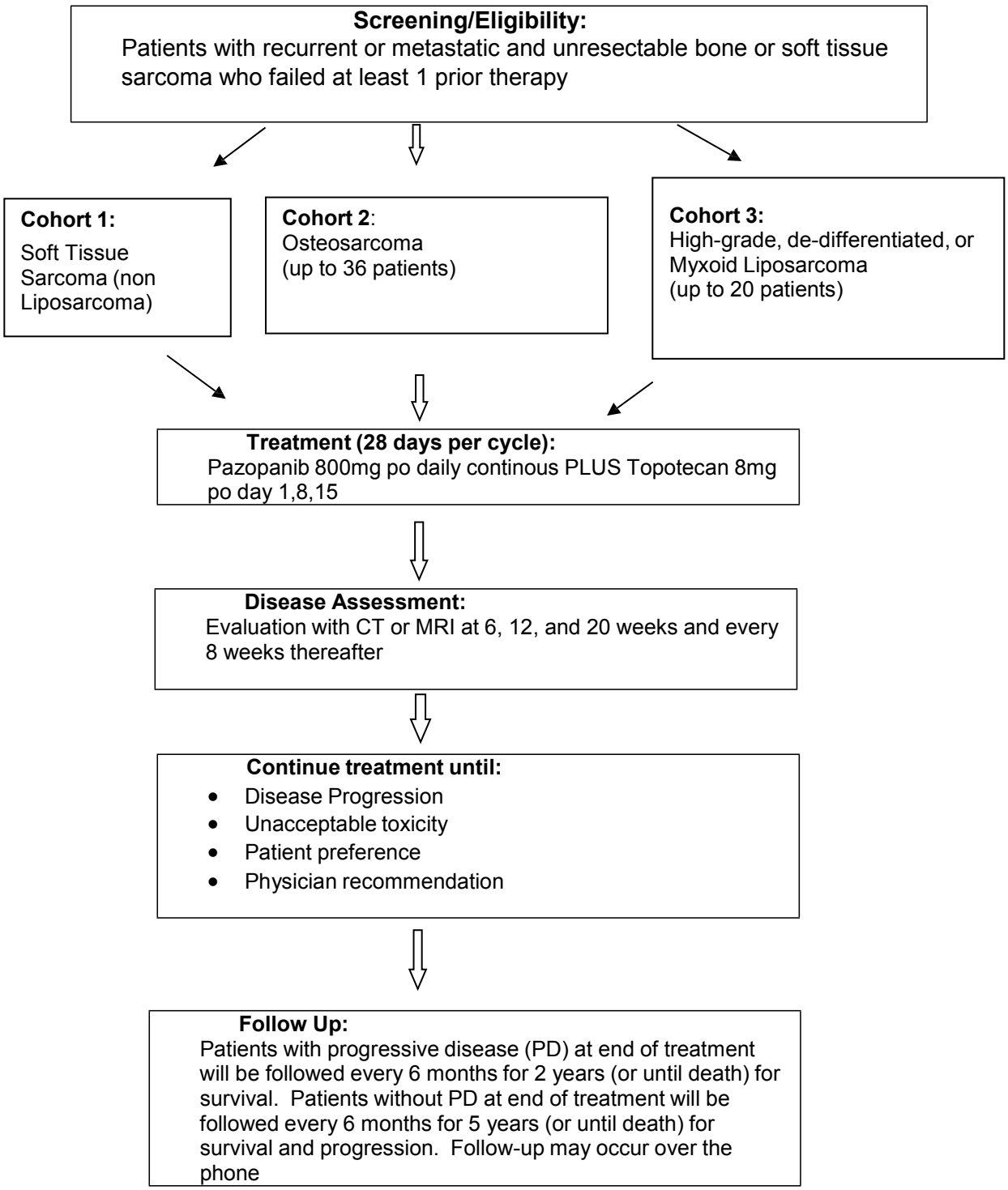
LIST OF ABBREVIATIONS

ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HFSR	Hand-foot-skin reaction
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MAPK	Mitogen Activated Protein Kinase
OS	Overall Survival
PD	Progressive Disease
PDGFR-α	Platelet Derived Growth Factor Receptor-alpha
PDGFR-β	Platelet Derived Growth Factor Receptor-beta
PFR	Progression-free rate
PO	*per oris*, oral
PR	Partial Response
PS	Performance Status
PTT	Partial thromboplastin time
QD	*quaque die*, once daily
RAF	Rapidly Accelerated Fibrosarcoma
RAS	Rat sarcoma
RECIST	Response Evaluation Criteria for Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
STS	Soft Tissue Sarcoma
TK	Tyrosine Kinase
TTP	Time to Progression
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

STUDY SCHEMA



STUDY SUMMARY	
Title	A Phase II Study of Pazopanib with Oral Topotecan in Unresectable or Metastatic Soft Tissue and Bone Sarcomas
Short Title	Pazopanib and Oral Topotecan in Soft Tissue and Bone Sarcomas
Version	06.26.20 Amendment 13
Study Design	Multicenter, phase II trial designed to estimate progression-free rate at week 12 of combination pazopanib and topotecan in patients with soft tissue sarcoma (STS), as well as provide preliminary evidence of benefit for patients with osteosarcoma or liposarcoma. This is a single arm two-stage Simon optimum Phase II study of pazopanib and topotecan with progression-free rate at 12 weeks as the primary outcome. The historic PD free rate at 12 weeks for single agent pazopanib is 55%. To detect a 20% improvement (an 11% absolute improvement) with the combination of pazopanib and topotecan in a single-arm two-stage optimum design and a one-tailed exact binomial p-value, a total of 92 evaluable patients is required to detect 55% vs 66% with 80% power and an alpha level of 10%. If 32 out of the first 55 patients are alive and progression free at 12 weeks, the trial may enroll up to 108 patients in order to acquire a total of 92 evaluable patients. At that time, if 56 or more out of 92 are alive and progression-free at 12 weeks, then the trial will conclude that the true 12 week PFS rate is at least 66%. There is a 63% probability of terminating the study after the first stage when the true rate is 55%. Up to 36 patients with osteosarcoma and 20 patients with liposarcoma will be enrolled to obtain exploratory information for patients with these two histologies. The DSMC reviewed the interim analysis data on 1/11/2017, and has approved cohort 1 to reopen to 96 total patients (to obtain 92 evaluable patients). In addition, based on the percentage of non-evaluable patients during the interim analysis, it was determined that a total of 108 patients would most likely need to be enrolled in order to obtain 92 evaluable patients. The remaining slots have been equally divided in 5 ways among the sites, with an expiration date of May 12, 2017. Status of accrual will be reassessed at that time, and the remaining slots will be divided accordingly.
Study Center(s)	Lead Institution: Robert H. Lurie Comprehensive Cancer Center of Northwestern University Participating Sites: University of Wisconsin, Mayo Clinic (Rochester, MN), Mayo Clinic (Phoenix, AZ), Mayo Clinic (Jacksonville, FL), Washington University, University of Minnesota, University of Iowa
Objectives	Primary Objective: Determine progression-free rate (PFR) at 12 weeks for patients with STS treated with Pazopanib and Oral Topotecan Secondary Objectives: 1) Determine the overall response rate (CR + PR) 2) Determine the clinical benefit rate (CR + PR + SD)

	4) Determine median PFR 5) Assess safety and tolerability 6) Estimate the PFR in patients with osteosarcoma 7) Estimate the PFR in patients with liposarcoma Exploratory objectives: **For Cohort 1 and 3** Quantify Cell-free circulating tumor DNA (ctDNA) at each time point, and correlate these results with demographic, diagnostic, treatment, and outcomes data. **For Cohort 2** Evaluate the correlation of PFR and OS to levels of sVEGFR2 and PIGF
Sample Size	A total of 164 patients may be enrolled including 108 patients with STS (to acquire 92 evaluable patients), and up to 36 patients with osteosarcoma and 20 patients with liposarcoma. The DMC reviewed the interim analysis data on 1/11/2017, and has approved cohort 1 to reopen to 96 total patients (to obtain 92 evaluable patients). In addition, based on the percentage of non-evaluable patients during the interim analysis, it was determined that a total of 108 patients would most likely need to be enrolled in order to obtain 92 evaluable patients.
Diagnosis & Key Eligibility Criteria	Patients with histologically confirmed diagnosis of metastatic or locally advanced unresectable: a. soft tissue sarcomas (non-liposarcoma) b. osteosarcoma c. liposarcoma- high grade, de-differentiated, or myxoid (exploratory) Patients must have measurable disease within 4 weeks prior to registration by RECIST 1.1 Patients must have had a minimum of 0 and a maximum of 4 prior chemotherapy regimens for recurrent/metastatic disease deetermined by cohort assignment. It will be up to the investigator to determine what constitutes a “regimen” in each case. The last dose of systemic therapy must have been given at least 4 weeks prior to initiation of therapy. Patients receiving BCNU or mitomycin C must have received their last dose at least 6 weeks prior to initiation of therapy.
Treatment Plan	Patients will be treated with Pazopanib 800mg oral daily, plus Topotecan 8mg orally day 1, 8, 15 every 28 days until disease progression or unacceptable toxicity occurs, or until discontinuation per patient preference or physician recommendation.
Statistical Methodology	PFR and OS will be estimated using Kaplan-Meier methods for each histologic group (STS, osteoscaroma, and liposarcoma). Response rates will be summarized by the observed proportion of patients with response, along with a 95% confidence interval. Toxicities will be tabulated and summarized by the number of patients experiencing each toxicity. A formal hypothesis test for the median PFR of the STS patients is planned; no formal hypothesis test is planned for the other two histologic groups.

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Soft tissue and Bone Sarcoma- disease background and current treatment strategies

Soft Tissue Sarcomas (STS) are malignant tumors arising from mesenchymal tissue in the extremities, trunk, retroperitoneum, or head and neck. STS comprise a heterogeneous group of tumors, each with distinct histological, cytological, and molecular features.[1] It is estimated that in the United States in 2014, there will be 12,020 new cases and 4,740 deaths from STS.[2] Treatment of early stage disease consists of surgical resection with or without adjuvant radiation therapy for select patients.[3-5] The data surrounding use of adjuvant chemotherapy is conflicting, as some studies suggest an improvement in disease free survival, with little or no improvement in overall survival.[6-8] Adjuvant therapy is often utilized in chemosensitive subtypes, such as rhabdomyosarcoma, osteosarcoma, and Ewing sarcoma. Despite a multimodality approach, development of distant metastases remains high, with 30-60% of patients developing advanced disease.

For advanced disease, there is an established clinical benefit from chemotherapy yet prognosis remains poor and 5 year overall survival rates remain less than 20%.[9] The median survival time for patients with metastatic disease is 12 months.10 Current chemotherapy options consist of single agent or combination doxorubicin, ifosfamide, dacarbazine, or gemcitabine. Therapy is often limited by substantial toxic effects and patients often relapse despite aggressive treatment. For most patients, the goal of therapy is palliative to reduce tumor size, tumor-related symptoms, and improve quality of life. A complete response to therapy is rare and the factors predicting response to chemotherapy are not the same as those that impact overall survival.[10]
Most patient develop progressive disease quickly and tumors become resistant to therapy within months. There are limited options available for subsequent treatment, therefore novel therapeutic strategies are needed in this area.

1.2 The Role of Angiogenesis in Soft Tissue sarcoma

Angiogenesis is an established mechanism for tumor growth, invasion and development of metastasis in several tumor types[11] and has been recently recognized as an important factor in advanced STS. Although the exact mechanisms for invasion and hematologic spread of sarcomas are not entirely clear, metastatic potential has been associated with degree of vascularization.[12] It has been long established that tumors require neovascularization to maintain growth beyond a certain size.[13] Tumor angiogenesis is largely driven by endothelial formation of new blood vessels from existing vasculature. Regulation of angiogenesis is complex, involving an intricate interplay between endothelial cells, support cells, bone marrow derived stem cells,
and growth factors within the tumor and tumor microenvironment. Under normal circumstances, regulation of angiogenesis is maintained through balance of pro-angiogenic and anti-angiogenic factors. In malignancy driven angiogenesis, the balance is shifted in favor of more pro-angiogenic signaling, often referred to as the angiogenic switch.[13-16]

Tumor angiogenesis is largely regulated through vascular endothelial growth factor (VEGF).[17-19] The VEGF pathway is made up of three receptors (VEGFR- 1, 2, 3) and seven ligands (VEGF A, B, C, D, E, PIGF-1, 2). These ligands bind to their related receptors on endothelial cells resulting in downstream intra-cellular signaling that promotes endothelial growth, migration, and survival outside of the existing vasculature.[20,21] VEGF-A is the key regulator of normal and tumor angiogenesis,[22] however evidence suggests that other pathways such as the platelet derived growth factor (PDGF) play a key role.[23,24] PDGF receptors (PDGFRα and PDGFRβ), are expressed on pericytes and smooth muscle cells, and regulate pericyte differentiation,

recruitment and regulation of tumor stroma, and regulation of vessel stability and vascular survival.[25,26] They can also function as growth factors, leading cells to progress through the cell-cycle and avoid apoptosis.[27-29]

VEGF is expressed in a number of STS[30] and the expression of VEGF has been associated with higher tumor grade, increased ability to metastasize, and decreased overall survival in certain subtypes of sarcoma.[31-34] For example, in leiomyosarcoma, higher VEGF serum levels were associated with worse prognosis and shorter overall survival.[30,35] Platelet derived growth factor (PDGFR) also plays a role in STS angiogenesis and proliferation, and PDGFR- beta expression has been associated with higher grade tumors.[36] Furthermore, hypoxia-inducible factor 1α (HIF-1), an upstream regulator of VEGF, was a predictor of metastatic potential in sarcomas.[37]
HIF-1 was found to be associated collagen modification promoting distant spread and decreased chemo-sensitivity and reduced apoptosis.[38,39] Therefore agents that disrupt tumor angiogenesis have become of interest in STS. Several phase II trials have been done to evaluate anti-angiogenic treatments.[40-43] However, only one phase III trial with Pazopanib has been completed to date.

1.3 Pazopanib in Sarcoma

Pazopanib, a synthetic indazolyl pyrimidine, is a multi-kinase inhibitor of VEGFR-1/2/3, and to a lesser degree PDGFR-α/β, FGFR-1/2, and c-Kit.[44-46] In vivo studies showed dose-dependent tumor growth inhibition in a variety of tumor xenografts by pazopanib (colon, melanoma, prostate, renal, breast, lung).[47] Pazopanib is thought to inhibit angiogenesis through attenuation of VEGFR-2 signaling. Pharmacokinetic analysis revealed that the steady-state concentration (Ctrough) for tumor growth inhibition in vivo was almost equivalent to the concentration required for in vivo inhibition of VEGFR-2 phosphorylation.[47]

Phase I studies determined Pazopanib 800mg daily as the recommended monotherapy dose.[48] There is now plentiful evidence that single agent pazopanib has clinical benefit in advanced sarcomas. The phase II study (VEG20002) evaluated single agent pazopanib in patients with relapsed or refractory soft tissue sarcoma.[43]
Treatment response data are available for 138 patients who received pazopanib 800 mg once daily. Ninety-nine percent of patients had received prior chemotherapy: 35 patients (25%) had received therapy in a (neo)-adjuvant setting, 83 (59%) had received therapy in an advanced setting, and 22 (16%) had received both. The primary endpoint was the progression-free rate, using Response Evaluation Criteria in Solid Tumors (RECIST) at 12 weeks after start of treatment. Patients with leiomyosarcoma, synovial sarcoma and “the other types of sarcoma” strata receiving pazopanib in VEG20002 experienced a 12 week progression free survival rate of ≥ 40%, the pre-defined threshold indicating anti-tumor activity. The liposarcoma stratum did not meet its prespecified endpoint at the end of stage 1 and did not progress to stage 2.

Based on the results of the VEG20002, a Phase III randomized, double blind, placebo controlled study (VEG110727) of pazopanib versus placebo in patients with soft tissue sarcoma (study excluded patients with GIST or liposarcoma) was initiated in 2008.[49] 372 patients were registered and 369 were randomly assigned to receive pazopanib (n=246) or placebo (n=123). Median progression-free survival was 4.6 months (95% CI 3.7–4.8) for pazopanib compared with 1.6 months (0.9–1.8) for placebo (hazard ratio [HR] 0.31, 95% CI 0.24–0.40; p<0.0001). Overall survival was 12.5 months (10.6–14.8) with pazopanib versus 10.7 months (8.7–12.8) with placebo (HR 0.86, 0.67–1.11; p=0.25). The most common adverse events were fatigue (60 in the placebo group [49%] vs 155 in the pazopanib group [65%]), diarrhea (20 [16%] vs 138 [58%]), nausea (34 [28%] vs 129 [54%]), weight loss (25 [20%] vs 115 [48%]),

and hypertension (8 [7%] vs 99 [41%]). The median relative dose intensity was 100% for placebo and 96% for pazopanib. Despite improvement is progression-free survival, response rate was only 6% for patients receiving pazopanib.

1.4 Topotecan in Sarcoma

Camptothecin agents have been evaluated in sarcoma patients for the last decade. This class of agents is attractive because of commercial availability, modest single agent activity, and demonstrated tolerability. Camptothecins exert cytotoxicity by stabilizing the covalent complex between DNA and topoisomerase I, the enzyme which relieves torsional strain of DNA. This stabilization process prevents religation of DNA, and the ensuing collision of the stabilized complex with the advancing replication fork results in double strand breaks and cell death. Topotecan is an orally available camptothecin analogue and has been shown to have activity against HIF1-α.[50]

Phase II studies of topotecan as salvage treatment for patients with soft tissue sarcoma have proven the drug to be well tolerated in anthracycline resistant patients with metastatic STS, and SD as best response has been documented in 38% of patients in one study and disease control rate was documented as 44% of patients in a second study.[51,52] Objective responses were only seen in patients with uterine leiomyosarcoma.[52]

1.5 Rationale for Combination Therapy

Efforts have been made to potentiate the effect of chemotherapy without increasing toxicity. One strategy is to use 'metronomic' dosing which uses lower, more frequent doses of cytotoxic agents rather than the maximum tolerated dose (MTD).[53,54] Continuous exposure to the drugs allows for similar tumor cell death as MTD however patients experience less daily and cumulative toxicity. Metronomic chemotherapy can also overcome drug resistance by shifting the therapeutic target from tumor cells to tumor vasculature as well.[55] Metronomic therapy produces an antiangiogenic effect through continued exposure on tumor endothelial cells,[56,57] blocking mobilization of endothelial progenitor cells from the bone marrow, and restoration of anti-cancer immune response.[55,58] Simultaneously using anti-angiogenics with chemotherapy provides synergistic effects and improved clinical outcomes. There is now preclinical and clinical evidence that adding antiangiogenic agents to metronomic chemotherapy enhances anti-tumor and antiangiogenic effects.[59-61] Therefore the combination of metronomic topotecan and pazopanib has become of interest. The theory for improved activity of this combination is based on targeting both the existing endothelial cells and bone marrow derived precursors, in addition to inhibition of HIF-1 alpha and induction of DNA damage by topotecan.

1.6 Pre-clinical and Clinical Evidence for Topotecan and Pazopanib in Solid Tumors

Support for this combination was demonstrated in mouse models of aggressive pediatric solid tumors.[59] Results confirmed that metronomic administration of topotecan and pazopanib produced a statistically significant delay in tumor growth and was able to reduced tumor size in sarcoma models. Combination therapy yielded significant antitumor activity and significant improvement in survival compared to the single agents in all models. Furthermore, reduction in circulating endothelial cells and tumor microvessel density correlated with tumor response, confirming antiangiogenic activity of treatments. Pharmacokinetic studies did not reveal any drug–drug interactions between the two drugs.

Based on this evidence, oral topotecan and pazopanib was evaluated in patients with advanced solid tumors as a phase I regimen. A two-stage, two-arm, phase I study of pazopanib and oral topotecan was performed in patients with advanced solid tumors to evaluate 2 different schedules of oral topotecan (weekly or daily x5 days) in combination with daily pazopanib.[62] Part 1 of this study evaluated the effect of pazopanib on the bioavailability of topotecan and Part 2 determined the maximum tolerated dose (MTD) of combination regimens. Treatment consisted of daily pazopanib with either once weekly topotecan in Part 2A or daily topotecan for five consecutive days in Part 2B. The bioavailability and safety results of daily pazopanib combined with weekly oral topotecan (Part2A) were presented at the annual ASCO meeting in 2013.

Data is available for 28 patients that received at least one dose of therapy- 7 patients in Part1; 21 patients in Part 2 (4 STS, 2 colorectal cancer, 2 breast cancer, 1 renal cell carcinoma, 5 ovarian cancer, 2 osteosarcoma, and 5 classified as “other”). Pharmacokinetic analysis revealed that topotecan AUC0-∞ increased 1.58-fold (90%CI: 1.09–1.29) and Cmax increased 1.78-fold (90%CI: 1.08-2.92) when given with pazopanib compared to single administration (n=7). However, neither of these parameters were increased for pazopanib when given with topotecan.

During, the dose escalation phase (Part2A), Topotecan was increased from 4mg to 10mg (days 1, 8, 15) and Pazopanib was increased from 400mg to 800mg (q28 days). Three dose-limiting toxicities (DLTs) were experienced: grade 3 hand-foot- syndrome, diarrhea and neutropenia. Two of 6 patients had DLT with the combination of pazopanib 800 mg/topotecan 10 mg thereby exceeding the MTD. The most frequent treatment-related toxicities were grade 3 anemia (3/28), leukocytopenia, neutropenia and fatigue (2/28 each). There were cases of severe and fatal hepatic failure (n=1) and hemorrhage (n=1), requiring that these parameters be monitored closely. Response evaluation was possible in 23patients: 9% achieved a PR (2/23);
57% achieved SD (13/23) and 35% developed PD (8/23). The phase II recommended dose of weekly Topotecan is 8mg orally day 1, 8, 15 every 28 days with pazopanib 800mg daily.

1.7 Rationale for this study

There are several reasons to consider the combination of oral topotecan and pazopanib in recurrent STS. There is prior evidence that topotecan and pazopanib individually have clinical benefit in patients with STS (although oral topotecan has not been evaluated in STS). The targets of both agents are relevant in metastatic STS, including VEGF and HIF-1 alpha. Both agents produce anti-angiogenic effects depending on method and dose of administration. Pazopanib inhibits the VEGF and PDGFR pathways and topotecan affects endothelial cells, blocks bone marrow derived endothelial precursors, and inhibits HIF-1, an upstream regulator of VEGF expression. The utilization of pazopanib in combination with oral topotecan is anticipated to produce a synergistic anti-tumor and worthwhile to explore in patients with STS. The desired effect of palliative chemotherapy is that tumor shrinkage or delay in progression will improve patients’ activity or wellbeing. With only a 6% response rate to single agent pazopanib, the addition of topotecan should potentiate the effect and improve response, thus providing increased palliation.

1.8 Exploratory Analysis

There is now data that anti-angiogenic therapy has some benefit in advanced osteosarcoma[63] providing rationale for further exploring this group of therapies in this disease subtype. In patients with relapsed and unresectable high-grade osteosarcoma, sorafenib, an orally active multikinase inhibitor of MAPK, VEGFRs, PDGFRs and KIT, produced a PFR at 4 months of 46%. In a multicenter phase II trial,

35 patients received sorafenib 400mg twice a day. 46% of patients required a treatment interruption or reduction due to toxicity. Median PFR and OS were 4 (95% CI 2-5) and 7 (95% CI 7-8) months, respectively. Six patients (17%) experienced PR/SD for ≥ 6 months.

Data exists to help construct baseline event free survival outcomes that can be used as a comparison for future phase II trials for recurrent osteosarcoma (J Clin Oncol. 2016 Sep 1;34(25):3031-8. doi: 10.1200/JCO.2015.65.5381. Epub 2016 Jul 11.) Using a single arm, 2 stage Phase II trial design: For stage I- If 4 or more of 19 patients have disease control of greater than 4 months then Stage 2 should be opened. The endpoint is that if 11 or more patients/ 36 have disease control at 4 months, then the agent is considered sufficiently efficacious for additional study.

While single agent pazopanib produced only modest responses in liposarcomas, the addition of oral topotecan to pazopanib is expected to yield higher response rates than pazopanib alone. The majority of patients evaluated in the phase II VEG20002 trial had tumors of low or intermediate grade (12/19 patients), which may have resulted in decreased efficacy in this group of patients. We will explore whether the combination of pazopanib and oral topotecan will result in clinical benefit when evaluated in patients with high grade, de-differentiated, or myxoid liposarcoma.

Therefore, we propose to conduct a phase II trial of combination pazopanib and oral topotecan in patients with unresectable or metastatic soft tissue sarcoma, as well as provide preliminary evidence of benefit for patients with osteosarcoma or liposarcoma to determine if further testing in these sarcoma subtypes is warranted. The target population for this study is appropriate given the toxicity and lack of efficacy of chemotherapy in patients with advanced disease.

2.0 OBJECTIVES & ENDPOINTS

2.1 Primary Objective & Endpoint

The primary endpoint is to determine progression free rate at week 12 for patients with soft tissue sarcoma (STS) treated with pazopanib plus oral topotecan. The endpoint will be the time from enrollment to progression, with progression defined as changes in RECIST 1.1 defined imaging, progression in non-target lesions as defined by RECIST 1.1, unequivocal clinical deterioration, or death from any cause.

2.2 Secondary Objectives & Endpoints

2.2.1 The objective is to determine the overall response rate for patients with STS treated with combination pazopanib and topotecan. The endpoint is the presence of response (ORR- CR+PR) per RECIST version 1.1 in cohort 1.

2.2.2 The objective is to determine the clinical benefit rate (CR+ PR + SD) for patients with STS treated with combination pazopanib and topotecan. The endpoint is the presence of clinical benefit (CR+ PR + SD) per RECIST version 1.1 in cohort 1

2.2.3 The objective is to determine median PFR for patients with STS treated with combination pazopanib and topotecan. The endpoint is the time from the first dose of the study treatment until death from any cause, up to a maximum follow-up of two years

2.2.4 The objective is to evaluate overall survival (OS) for patients with STS treated with combination pazopanib and topotecan. The endpoint is to determine OS for patients with STS treated with combination pazopanib and topotecan.

2.2.5 The objective is to assess safety and tolerability for patients treated with combination pazopanib and topotecan. The endpoint is the presence of all toxicities outlined in NCI CTCAE version 4.03 from time of first treatment.

2.2.6 The objective is to estimate the PFR for patients with osteosarcoma treated with combination pazopanib and topotecan. The endpoint for patients with osteosarcoma, time from treatment to progression, based upon changes in RECIST 1.1 defined imaging, progression in non-target lesions as defined by RECIST 1.1, uniequivocal clinical deterioration, or death from any cause.

2.2.7 The objective is to estimate the PFR for patients with liposarcoma treated with combination pazopanib and topotecan. The endpoint for patients with liposarcoma, time from treatment to progression based upon changes in RECIST 1.1 defined imaging, progression in non-target lesions as defined by RECIST 1.1, uniequivocal clinical deterioration, or death from any cause.

2.3 Exploratory Objective & Endpoint

For cohort 1 and 3: Quantify Cell-free circulating tumor DNA (ctDNA) at each time point, and correlate these results with demographic, diagnostic, treatment, and outcomes data**.**

For cohort 2:
The objective is to estimate the correlation of PFR and OS to levels of sVEGFR2 and PIGF. To meet this endpoint we will collect samples at baseline, 4 weeks, 8 weeks, and 12 weeks to both verify the results of Sleijfer et al and to determine if there is an even earlier correlation that can be detected between levels of these cytokines and PFR as well as OS which may allow us to better predict treatment response early on in therapy.

3.0 PATIENT ELIGIBILITY

The target population for this phase II study is patients with recurrent or metastatic and non-resectable soft tissue and bone sarcomas who have failed at least one prior therapy. This will be a multicenter trial conducted at Robert H. Lurie Comprehensive Cancer Center of Northwestern University. Northwestern University will serve as the lead site and coordinating center for this study. Participating sites will include the University of Iowa, Mayo Clinic (Rochester, Jacksonville, and Scottsdale), Washington University, University of Wisconsin, and University of Minnesota.

A total of 164 patients may be enrolled including 108 patients with STS (to acquire 92 evaluable patients), and up to 36 patients with osteosarcoma and 20 patients with liposarcoma. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, or to the local PI at each participating site.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must provide written informed consent prior to performance of study-specific procedures or assessments and must be willing to comply with treatment and follow-up.

3.1.2 Patients must be age ≥ 18 years.

3.1.3 Patients must have a histologically confirmed diagnosis of metastatic or locally advanced, unresectable :

- soft tissue sarcomas (non-liposarcoma)
- osteosarcoma
- liposarcoma- high grade, de-differentiated, or myxoid

NOTE: *Pathology is not required to be reviewed at the treating institution. A copy of the pathology report is sufficient for eligibility purposes*

3.1.4 Patients must exhibit an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1

3.1.5 Patients must have measurable disease within 4 weeks prior to registration by RECIST 1.1, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >= 20 mm with conventional techniques or as >= 10mm with spiral CT scan.

3.1.6 **Cohort 1**: Patients must have had a minimum of 1 and a maximum of 4 prior chemotherapy regimens for recurrent/metastatic or locally advanced/unresectable disease. It will be up to the investigator to determine what constitutes a “regimen” in each case.
Cohort 2: Patients may have had any number of prior therapies for recurrent/metastatic or locally advanced/unresectable disease. There are no restrictions.
Cohort 3: Patients must have had a minimum of 1 and maximum of any number of prior chemotherapy regimens for recurrent/metastatic or locally advanced/unresectable disease.
All cohorts: The last dose of systemic therapy must have been given at least 28 days prior to initiation of therapy. Patients receiving BCNU or mitomycin C must have received their last dose at least 6 weeks prior to initiation of therapy.

3.1.7 Patients with brain metastasis are eligible for participation ONLY if they have been treated with definitive surgery or radiation (surgery ± radiotherapy, radiosurgery, or gamma knife) and meet both of the following criteria: a) are asymptomatic and b) have no requirement for steroids or enzyme-inducing anticonvulsants in prior 12 week interval.

3.1.8 Patients must have adequate organ function within 14 days prior to registration, as defined below:

System	Laboratory Values
Hematology	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin[a]	≥9 g/dL (5.6 mmol/L)
Platelets[a]	≥100 X 10^9/L
Prothrombin time (PT) or international normalized ratio (INR)[b]	≤1.2 X ULN
Activated partial thromboplastin time (aPTT)	≤1.2 X ULN
Hepatic	
Total bilirubin	≤1.5 X ULN
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)[c]	≤2.5 X ULN
Renal	
Serum creatinine	≤1.5 mg/dL (133 µmol/L)
OR, if >1.5 mg/dL: Calculated creatinine clearance (Cl_{CR})	≥50 mL/min
Urine Protein to Creatinine Ratio (UPC;)[d]	<1
, 24-hour urine protein, if required[d]	<1g

a. Subjects may not have had a transfusion within 7 days of screening assessment.

b. Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.

c. Concomitant elevations in bilirubin and AST/ALT above 1.0 x ULN (upper limit of normal) are not permitted.

d. If UPC ≥1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value <1 g to be eligible. Use of urine dipstick for renal function assessment is not acceptable.

3.1.9 Females of child-bearing potential (FOCBP) and males must agree to use adequate contraception (see Section 4.3.12) prior to study entry, for the duration of study participation, and for 30 days following completion of therapy. Should a female patient become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

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

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

3.1.10 FOCBP must have a negative pregnancy test within 7 days prior to registration on study.
NOTE: Female patients who are lactating should discontinue nursing prior to the first dose of study drug and should refrain from nursing throughout

the treatment period and for 14 days following the last dose of study drug

3.1.11 Are able to swallow and retain oral tablets.

3.2 Exclusion Criteria

3.2.1 Patients with any of the following sarcoma histologic subtypes will not be eligible for participation:

- Alveolar soft-part sarcoma
- Chondrosarcoma
- Dermatofibrosarcoma
- Ewing sarcoma
- GIST
- Kaposi sarcoma (non-HIV and HIV related disease)
- Mixed mesodermal tumor/carcinosarcoma
- Low grade (grade 1) sarcomas
- Rhabdomyosarcoma (embryonal, alveolar)
- Interdigitating dendritic sarcoma
- Giant cell tumor of the bone

3.2.2 Patients must not have received prior treatment with pazopanib or topotecan.

3.2.3 Patients must not have an active secondary malignancy.

3.2.4 Prior malignancy, unless they have been disease-free for 3 years, or have a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma

3.2.5 Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to:

- Active peptic ulcer disease
- Known intraluminal metastatic lesion/s with risk of bleeding
- Inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease), or other gastrointestinal conditions with increased risk of perforation
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment

3.2.6 Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to:

- Malabsorption syndrome
- Major resection of the stomach or small bowel

3.2.7 Corrected QT interval (QTc) > 480 msecs using Bazett's formula (QTc= QT/√RR). EKG for screening must be within 28 days prior to registration.

3.2.8 History of any one or more of the following cardiovascular conditions within the past 12 months:

- Cardiac angioplasty or stenting
- Myocardial infarction
- Unstable angina
- Coronary artery bypass graft surgery
- Symptomatic peripheral vascular disease
- Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA) (Appendix C)

3.2.9 Left ventricular ejection fraction < 45% in patients with prior anthracycline use or otherwise at risk for left ventricular systolic dysfunction.

3.2.10 Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg]

NOTE: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Following antihypertensive medication initiation or adjustment, blood pressure (BP) must be re-assessed three times at approximately 2-minute intervals. At least 24 hours must have elapsed between anti-hypertensive medication initiation or adjustment and BP measurement. These three values should be averaged to obtain the mean diastolic blood pressure and the mean systolic blood pressure. The mean SBP / DBP ratio must be <140/90 mmHg (OR 150/90 mm Hg, if approved by PI and the QAM) in order for a patient to be eligible for the study (see Section 5.2.3.6 for details on BP control and re-assessment prior to study enrollment).

3.2.11 History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.
Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks prior to study treatment are eligible

3.2.12 Major surgery or trauma within 28 days prior to first dose of study treatment and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major surgery).

3.2.13 Evidence of active bleeding or bleeding diathesis.

3.2.14 Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage

- Large protruding endobronchial lesions in the main or lobar bronchi are excluded; however, endobronchial lesions in the segmented bronchi are allowed.

  Lesions extensively infiltrating the main or lobar bronchi are excluded; however, minor infiltrations in the wall of the bronchi are allowed

3.2.15 Recent hemoptysis (≥½ teaspoon [2.5 mL]) of red blood within 8 weeks before first dose of study drug).

3.2.16 Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with patient's safety, provision of informed consent, or compliance to study procedures

3.2.17 Unable or unwilling to discontinue use of strong inducers and inhibitors of CYP450 listed in Appendix for at least 14 days prior to the first dose of study treatment and for the duration of the study (Appendix A). CYP3A4 substrates can be administered, but investigators will need to be aware of possible increased or decreased effectiveness of the non-study drug and this should be recorded in concomitant medications. BCRP and PgP inducers and inhibitors should be used with caution if another alternative drug is not able to be used (Appendix A and B)
Note: As this list is constantly evolving, if a medication is incorrectly documented as prohibited in this protocol, documentation from the site pharmacist to the contrary will be acceptable for the purposes of registration.

3.2.18 Treatment with any of the following anti-cancer therapies:

- radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of study treatment

3.2.19 Administration of any investigational drug within 28 days prior to receiving the first dose of study treatment.

3.2.20 Any ongoing toxicity related to prior anti-cancer therapy that is >Grade 1 and/or that is progressing in severity (exceptions include alopecia, fatigue, and hematologic toxicities not included in 3.1.8).

3.2.21 Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib or topotecan.

3.3 Inclusion of Women and Minorities:

Both women and men and members of all races and ethnic groups are eligible for this trial.

3.4 Population and Accrual Overview

The target population for this phase II trial is patients with recurrent or metastatic soft tissue and bone sarcoma who have failed at least one prior therapy. This will be a multi-center trial with the Robert H. Lurie Comprehensive Cancer Center of Northwestern University serving as the lead institution and coordinating center. Patients at Northwestern may be referred to the Principal Investigator (PI). Patients at each of the participating sites may be referred to the respective local PI at each site. 108 patients (to acquire 92 evaluable patients) with STS may be enrolled in this trial. This number does not include the possible up to 20 patients with osteosarcoma and 20 patients with liposarcoma who may be enrolled into this trial as exploratory cohorts.

4.0 TREATMENT PLAN

4.1 Overview

Patients will take oral pazopanib (800mg starting dose) once daily AND oral toptecan (8 mg starting dose) on days 1, 8, and 15 of each 28 day cycle. Treatment will continue until disease progression or unacceptable toxicity occurs, or until discontinuation per patient preference or physician recommendation. Patients who are removed from study treatment for toxicity should be followed until toxicity resolves to grade 1 or baseline. Patients **with PD** at end of treatment will be followed every 6 months for 2 years (or until death) for survival. Patients **without PD** at end of treatment will be followed every 6 months for 5 years (or until death) for survival and progression.

4.2 Treatment Administration

Agent	Dose	Route	Schedule	Cycle Length
Pazopanib	800 mg (Starting Dose)	PO	Per day	4 weeks (28 days)
Topotecan	8 mg (Starting Dose)	PO	Day 1, 8, & 15 of each cycle	

4.2.1 Study Drug Administration

Patients will receive pazopanib at a dose of 800 mg/day (4 x 200mg tablets). Pazopanib should be taken orally, without food, at least one hour before or two hours after a meal, with up to 200 mL of water. Patients will concurrently receive topotecan 8 mg (8 x 1-mg capsules) to be taken orally on day 1, 8, and 15 of a 28 day cycle. Topotecan can be taken with or without food. Cycles will be repeated every 4 weeks.

On days of a scheduled clinic visit, the dose of pazopanib and topotecan should be taken *after* visit procedures are completed. Treatment with pazopanib and topotecan will continue if tolerated and in the absence of documented disease progression or unacceptable toxicity. If a dose is vomited or if a dose is missed for any reason, the dose should not be made up. Patients will be given a medication diary to record all doses taken, doses missed, and daily adverse events experienced. This will be collected and reviewed at study visits.

4.3 Toxicity Management, Dose Delays/Modifications & Supportive care

Any patient who receives at least one dose of study therapy will be evaluable for toxicity endpoints. Each patient will be assessed for the development of toxicity according to the timeframe referenced in the Schedule of Events table). Toxicity will be assessed according to CTCAE v. 4.03.

After cycle 1 day 1 of therapy, defined as 4 weeks of therapy, cycle 1 day 15, cycle 2 day 1, cycle 2 day 15, cycle 3 day 1, and day one of all subsequent cycles may be administered provided the patient meets the following criteria:

- ANC ≥ 1500/mm2
- Platelet count ≥ 75,000
- Hemoglobin ≥ 9 g/dL (after transfusion if necessary).
- Non-hematologic toxicity recovered to ≤ grade 1 or tolerable grade 2
- No evidence of progressive disease

Note: For cycle 1 day 15 and cycle 2 day 15, dosing should only commence AFTER day 15 labs have been reviewed to ensure the above criteria are met. If the patient does not meet the above criteria, study treatment should be held and labs and assessment should be done at least weekly until patient meets the above criteria (patient can be assessed earlier than one week at physician's discretion). If when reassessed, the patient meets the treatment criteria above, proceed with treatment at the dose the patient was receiving during the previous cycle. If patient does not meet the above criteria after a one-week delay, then treatment will continue to be held, and the patient will continue to be evaluated weekly. Treatment can be held for a total of 3 consecutive weeks to allow for treatment related toxicities to resolve. In the case that treatment has been held for 3 weeks for treatment related toxicities, the dose reduction for the next upcoming cycle should be based on the most severe toxicity experienced in the current cycle. If a patient develops another severe toxicity at the reduced dose or if they experience a life-threatening toxicity at any time, they will be removed from study per the dose modification parameters below. If a subject is able to resume treatment after an interruption of ≤3 weeks, missed doses will not be made up (i.e. the cycle duration will remain unchanged).

Patients with stable or responding disease may be retreated at the same dose (both Topotecan and Pazopanib) or at a reduced dose level, depending upon the adverse events observed in the current cycle and any adverse events present on the first day of the next cycle. If multiple toxicities are seen, the dose administered in a subsequent cycle should be based on the most severe toxicity experienced in the current cycle. Any doses that are held or delayed will be considered skipped and will not be made up. Patients should not deviate from the 28 day cycle (+ or – 3 days).

Patients will be withdrawn from the study if they fail to recover to grade ≤ 1 or tolerable grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a treatment-related toxicity within 3 weeks, or if the dose is interrupted > 8 weeks for a non-treatment related reason, unless the investigators (PI, local PI, and QAM) agree that the subject should remain in the study because of evidence that the patient is/may continue to derive benefit from continuing study treatment.

Topotecan:

Three dose reductions are permitted, based on side effects experienced, from 8 mg to 6, 6mg to 4, 4mg to 2. Further dose reduction is not allowed. Patients may be maintained on the lower dose of topotecan during treatment if deemed to be deriving benefit from the drug. Doses that are reduced for topotecan related toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

Dose Level	Topotecan
0 (starting dose)	8 mg
-1	6 mg
-2	4 mg
-3	2 mg

Pazopanib:
Pazopanib may be held up to 3 weeks waiting for toxicities to resolve. Three dose reductions are permitted, from 800 to 600 or from 600 to 400 or from 400 to 200 mg daily based on side effects experienced. Further dose reduction is not allowed. Patients may be maintained on the lower dose of pazopanib during treatment if deemed to be deriving benefit from the drug. Doses that are reduced for pazopanib related toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

Table I- Dose Modification Algorithms for Potential Treatment-Related Adverse Events[c]

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension	
(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).	Step 1. Continue pazopanib and topotecan at the current dose. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[a] blood pressure (BP). If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(B). Asymptomatic SBP ≥170 mmHg, or DBP ≥110 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	Step 1.Consider reducing or interrupting pazopanib, as clinically indicated. Continue topotecan at the current dose. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Step 4. Once BP is well-controlled, restart IP dose-reduced by 200 mg if IP was interrupted.
(C). Symptomatic hypertension or recurring SBP ≥170 mmHg, or DBP ≥110 mmHg, despite modification of antihypertensive medication(s)	Step 1. Interrupt pazopanib. Continue topotecan at the current dose. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. 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 also recommended.

	Step 4. Once BP is well-controlled, restart pazopanib dose-reduced by 200 mg.
(D). Refractory hypertension unresponsive to above interventions.	Discontinue patient from protocol treatment and continue follow-up per protocol.
Prolongation of QTc Interval: If the QTc is prolonged, the ECG should be manually read to ensure accuracy of the reading. The values below refer to manually-read ECGs.	
500 msec > QTc ≥ 480 msec	Continue pazopanib; monitor as clinically indicated. Continue topotecan at the current dose.
QTc ≥500 msec	Discontinue patient from protocol treatment and continue follow-up per protocol.
Proteinuria	
UPC <3	Continue pazopanib and topotecan at the current dose; monitor as clinically indicated
UPC ≥3 or 24-h urine protein ≥3g	Step 1. Interrupt pazopanib Continue topotecan at the current dose. Step 2. Weekly UPC or 24-hr urine protein monitoring until UPC is <3 or 24-hr urine protein is <3 grams. Then restart pazopanib dose-reduced by 200 mg. Step 3. If UPC ≥3 or 24-h urine protein ≥3g recurs at current dose, repeat steps 1 and 2. Step 4. If UPC ≥3 or 24-hr urine protein ≥3 recurs at current dose and the pazopanib dose can no longer be reduced, discontinue protocol treatment and continue follow-up per protocol.
Hemorrhage /Bleeding: Investigate and document underlying etiology of the bleeding	
Grade 1	For hemoptysis, interrupt pazopanib and contact the NU QAM and PI to discuss whether further treatment with pazopanib is appropriate. Continue topotecan at the current dose. For other Grade I hemorrhage/bleeding events, continue pazopanib and topotecan at the current dose; monitor as clinically indicated.
Grade 2	Step 1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue protocol treatment and continue follow-up per protocol. Otherwise, interrupt pazopanib until the AE resolved to ≤ Grade 1. Continue topotecan at the current dose. Step 2. Restart pazopanib; consider reducing dose and monitor as clinically indicated. Continue topotecan at the current dose.
Grade 3 or 4, or Recurrent ≥ Grade 2 event after dose interruption/reduction.	Discontinue protocol treatment and continue with follow-up per protocol.

Venous Thrombosis (DVT, PE)	
Grade 2	Continue pazopanib and topotecan at the current dose; monitor as clinically indicated
Grade 3	Step 1. Interrupt pazopanib. Continue topotecan at the current dose. Step 2. Initiate and monitor anticoagulation as clinically indicated. Step 3. Resume pazopanib at reduced dose only if all of the following criteria are met: • The subject must have been treated with anticoagulant at the desired level of anticoagulation for at least one week. • No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment. Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, international normalized ratio (INR) should be monitored within three to five days after any change in IP dosing (eg, re-initiating, escalating/de-escalating, or discontinuing IP), and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation
Grade 4 and/or PE	Discontinue protocol treatment and continue follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any Grade	Discontinue protocol treatment and continue follow-up per protocol.
Thrombocytopenia: Investigate and document underlying cause	
Grade 1	Continue pazopanib and topotecan at current dose; monitor as clinically indicated.
Grade 2	Step 1. Interrupt topotecan and pazopanib until toxicity resolves to ≤ Grade 1. Step 2. Restart topotecan and pazopanib at the current dose or reduce dose by 1 level per physician discretion. If no recovery to ≤ Grade 1 within 3 weeks, discontinue protocol treatment and follow-up per protocol. If patient is deriving clinical benefit, please contact QAM and PI.
Grade 3 or 4	Step 1. Interrupt pazopanib and topotecan until toxicity resolves to ≤ Grade 1.

	Step 2. Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated. Restart topotecan at the current dose or reduce dose by 1 level per physician discretion. If no recovery to ≤ Grade 1 or recurrent Grade 3 or 4 thrombocytopenia at the current dose, discontinue protocol treatment and follow-up per protocol.
Neutropenia: Investigate and document underlying cause.	
Neutrophils ≥ 1.5	Continue pazopanib and topotecan at current dose; monitor as clinically indicated.
Neutrophils < 1.5	1. Interrupt pazopanib and topotecan dosing until neutrophils resolve to ≥ 1.5. 2. Restart topotecan and pazopanib at the current dose or reduce dose by 1 level per physician discretion. If no recovery to ≥ 1.5 within 3 weeks, discontinue protocol treatment and follow-up per protocol. If patient is deriving clinical benefit, please contact QAM and PI.
Anemia: Investigate and document underlying cause.	
Hemoglobin ≥ 9	Continue pazopanib and topotecan at current dose; monitor as clinically indicated.
Hemoglobin < 9	1. Interrupt pazopanib and topotecan dosing until hemoglobin resolves to ≥ 9. 2. Restart topotecan and pazopanib at the current dose or reduce dose by 1 level per physician discretion. If no recovery to ≥ 9 within 3 weeks, discontinue protocol treatment and follow-up per protocol. If patient is deriving clinical benefit, please contact QAM and PI.
Palmar-plantar Erythrodysesthesia Syndrome	
Grade 1 Minimal skin changes or dermatitis without pain (erythema, oedema, hyperkeratosis)	1. Continue pazopanib and topotecan at present dose
Grade 2 Skin changes with pain; limiting instrumental activities of daily living (ADLs) (peeling, blisters, oedema, bleed, hyperkeratosis)	1. Hold pazopanib. Continue topotecan at current dose. 2. Treat as clinically appropriate 3. Upon resolution to Level 1 or better restart pazopanib with a dose reduction to 400 mg 4. If recurrent at the current dose consider a further dose reduction to 200mg or discontinuation
Grade 3 Severe skin changes with pain and limiting self care ADLs	1. Discontinue protocol treatment

Other Treatment Related Adverse Events[b,c,.d]	
Grade 1 or tolerable Grade 2	Continue pazopanib and topotecan at current dose; monitor as clinically indicated.
Intolerable Grade 2 or Grade 3	Step 1. Interrupt pazopanib and topotecan until toxicity resolves to ≤ Grade 1. Step 2. Restart topotecan and pazopanib at the current dose or reduce dose by 1 level per physician discretion.
Grade 4	Discontinue protocol treatment and continue follow-up per protocol.

a. Well-controlled BP defined as SBP <140 mmHg and mean DBP <90 mmHg.
b. AEs are graded according to NCI Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4.03)
Abbreviations: BP, blood pressure; IP, investigational product.
c. If patient has completed 12 weeks of combination protocol therapy, and one protocol agent should be stopped per the above table, patient may be able to continue single agent therapy patient is deriving benefit and if approved by PI and QAM. This is based on how combination therapy would be administered outside of a clinical trial setting.
d. Dose modifications should only be made after patient is given adequate supportive care.

Dose Modifications and Management of Liver toxicity

Recommendations for pazopanib dose interruptions/modifications in case of liver-related treatment-emergent AEs are provided in Table III. As a general rule, since many subjects are taking multiple concurrent medications, it is critical to (a) do a thorough evaluation of the subject's concurrent medications (and ensure all are recorded in appropriate forms) , and (b) identify and discontinue those with known hepatotoxicity and replace with a non-hepatotoxic equivalent for the same indication if necessary. Record alcohol use on appropriate forms. Liver dysfunction must be fully evaluated even if clinical signs and symptoms indicate progression of liver tumor lesions. Imaging studies must be obtained to document potential progression of malignancy.

Table II Guidelines for Management of Treatment Emergent Hepatotoxicity

Event	Dose Modification Algorithms
(A). ALT of ≤ 3.0 x ULN	Continue pazopanib and topotecan at current dose with full panel LFTs[a] monitored as per protocol.
(B). ALT >3.0 x ULN to ≤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)	**Liver Event Monitoring Criteria:** (1) Continue pazopanib and topotecan 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. **Recurrence – Liver Event Stopping Criteria[c]:** Discontinue protocol treatment 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 or baseline.

(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:[c]** (1) Interrupt pazopanib until toxicity resolves to ≤Grade 1 or baseline. Continue topotecan at current dose. (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 or baseline. (4) If the potential benefit for reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose of ≤400 mg daily and monitor liver function weekly for 8 weeks. **Recurrence – Liver Event Stopping Criteria[c]:** Discontinue protocol treatment 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 or baseline.
(D). ALT >3.0 x ULN **with** concomitant elevation in bilirubin[b] (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) or **with** hypersensitivity symptoms (e.g., fever, rash).	**Liver Event Stopping Criteria[c]:** (1) Discontinue protocol treatment immediately. (2) 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 or baseline.
For isolated total bilirubin 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. 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; LFT liver function tests; ULN upper limit of normal

4.3.1 Pregnancy/Lactation/Contraception

Pre-clinical studies in animals have shown reproductive toxicity. If the patient becomes pregnant while receiving pazopanib or topotecan, the potential hazard to the fetus should be explained to the patient. Women of childbearing potential should be

advised to avoid becoming pregnant while receiving treatment with pazopanib or topotecan. Pazopanib or topotecan should not be used during pregnancy or lactation.

Acceptable contraception methods, when used consistently and in accordance with both the product label and instructions of the physician are as follows:

- Complete abstinence from sexual intercourse during duration and treatment and for at least 30 days after the last dose of investigational product.
- Oral contraceptive, either combined estrogen/progesterone or progesterone alone.
- Injectable progestogen.
- Implants of levonorgestrel.
- Estrogenic vaginal ring.
- Percutaneous contraceptive patches.
- Intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year.
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female patient's entry into the study, and this male is the sole partner for that patient.
- Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository).

4.4 Concomitant Medications/Treatments

Use of concomitant medications for supportive care purposes will be per treating investigator's discretion.

4.4.1 G-CSF Administration

If neutrophil count < 1500/mm3 or platelet count < 75,000/mm3, hold topotecan until counts resolve to < grade 2 CTC grade toxicity. If neutrophil count remains <
1500/mm3 x 1 week or more, granulocyte colony stimulating factor may be used to support. If neutrophil count achieves level > 1500/mm3, patient may resume treatment with oral topotecan. If toxicities do not resolve to < CTC grade 2 after 3 weeks of drug hold, and with G-CSF support patient must be removed from study. Platelet counts that do not resolve to < CTC grade 2 after 3 weeks require removal of patient from treatment.

4.4.2 Antiemetics

The use of antiemetics will be left to the investigators' discretion.

4.4.3 Palliative Care

Palliative radiation and surgery are allowed on this trial IF they are not being used to address a target lesion as defined in RECIST 1.1. Any patient who requires palliative care to a target lesion should be removed from protocol treatment. If necessary, the following parameters should be used.

- Palliative radiation: Protocol treatment should be held 7 days before, during, and 7 days after palliative radiation, or at the discretion of the site radiation oncologist. If treatment is not resumed within 3 weeks, case will be reviewed by QAM and PI to determine whether or not patient can restart treatment.
- Palliative surgery: Protocol treatment should be held 7 days before and until the wound is healed. If treatment is not resumed within 3 weeks, case will be

reviewed by QAM and PI to determine whether or not patient can restart treatment.

4.4.4 **OTHER Concomitant Medications**
Therapies considered necessary for the well-being of the patient may be given at the discretion of the investigator. Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. All concomitant medications must be recorded. For patients with known hypertension on BP medications, strict compliance with treatment should be reinforced.

4.4.5 **Concomitant Medications discouraged while on study**

- Strong inducers and inhibitors of CYP450 listed in Appendix A
- CYP3A4 substrates can be administered, but investigators will need to be aware of possible increased or decreased effectiveness of the non-study drug and this should be recorded in concomitant medications.
- BCRP and PgP inducers and inhibitors should be used with caution if another alternative drug is not able to be used (listed in the Appendix B).
  - *Note: As this list is constantly evolving, if a medication is incorrectly documented as prohibited in this protocol, documentation from the site pharmacist to the contrary will be acceptable*
- Other Anticancer or Experimental Therapies: No other anticancer therapy (including chemotherapy, radiation, hormonal treatment or immunotherapy) of any kind is permitted during the study period. No other drug under investigation may be used concomitantly with the study drug.

4.5 Duration of Therapy
If a patient is felt to be deriving benefit from the agents and is stable at the conclusion of the trial, patients are allowed to continue therapy with stable disease by RECIST 1.1. This will be based on discussion with the patient, the PI, and sponsor. It may be possible to continue both drugs at that point, assuming availability of agents and no change in the status regarding pazopanib or topotecan with respect to sarcomas.

A patient may be removed from therapy if, in the judgment of the investigator, general or specific changes in the patient's condition render the patient unacceptable for further treatment.

4.6 Duration of Follow Up
Patients with PD at end of treatment will be followed every 6 months for 2 years (or until death) for survival. Patients without PD at end of treatment will be followed every 6 months for 5 years (or until death) for survival and progression. Follow-up may occur over the phone. Patients who are removed from study treatment for toxicity should be followed until toxicity resolves to grade 1 or baseline.

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

- Patient voluntarily withdraws from treatment (follow-up permitted)
- Patient withdraws consent (no follow-up permitted)
- Patient is unable to comply with protocol requirements

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

4.8 Patient Replacement

If a patient is registered but withdraws or is taken off treatment before receiving any doses of study medication, he or she will then be replaced.

5.0 STUDY PROCEDURES

		CYCLE 1[m]				CYCLE 2[m]							
	Screening [a,b]	Day 1 [b]	Day 8	Day 15	Day 21	Day 1	Day 8	Day 15	Day 21	D1 - Odd Cycles[m]	D1 - Even	End of Tx[n]	Follow Up [i]
Informed Consent	X												
History/ Progress Notes	X	X				X				X	X	X	
Physical Exam with full Vital Signs[c]	X	X				X				X	X	X	
Blood Pressure (BP) only[c]			X	X	X		X	X	X	X	X		
ECOG Performance Status	X	X				X				X	X	X	
Toxicity Assessment	X	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]		X[o]	X[o]	X[o]	X	X [j]
Chemistry labs[f]	X	X		X		X		X		X	X	X	
CBC with Differential[h]	X	X		X		X		X		X	X	X	
Pregnancy Test [g]	X												
Urine Protein/ Creatinine Ratio	X	X				X				X	X		
TSH(T4) [e]	X	X								X			
PT/INR, PTT	X	X				X				X	X		
EKG [d]	X					X					X		
MUGA or Echo[p]	X	As clinically indicated											
Radiology Assessment [k]	X	Radiology assessment at week 6, 12, 20 and every 8 weeks thereafter.											X [i]
RECIST	X				X					X			
Pazopanib[q]		Days 1-28											
Topotecan[q]		X	X	X		X	X	X		X	X		
Correlative blood sample[l]	X					X				X[l]	X[l]		
Follow-up													X[i]

a. Pre-study procedures done within 7 days of C1D1 do not need to be repeated on C1D1.
b. Pre-study H&P and all labs must be < 15 days before registration. Tumor measurements and radiologic evaluations must be ≤ 4 weeks before registration. Screening EKG must be within 28 days prior to registration. H&P and all labs do not need to be repeated on day 1 if done within 7 days of treatment initiation.
c. Vital signs to include height (height is recorded at screen visit only), weight, blood pressure, pulse, temperature and respirations. In addition to this full set of vitals each cycle, a measurement of blood pressure (BP) should be taken every 7 days (+/- 3). These weekly blood pressure measurements can be assessed by any method (i.e. at home or by another physician) as long as the study physician is informed of the measurement, verifies any measurement that is not normal and takes appropriate action to manage hypertension, as defined by the protocol. A blood pressure log will be maintained to aid in monitoring and should be uploaded into NOTIS each cycle for the duration of treatment (See appendices).
d. EKG: Performed on Cycle 2 day 1 and then day 1 of every even cycle until end of treatment (+/-3 days). EKG for screening must be within 28 days prior to registration.
e. Thyroid function test (TSH) are monitored every 12 weeks (+/-3 days). TSH is mandatory, but T4 should be restricted to only those with abnormal TSH levels.
f. Chemistry labs include a comprehensive chemistry panel (Liver function tests (LFT) and Comprehensive Metabolic Panel (CMP)). Monitoring of LFTs: Monitor serum liver tests before initiation of treatment with pazopanib and at Cycle 1 day 15, Cycle 2 day 1, Cycle 2 day 15, and day 1 of every cycle thereafter(+/- 3 days). CMP and LFTs should include: Bilirubin, Glucose, BUN, Calcium, Total Protein, Albumin, ALT, AST, GFR, Sodium, Potassium, Chloride, Carbon Dioxide, Alk Phos, Creatinine, Magnesium, and GGT.
g. Only for women of childbearing potential; must be tested within 7 days prior to registration.
h. Complete Blood Count (CBC): Performed on day 1 and 15 of cycles 1 and 2 (+/- 3 days) then day 1 of each cycle (+/-3 days). For patients experiencing significant cytopenias felt possibly related to Topotecan, CBCs should be obtained more frequently (weekly or more frequently) to assess timing for retreatment or need for G-CSF or transfusion support.
i. Patients **with PD** at end of treatment will be followed every 6 months for 2 years (or until death) for survival (from the last day of treatment). Patients **without PD** at end of treatment will be followed every 6 months for 5 years (or until death) for survival and progression (from the last day of treatment). Follow-up may occur over the phone.
j. Patients who are removed from study treatment for toxicity should be followed until toxicity resolves to grade 1 or baseline.
k. Radiology assessment by CT or MRI will be done at Week 6, Week 12, Week 20 and every 8 weeks (+/- 7 days) thereafter. After 1 year of protocol treatment, patient may be switched to scans every 12 weeks (+/- 7 days) at the discretion of the patient and treating physician.
l. Blood samples for mandatory correlative study will be collected at screening or on Cycle 1 Day 1 prior to treatment, and day 1 of Cycle 2, 3, and 4 , (+/-3 days) as in section 9.1.
m. Unless otherwise noted, on-therapy windows for testing will be as follows: imaging scans should be completed within +/- 1 week of the target time point, and labs and physical examinations within +/- 3 days of the target time point.
n. End of treatment visit must occur within 30 days following the last day of treatment, particularly prior to patient starting new treatment.
o. Patient to call coordinator weekly to report toxicities- if no toxicities to be reported, patient need not call in. Toxicities should be followed for 30 days after last dose of study treatment, however, new toxicities that arise within the 30 day period definitely related to new anti-cancer treatment and NOT related to study treatment do not need to be reported.
p. ONLY required for patients with prior anthracycline use OR otherwise at risk for left ventricular systolic dysfunction. May be assessed by MUGA or echocardiogram.
q. Day 1 of each cycle should be every 28 days. In the event that this day falls on a holiday or other such event, study team should use +/- 3 day window to complete pre-treatment procedures, and dispense protocol agents to patients with instructions to commence treatment on day 1. Any missed doses will not be made up and should be skipped to maintain a 28-day cycle.

6.0 ENDPOINT ASSESSMENT

6.1 Definitions

6.1.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques (CT, MRI, x-ray) or as >10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Lymph nodes are considered measurable in RECIST 1.1 if their short diameter exceeds 15 mm. Lymph nodes are considered normal if they have a short axis of less than 10 mm; this applies to determination of response as well. Lesions that are previously irradiated must show
clear evidence of progression over a minimum of 3 months to include as measurable. This period of time is used to discount tumor edema in an irradiated field as a false sign of disease progression.

6.1.2 Non Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non- measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (specifically abdominal masses not followed by CT or MRI), and cystic lesions are all non-measurable.

6.1.3 Target Lesions

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

6.1.3.1 Evaluation of Target Lesions

Complete Response (CR)
Disappearance of all target lesion

Partial response (PR)
At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

Progressive Disease (PD)
At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Progression must also involve an increase in size of measurable lesions by at least 5 mm, to minimize the possibility that small changes in a small number of target lesions is falsely interpreted as progression.

Stable Disease (SD)
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

6.1.4 Non-Target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.4.1 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions

Note: If tumor markers are initially above the upper normal limit, they must normalize
for a patient to be considered in complete clinical response.

Incomplete Response/Stable Disease (SD)

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Please refer to the RECIST 1.1 guidelines for a discussion of "unequivocal progression".

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

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Since this is not a randomized study, confirmation of a clinical response is required as per RECIST 1.1; it is not required for randomized studies in RECIST 1.1.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 week Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 week Confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 week from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

6.2 Antitumor Effect

For the purposes of this study, patients should be re-evaluated for response at 6 weeks, 12 weeks and then every 2 cycles thereafter. In addition to a baseline scan, confirmatory scans should also be obtained a minimum of 4 weeks following initial documentation of objective response. The investigator may opt to have the follow up scan performed according to the schedule (without an extra scan) as this follows the intent of the RECIST guidelines.

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1.64 Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria, as defined below. In contrast, measurable disease in lymph nodes is determined based on the lymph node short axis.

6.3 Evaluable for objective response:

All patients enrolled in the study should be assessed for response to treatment, even if there are major protocol treatment deviations or patients exhibit objective disease progression prior to the end of cycle 1.

All conclusions should be based on all enrolled patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, treating an ineligible patient, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals for response rate should also be provided.

All patients who were enrolled on the trial should be included in the main analysis of the response rate. Thus, an incorrect treatment schedule or drug administration does not result in exclusion. However, if a patient is removed from treatment prior to their 12 week assessment for reasons other than disease progression or death, they will be considered non-evaluable for response if approved by the DMC.

6.4 Methods for Evaluation of Measurable Disease

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

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

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI
These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Cytology, Histology
The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is or stable disease (an effusion may be a side effect of the treatment) and progressive disease

6.5 Primary Endpoint
Time from enrollment to progression, with progression defined as changes in RECIST 1.1 defined imaging, progression in non-target lesions as defined by RECIST 1.1, unequivocal clinical deterioration, or death from any cause.

6.6 Secondary Endpoints
- The presence of response (ORR- CR+PR) per RECIST version 1.1 in cohort 1.
- The presence of clinical benefit (CR+ PR + SD) per RECIST version 1.1 in cohort 1.
- The time from the first dose of the study treatment until death from any cause, up to a maximum follow-up of two years.
- The endpoint is to determine OS for patients with STS treated with combination pazopanib and topotecan.
- The presence of all toxicities outlined in NCI CTCAE version 4.03 from time of first treatment.
- The endpoint for patients with osteosarcoma, time from treatment to progression, based upon changes in RECIST 1.1 defined imaging, progression in non-target lesions as defined by RECIST 1.1, uniequivocal clinical deterioration, or death from any cause.
- The endpoint for patients with liposarcoma, time from treatment to progression based upon changes in RECIST 1.1 defined imaging, progression in non-target lesions as defined by RECIST 1.1, uniequivocal clinical deterioration, or death from any cause.

6.7 Exploratory Endpoint
For cohort 1 and 3: Quantify Cell-free circulating tumor DNA (ctDNA) at each time point, and correlate these results with demographic, diagnostic, treatment, and outcomes data**.** For cohort 2: Verification of results of Sleijfer et al and to determine if there is an even earlier correlation that can be detected between levels of these cytokines and PFR as well as OS which may allow us to better predict treatment response early on in therapy

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (http://cancer.northwestern.edu/CRO/data/DataandSafetyMonitoringPlanMay2014.pdf). The level of risk attributed to this study requires high-intensity monitoring as outlined in the DSMP.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 for timepoints). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

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

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

7.2 Definitions & Descriptions

7.2.1 Adverse Event

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

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

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

7.2.2 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 v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html

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

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

7.2.3 Serious Adverse Events (SAEs)

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

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

- **Results in *death*.**
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **Is *life-threatening*.**
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- **Requires *in-patient hospitalization* or *prolongation of existing hospitalization* for ≥ 24 hours.**
- **Results in *persistent or significant disability or incapacity*.**
- **Is a *congenital anomaly/birth defect.***
- **Is an *important medical event*.**
  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.
  For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.2.4 Unanticipated Problems Involving Risks to Subject or Others

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

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

7.3 Adverse Event Reporting

7.3.1 Routine Reporting

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

7.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment, unless definitely attributable to new anti-cancer treatment and NOT study treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v 4.03.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unlikely: AE not likely to be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event.
   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
   - the current protocol
   - the drug package insert
   - the current Investigator's Brochure

7.3.3 Expedited Reporting of SAEs/Other Events

7.3.3.1 Reporting to the Northwestern University 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.

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

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

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

7.3.3.2 Reporting to the Northwestern University IRB

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

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment)
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 5 working days of notification.

- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

7.3.3.3 Reporting to the FDA

All reporting to the FDA will be completed by the Northwestern Quality Assurance (QA) department.

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

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DMC).

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

7.3.3.4 Reporting to Novartis

(NOTE: As of the 2nd March 2015, Novartis has taken over the pharmacovigilance activities.)

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

- after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment/participation
- 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
- 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; 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 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) Novartis Study Code (CPZP034BUS52T) must be on the SAE coversheet. Should the designated SAE Fax # be non-functional please send SAEs to the designated SAE mailbox: clinicalsafetyop.phuseh@novartis.com. 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 5 working days.

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. A 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 will be kept per local standard operating procedures.

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.

8.0 DRUG INFORMATION

8.1 Topotecan

8.1.1 Other names: HYCAMTIN (Topotecan hydrochloride)

8.1.2 Classification - type of agent: Topotecan is a topoisomerase 1 inhibitor.

8.1.3 **Mode of action**: The anti-tumor activity of topotecan involves the inhibition of topoisomerase-I, an enzyme intimately involved in DNA replication as it relieves the torsional strain introduced ahead of the moving replication fork. Topotecan inhibits topoisomerase-I by stabilizing the covalent complex of enzyme and strand-cleaved DNA which is an intermediate of the catalytic mechanism. The cellular sequela of inhibition of topoisomerase-I by topotecan is the induction of protein-associated DNA single-strand breaks.

8.1.4 **Storage and stability:** Store refrigerated 2º to 8ºC (36º to 46ºF). Store the bottles protected from light in the original outer cartons.

8.1.5 **Protocol dose specifics:** 8 milligrams orally on day 1, 8, 15 of a 28 day cycle. Drug to be taken with or without food.

8.1.6 **Preparation:** No preparation is required.

8.1.7 **Route of administration for this study:** Oral (by mouth**)**

8.1.8 **Incompatibilities:** As with other myelosuppressive cytotoxic agents, greater myelosuppression is likely to be seen when topotecan is used in combination with other cytotoxic agents (e.g. paclitaxel or etoposide) thereby necessitating dose reduction. However, in combining with platinum agents (e.g. cisplatin or carboplatin), there is a distinct sequence-dependent interaction depending on whether the platinum agent is given on day 1 or 5 of the topotecan dosing. If the platinum agent is given on day 1 of the topotecan dosing, lower doses of each agent must be given compared to the doses which can be given if the platinum agent is given on day 5 of the topotecan dosing. When topotecan (0.75 mg/m2/day for 5 consecutive days) and cisplatin (60 mg/m2/day on Day 1) were administered intravenously in 13 patients with ovarian cancer, mean topotecan plasma clearance on Day 5 was slightly reduced compared to values on Day 1. As a result, systemic exposure of total topotecan, as measured by AUC and Cmax, on Day 5 were increased by 12% (95% CI; 2%, 24%) and 23% (95% CI; —7%, 63%), respectively. No pharmacokinetic data are available following topotecan (0.75 mg/m2/day for 3 consecutive days) and cisplatin (50 mg/m2/day on Day 1) in patients with cervical cancer.

When oral topotecan was combined with cisplatin in a randomized Phase 3 study in chemotherapy-naïve, extensive disease, small cell lung cancer patients, the regimen of oral topotecan (1.7 mg/m2/d for 5 days) with i.v. cisplatin (60 mg/m2 on day 5) was selected.

Topotecan is a substrate for both ABCG2 (BCRP) and ABCB1 (P-glycoprotein). Inhibitors of ABCB1 and ABCG2 (eg. elacridar) administered with oral topotecan increased topotecan exposure. The effect of elacridar on the pharmacokinetics of intravenous topotecan was much less than the effect on oral topotecan Cyclosporin A (an inhibitor of ABCB1, ABCC1 [MRP-1], and CYP3A4) with oral topotecan increased topotecan AUC.

Patients should be carefully monitored for adverse events when oral topotecan is administered with a drug known to inhibit ABCG2 or ABCB1

The pharmacokinetics of topotecan after oral administration were generally Unchanged when coadministered with ranitidine.

NOTE: Refer to Appendix B for oral topotecan drug interactions.

8.1.9 Availability & Supply: Please complete the drug order form located on the protocol page in NOTIS. This form includes directions for ordering**.**

8.1.10 Side effects
Please refer to current IB for details and a complete list of side-effects.

8.1.11 Nursing implications
Bone Marrow Suppression
Inform patients that topotecan decreases blood cell counts such as white blood cells, platelets, and red blood cells. Instruct patients to notify their healthcare provider promptly for fever or other signs of infection such as chills, cough, or burning pain on urination. Advise patients that frequent blood tests will be performed while taking topotecan to monitor for bone marrow suppression.

Embryofetal Toxicity
Advise patients on pregnancy planning and prevention. Advise females of reproductive potential to use highly effective contraception during treatment and for 1 month following treatment with topotecan.
Advise males with a female sexual partner of reproductive potential to use effective contraception during and for 3 months after treatment.

Nursing Mothers
Advise patients to discontinue nursing during treatment with topotecan.

Infertility
Advise male and female patients of the potential risk for impaired fertility and possible family planning options.

Diarrhea
Inform patients that topotecan capsules cause diarrhea which may be severe and life-threatening. Instruct patients how to manage and/or prevent diarrhea and to inform their physician if severe diarrhea occurs during treatment with topotecan capsules.

8.1.12 Return and Retention of Study Drug: Unused or defective drug will be destroyed. Sponsor Novartis should be notified of this action.

8.2 Pazopanib

8.2.1 Other names: Votrient; GW786034B

8.2.2 Classification - type of agent: Multi-target tyrosine kinase inhibitor (TKI)

8.2.3 Mode of action: Pazopanib is an orally administered, potent multi-target tyrosine kinase inhibitor (TKI) of Vascular Endothelial Growth Factor Receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor (PDGFR)-α and –β, and stem cell

factor receptor (c-KIT), with IC50 values of 10, 30, 47, 71, 84 and 74 nM, respectively.

8.2.4 Storage and stability: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)

8.2.5 Protocol dose specifics: 800 mg (4x200mg) pazopanib per day should be taken orally without food at least one hour before or two hours after a meal.

8.2.6 Preparation
No preparation is required.

8.2.7 Route of administration for this study
Oral (by mouth)

8.2.8 Incompatibilities: Refer to Appendix A1 for a list of general drugs that should be avoided with pazopanib.

In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib.

Agents that may Increase pazopanib Blood Concentrations
CYP3A4 Inhibitors: Co-administration of pazopanib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase pazopanib concentrations. Grapefruit juice may also increase plasma concentrations of pazopanib. Administration of 1500 mg lapatinib a substrate and weak inhibitor of CYP3A4, Pgp and BCRP with 800 mg pazopanib resulted in an approximately 50 % to 60 % increase in mean pazopanib AUC(0-24) and Cmax compared to administration of 800 mg pazopanib alone. Co-administration of pazopanib with a CYP3A4, Pgp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma pazopanib concentrations. Combination with strong CYP3A4 inhibitors should therefore be avoided, or selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended. A dose reduction of pazopanib should be considered when it must be coadministered with strong CYP3A4 inhibitors (see Dosage and Administration).

Agents that may Decrease pazopanib Blood Concentrations
CYP3A4 Inducers: CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended.

Effects of Pazopanib on CYP Substrates
In vitro studies with human liver microsomes showed that pazopanib inhibited CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2E1. Potential induction of human CYP3A4 was demonstrated in an in vitro human PXR assay. Clinical pharmacology studies, using pazopanib 800 mg once daily, have demonstrated that pazopanib does not have a clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate), warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer patients. Pazopanib resulted in an increase of approximately 30 % in the mean AUC and Cmax of midazolam (CYP3A4 probe substrate) and increases of 33% to 64% in the ratio of

dextromethorphan to dextrorphan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Co-administration of pazopanib 800 mg once daily and paclitaxel 80 mg/m2 (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26 % and 31 % in paclitaxel AUC and Cmax, respectively.

Effects of Pazopanib on Other Enzymes and Transporters
In vitro studies also showed that pazopanib is a potent inhibitor of UGT1A1 and OATP1B1 with IC50 of 1.2 and 0.79 μM respectively. Pazopanib may increase concentrations of drugs primarily eliminated through UGT1A1 and OATP1B1.

Effect of concomitant use of Pazopanib and Simvastatin
Concomitant use of pazopanib and simvastatin increases the incidence of ALT elevations. Across monotherapy studies with pazopanib, ALT > 3x ULN was reported in 126/895 (14%) of patients who did not use statins, compared with 11/41 (27%) of patients who had concomitant use of simvastatin (p= 0.038). If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for pazopanib posology and discontinue simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.

Effect of proton pump inhibitors and gastric pH on Pazopanib
Administration of pazopanib with a proton pump inhibitor (PPI) results in a 40% reduction in AUC and time to Cmax of pazopanib. Therefore, proton pump inhibitors should be avoided with pazopanib. Drugs that raise gastric pH should also be avoided. If such drugs are needed, short acting antacids should be considered in place of PPIs and H2 receptor antagonists. Separate antacid and pazopanib dosing by several hours to avoid reduction in pazopanib exposure.

Effect of Food on Pazopanib
Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and Cmax. Therefore, pazopanib should be administered at least 1 hour before or 2 hours after a meal.

8.2.9 Availability & Supply: Please complete the drug order form located on the protocol page in NOTIS. This form includes directions for ordering.

Currently all sites are using Pazopanib clinical supply that is provided by GlaxoSmithKline (GSK). As each site exhausts this supply, sites will transition to commercial Pazopanib supply provided by Novartis.

As of March 2016 Votrient (Pazopanib) commercial supply with auxiliary label will also be available for the study, provided by Novartis. This commercial supply study drug should be administrated and stored according to the instructions specified on the drug labels. There is no set date when commercial supply will take over the clinical supply. It will depend on when the clinical supply is exhausted at each site.

8.2.10 Side effects
Please refer to current IB for details and a complete list of side-effects.

8.2.11 Nursing implications
• Therapy with pazopanib may result in hepatobiliary laboratory abnormalities. Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of pazopanib and at Weeks 3, 5, 7, and 9. Thereafter, monitor at Month 3 and at Month 4, and as clinically indicated. Inform patients that they should report signs and symptoms of liver dysfunction to their healthcare provider right away.

• Prolonged QT intervals and torsades de pointes have been observed. Patients should be advised that ECG monitoring may be performed. Patients should be advised to inform their physicians of concomitant medications.

• Cardiac dysfunction (such as CHF and LVEF decrease) has been observed in patients at risk (e.g., prior anthracycline therapy) particularly in association with development or worsening of hypertension. Patients should be advised to report hypertension or signs and symptoms of congestive heart failure.

• Serious hemorrhagic events have been reported. Patients should be advised to report unusual bleeding.

• Arterial thrombotic events have been reported. Patients should be advised to report signs or symptoms of an arterial thrombosis.

• Reports of pneumothorax and venous thromboembolic events including pulmonary embolus have been reported. Patients should be advised to report if new onset of dyspnea, chest pain, or localized limb edema occurs.

• Advise patients to inform their doctor if they have worsening of neurological function consistent with RPLS (headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances).

• Hypertension and hypertensive crisis have been reported. Patients should be advised to monitor blood pressure early in the course of therapy and frequently thereafter and report increases of blood pressure or symptoms such as blurred vision, confusion, severe headache, or nausea and vomiting.

• GI perforation or fistula has occurred. Advise patients to report signs and symptoms of a GI perforation or fistula.

• VEGFR inhibitors such as pazopanib may impair wound healing. Advise patients to stop pazopanib at least 7 days prior to a scheduled surgery.

• Hypothyroidism and proteinuria have been reported. Advise patients that thyroid function testing and urinalysis will be performed during treatment.

• Serious infections including some with fatal outcomes have been reported. Advise patients to promptly report any signs or symptoms of infection.

• Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.

• Gastrointestinal adverse reactions such as diarrhea, nausea, and vomiting have been reported with pazopanib. Patients should be advised how to manage diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs.

• Patients should be advised to inform their healthcare providers of all concomitant medications, vitamins, or dietary and herbal supplements.

• Patients should be advised that depigmentation of the hair or skin may occur during treatment with pazopanib.

• Patients should be advised to take pazopanib without food (at least 1 hour before or 2 hours after a meal).

8.2.12 Return and Retention of Study Drug: Unused or defective drug will be destroyed. Sponsor Novartis should be notified of this action.

9.0 CORRELATIVES/SPECIAL STUDIES

For Cohort 1 and 3:
Cell-free circulating tumor DNA (ctDNA) will be analyzed using the CAPP-Seq method [1,2], a targeted hybrid capture-based NGS method, or the commercial version of CAPP-Seq called AVENIO [3]. Hybrid capture-based NGS was recently developed to improve the detection of multiple cancer mutations with high sensitivity and without significant prior knowledge of the alterations [4–6]. In this "hybrid capture" approach, relevant DNA sequences are hybridized to biotinylated probes [1]. Biotin is bound to streptavidin beads and then unbound DNA is washed away to "pull down" the bait DNA for NGS analysis [1]. Using this principle, Newman and Bratman et al. implemented an ultrasensitive ctDNA detection technique called Cancer Personalized Profiling by Deep Sequencing (CAPP-Seq) [1]. Recurrently mutated genomic regions in the population of a given cancer type are identified through bioinformatic analysis of cancer WES and/or WGS data from databases such as The Cancer Genome Atlas (TCGA) and Catalog of Somatic Mutations in Cancer (COSMIC) [1]. Biotinylated probes are designed against these recurrently mutated regions, and are referred to collectively as the "Selector" [1]. The "Selector" is applied to cell-free DNA from cancer patients, which is followed by NGS in order to quantitate ctDNA with a detection limit of ~0.01% [1,5]. The detection limit was significantly improved to ~0.001% when a NGS error-correction strategy called integrative digital error suppression (IDES) was implemented [2]. This strategy utilized UMIs to reduce the effect of PCR errors and a bioinformatic error correction step called "polishing" to reduce the effect of stereotypical background artifacts [2].

For this project, we will be applying CAPP-Seq to blood and tissue as we have done previously [1,2,7], by isolating DNA from ~10 mL of plasma, inputting ~32 ng into the CAPP-Seq library preparation protocol which starts with adapter ligation, performing PCR, then targeted hybrid capture, and then NGS on a NovaSeq, HiSeq4000 or a NextSeq. We then will analyze the results using the CAPP-Seq or AVENIO bioinformatics pipeline which enables variant-calling and calculation of variant allele fractions (VAFs) which are averaged at each time point to yield the mean VAF. We will use this measure, as well as the ctDNA concentration (VAF x cfDNA concentration) to quantify ctDNA at each time point, and correlate these results with demographic, diagnostic, treatment, and outcomes data.

For Cohort 2:
Sleijfer et al. recently published a translational study in which they evaluated whether cytokine levels in the patients enrolled in EORTC 62043, the phase II study of pazopanib in soft tissue sarcoma, correlated with PFR and OS. They measured levels of several cytokines at baseline and 12 weeks after beginning pazopanib therapy and demonstrated that baseline levels were not predictive, but that high sVEGFR2 and low PIGF were associated with a more favorable PFR at 12 weeks (OR 0.636, 95% CI 0.413-0.977, P=0.039) and (OR 1.081, 95% CI 1.007-1.160, P=0.0318) respectively. There was also a trend toward high sVEGFR2 at week 12 and increased OS and a statistically significant association between low PIGF levels at week 12 and longer OS (HR 1.061, 95% CI 1.025-1.099, P=0.0009) 6.

We propose to measure sVEGFR2 and PIGF levels in blood to both verify the results of Sleijfer et al and to determine if there is an even earlier correlation that can be detected between levels of these cytokines and PFR as well as OS which may allow us to better predict treatment response early on in therapy.

9.1 Sample Collection Guidelines (please see the lab manual for full details)

Mandatory whole blood samples will be collected at screening or predose on Cycle 1 Day 1, and day 1 of Cycles 2, 3, and 4. Approximately 20 ml of anticoagulated whole blood will be collected in 2 EDTA purple top tubes and 1 SST red top tube at each timepoint. Whole blood for DNA, mononucleated cells, and serum should be immediately prepared from the 2 EDTA purple top tubes and SST red top tube, respectively, and frozen down to -80˚ C prior to shipment using standard laboratory techniques. Samples should be labeled with the corresponding patient's study ID number, initials, and date of collection.

9.2 Sample Processing, Storage, and Shipment

Prepared, frozen blood samples should be shipped on dry ice to the Van Tine Lab at Washington University (see address below). Samples may be sent in batches approximately every 2 months. Once received, specimens will be processed in the Tissue

Core Procurement Facility at Washington University to store nucleated blood cells, DNA, and serum for potential future molecular biomarker studies.

Blood samples for correlative study should be sent to the following address:

Oncology – Van Tine lab
4515 McKinley Building, 3rd Floor
4523 Clayton Avenue
St. Louis, MO 63110

9.1 Sample Collection Guidelines (please see the lab manual for full details)

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10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a single arm two-stage Simon optimum Phase II study of pazopanib and topotecan with progression-free rate at 12 weeks as the primary outcome. The historic PD free rate at 12 weeks for single agent pazopanib is 55%. To detect a 20% improvement (an 11% absolute improvement) with the combination of pazopanib and topotecan in a single-arm two-stage optimum design and a one-tailed exact binomial p- value, a total of 92 evaluable STS patients is required to detect 55% vs 66% with 80%

power and an alpha level of 10%. If 32 out of the first 55 patients are alive and progression free at 12 weeks, the trial may enroll up to 108 patients in order to acquire a total of 92 evaluable patients. At that time, if 56 or more out of 92 are alive and progression-free at 12 weeks, then the trial will conclude that the true 12 week PFS rate is at least 66%. There is a 63% probability of terminating the study after the first stage when the true rate is 55%. See sections 6.0 and 7.0 for definitions of evaluable patients for response and adverse event information.

Osteosarcoma/Liposarcoma exploratory group:
Up to 36 patients with osteosarcoma and 20 patients with liposarcoma will be enrolled to obtain exploratory information for patients with these two histologies. Although the sample sizes in these two cohorts were selected for feasibility rather than to power a specific hypothesis, 56 subjects will provide estimates of PFR and OS with sufficient precision to support additional study of pazopanib in these patients.

10.2 Sample Size and Accrual

A total of 92 evaluable STS patients is required to detect 55% vs 66% with 80% power and an alpha level of 10%. If 32 out of the first 55 patients are alive and progression free at 12 weeks, this trial may enroll up to 108 STS patients in order to accrue a total of 92 evaluable patients. If the trial has not yet achieved 32 responses, may be suspended to enrollment to allow the 55th patient to reach week 12 of treatment for evaluation.

In addition, up to 36 patients with osteosarcoma and 20 patients with liposarcoma will be enrolled to obtain exploratory information for patients with these two histologies. Data exists to help construct baseline event free survival outcomes that can be used as a comparison for future phase II trials for recurrent osteosarcoma (J Clin Oncol. 2016 Sep 1;34(25):3031-8. doi: 10.1200/JCO.2015.65.5381. Epub 2016 Jul 11.)
Using a single arm, 2 stage Phase II trial design: For stage I- If 4 or more of 19 patients have disease control of greater than 4 months then Stage 2 should be opened. The endpoint is that if 11 or more patients/ 36 have disease control at 4 months, then the agent is considered sufficiently efficacious for additional study.

As the study has been using 12 week and 20 week endpoints, we can use 20 weeks instead of 16 weeks as a surrogate endpoint.

The DMC reviewed the interim analysis data on 1/11/2017, and has approved cohort 1 to reopen to 96 total patients(to obtain 92 evaluable patients). In addition, based on the percentage of non-evaluable patients during the interim analysis, it was determined that a total of 108 patients would most likely need to be enrolled in order to obtain 92 evaluable patients.

The remaining slots have been equally divided in 5 ways among the sites, with an expiration date of May 12, 2017. Status of accrual will be reassessed at that time, and the remaining slots will be divided accordingly.

The 16 additional osteosarcoma slots will only be available at Northwestern (NMH).

10.3 Data Analyses Plans

PFR and OS will be estimated for each histologic group (STS, osteoscaroma, and liposarcoma) using Kaplan-Meier methods. Response rates will be summarized by the observed proportion of patients with response, along with a 95% confidence interval. Toxicities will be tabulated and summarized by the number of patients experiencing each toxicity. A formal hypothesis test for the median PFR of the STS patients is planned; no formal hypothesis test is planned for the other two histologic groups.

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.

For patients with limited English proficiency who are approached for participation in the study, an IRB approved short form will be used. In addition, the services of an interpreter fluent in both English and the language understood by the potential study patient will be obtained. The patient will be re-consented using the IRB approved translated consent in the language understood by the patient, when available. The exact process will be conducted in accordance to local IRB guidelines and policies.

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 GlaxoSmithKline. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

Patients may not begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Research Office at Northwestern University before enrollment to study. Please contact the assigned Quality Assurance Monitor (QAM) or email the QA Department (croqualityassurance@northwestern.edu) for questions regarding patient registration.

Prior to registration, eligibility criteria must be confirmed by the assigned QAM. The study coordinator will screen all subjects for potential registration via the web-based application NOTIS (Northwestern Oncology Trial Information System), which is available at: https://notis.nubic.northwestern.edu. Please note that a username and password is required to use this program, and will be provided during site activation prior to training on the NOTIS system.

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)

Training on eCRF completion will be provided at the time of site activation.

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

11.4 Data Submission

Once a subject is confirmed and registered to the study, eCRFs should be submitted according to the detailed data submission guidelines (provided in a separate document). Please see the data submission guidelines located on the protocol page in NOTIS.

Please contact croqualityassurance@northwestern.edu for further details

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 Participating Site Questionnaire 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 Participating Site Questionnaire.

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:
http://cancer.northwestern.edu/CRO/data/DataandSafetyMonitoringPlanMay2014.pdf

The level of risk attributed to this study requires high-intensity monitoring as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to the Appendices for additional data submission instructions.

11.7 Adherence to the Protocol

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

11.7.1 Emergency Modifications

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

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

11.7.2 Other Protocol Deviations

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

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

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of 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. 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.

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APPENDICES

APPENDIX A1. GENERAL DRUGS TO BE AVOIDED WITH PAZOPANIB

- **CYP3A4 STRONG INHIBITORS**
- **CYP3A4 STRONG INDUCERS**
- **CYP SUBSTRATES**
- **SIMVASTATIN (USED WITH CAUTION)**
- **PROTON PUMP INHIBITORS AND H2 RECEPTOR BLOCKERS**

APPENDIX A2. Table of Drugs known to be metabolized by CYP450 isoenzymes 2D6 and 3A4 (to be avoided with pazopanib)

CYP3A3/4	
Substrates	
Acetaminophen	Chlorpromazine
Aifentanil	Cimetidine
Alosetron	Cisapride
Alprazolam	Citałopram
Amiodarone	Clarithromycin
Amitriptyline (minor)	Clindamycin
Amlodipine	Clomipramine
Anastrozole	Clonazepam
Androsterone	Clozapine
Antipyrine	Cocaine
Astemizole	Codeine (demethylation)
Atorvastatin	Cortisol
Benzphetamine	Cortisone
Bepridil	Cyclobenzaprine (demethylation)
Bexarotene	Cyclophosphamide
Bromazepam	Cyclosporine
Bromocriptine	Dapsone
Budesonide	Dehydroepiandrostendione
Bupropion (minor)	Delavirdine
Buspirone	Desmethyldiazepam
Busutfan	Dexamethasone
Caffeine	Dextromethorphan (minor, N-demethylation)
Cannabinoids	
Carbamazepine	Diazepam (minor; hydroxylation, N-demethylation)
Cevimeline	
Cerivastatin	Nefazodone
Digitoxin	Nelfinavir
Diltiazem	Nevirapine
Disopyramide	Nicardipine
Docetaxel	Nifedipine
Dolasetron	Niludipine
Donepezil	Nimodipine
Doxorubicin	Nisoldipine
Doxycycline	Nitrendipine

Dronabinol	Omeprazole (sulfonation)
Enalapril	Ondansetron
Erythromycin	Oral contraceptives
Estradiol	Orphenadrine
Ethinyl estradiol	Paclitaxel
Ethosuximide	Pantoprazole
Etoposide	Pimozide
Exemestene	Pioglitazone
Dofetilide (minor)	Pravastatin
Felodipine	Prednisone
Fentanyl	Progesterone
Fexotenadine	Proguanil
Finaxteride	Propafenone
Fluoxetine	Quercetin
Flutamide	Quetiapine
Glyburide	Quinidine
Granisetron	Quinine
Halofantrine	Repaglinide
Hydrocortixone	Retinoic acid
Hydroxyarginine	Rifampin
Ifosfamide	Risperidone
Imipramine	Ritonavir
Indinavir	Salmeterol
Isradipine	Saquinavir
Itraconazole	Sertindole
Ketoconazole	Sertraline
Lansoprazole	Sibutramine
Letrozole	Sildenafil citrate
Levobupivicaine	Simvastatin
Lidocaine	Sirolimus
Loratadine	Sufentanil
Losartan	Tacrolimus
Lovastatin	Tamoxifen
Methadone	Temazepam
Mibefradil	Teniposide
Miconazole	Terfenadine
Midazolam	Testosterone
Mifepristone	Tetrahydrocannabinol
Mirtazapine (N-demethylation)	Theophylline
Montelukast	Tiagabine
Navelbine	Tolterodine
Toremifene	Vincristine
Trazodone	Warfarin (R-warfarin)
Tretinoin	Yohimbine
Triazolam	Zaleplon (minor pathway)
Troglitazone	Zatoestron
Troleandomycin	Zileuton
Venlafaxine (N-demethylation)	Ziprasidone
Verapamil	Zolpidem
Vinblastine	Zonisamide

Inducers	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Ethosuximide	Progesterone
Glucocorticoids	Rifabutin
Griseofulvin	Rifampin
Nafcillin	Rofecoxib (mild)
Nelfinavir	St John's wort
Nevirapine	Sulfadimidine
Oxcarbazepine	Sulfinpyrazone
Phenobarbital	Troglitazone
Phenylbutazone	
Inhibitors	
Amiodarone	Ketoconazole
Anastrozole	Metronidazole
Atazanavir	Mibefradil
Azithromycin	Miconazole (moderate)
Cannabinoids	Nefazodone
Cimetidine	Nelfinavir
Clarithromycin	Nevirapine
Clotrimazole	Norfloxacin
Cyclosporine	Norfluoxetine
Danazol	Omeprazole (weak)
Delavirdine	Oxiconazole
Dexamethasone	Paroxetine (weak)
Diethyldithiocarbamate	Propoxyphene
Diltiazem	Quinidine
Dirithromycin	Quinine
Disulfiram	Quinupristin and dalfopristin
Entacapone (high dose)	Ranitidine
Erythromycin	Ritonavir
Ethinyl estradiol	Saquinavir
Fluconazole (weak)	Sertindole
Fluoxetine	Sertraline
Fluvoxamine	Telithromycin
Gestodene	Troglitazone
Grapefruit juice	Troleandomycin
Indinavir	Valproic acid (weak)
Isoniazid	Verapamil
Itraconazole	Voriconazole
	Zafirlukast
	Zileuton

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In : Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 8th ed. Hudson, OH; LexiComp Inc. 2000: 1364-1371)

APPENDIX B. TABLE OF ORAL TOPOTECAN DRUG INTERACTIONS

Breast Cancer Resistance Protein (ABCG2, BCRP, MXR) Inhibitors and Inducers
Antiestrogens: tamoxifen, toremifene
Antiretrovirals, Protease inhibitors: ritonavir, nelfinavir, saquinavir
Proton pump inhibitors: pantoprazole, omeprazole
Others: diethylstillbesterol, estrone, flavopiridol, novobiocin, reserpine, carbamazepine
P-glycoprotein (ABCB1, P-gp, MDR1) Inhibitors and Inducers
Antifungals: Itraconazole, etraconazole, ketoconazole, clotrimazole
Antiretrovirals, Protease inhibitors: amprenavir, indinavir, ritonavir, nelfinavir, saquinavir
Antibiotics: erythromycin, rifampin
Calcium channel blockers: diltiazem, nicardipine, verapamil
Anticonvulsants: carbamazepine, phenobarbital
Analgesics: meperidine, methadone, morphine, pentazocine
Immune modulators: Valspodar
Others: Atorvastatin, bromocriptine, carvedilol, omeprazole, progesterone, quinine, dexamethasone (large doses), phenothiazine, retinoic acid, St. John's wort

APPENDIX C. NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

The **New York Heart Association (NYHA) Functional Classification** provides a simple way of classifying the extent of heart failure. It places patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain:

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.	No objective evidence of cardiovascular disease
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.	Objective evidence of minimal cardiovascular disease
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.	Objective evidence of moderately severe cardiovascular disease
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.	Objective evidence of severe cardiovascular disease

APPENDIX D – DATA COLLECTION & SUBMISSION GUIDELINES

Please see the data submission guidelines located on the protocol page in NOTIS.

APPENDIX E – DATA SAFETY MONITORING PLAN

http://cancer.northwestern.edu/CRO/data/DataandSafetyMonitoringPlanMay2014.pdf

Note: Link inserted in appropriate sections

APPENDIX F- PATIENT MEDICATION DIARY

NU 14S03: Topotecan

Dispensed date: ____ Patient's Study ID_____Patient's Initials _____ **Cycle # _____**

Instructions to the Patient:

1. You will take capsules of topotecan by mouth once a week for the first three weeks. On the fourth week you will not take topotecan.
2. You should swallow the capsules whole with at least 1 cup (8 ounces) of water, with or without food.
3. If you vomit on a day where you take both medications, you will take your next dose of topotecan one week later and your next dose of pazopanib the following day.

Topotecan dose: _____mg			
Day	**Date**	**Time Taken**	**Comments (please note if you vomit/and any other symptoms you experience)**
1		____a.m. ____p.m.	
2		**DO NOT TAKE TOPOTECAN ON THESE DAYS.**	
3			
4			
5			
6			
7			
8		____a.m. ____p.m.	
9		**DO NOT TAKE TOPOTECAN ON THESE DAYS.**	
10			
11			
12			
13			
14			
15		____a.m. ____p.m.	
16			
17			

18		**DO NOT TAKE TOPOTECAN ON THESE DAYS.**
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		

Physician's office will complete this section:

1. Total # of pills dispensed: _____
2. Total # of pills taken this cycle:_____
3. Total # of pills returned:_____
4. Patient's signature: _____Date:_____
5. Reviewer's signature:_____ Date:_____

NU 14S03 Medication Diary: Pazopanib

Dispensed date: _____ Patient's Study ID_____Patient's Initials ___ Cycle#_____

Instructions to the Patient:

1. Take pazopanib by mouth 1 time every day at about the same time each day. Take it on an empty stomach (at least 1 hour before and 2 hour after eating) with about 1 cup (8 ounces) of water.
2. If you vomit on a day where you only take pazopanib, the next dose would be the following day. If you vomit on a day where you take both medications, you will take your next dose of topotecan one week later and your next dose of pazopanib the following day.

Pazopanib ___ mg once daily			
Day	**Date**	**Time Taken**	**Comments (please note if you vomit/and any other symptoms you experience)**
1		____a.m. ____p.m.	
2		____a.m. ____p.m.	
3		____a.m. ____p.m.	
4		____a.m. ____p.m.	
5		____a.m. ____p.m.	
6		____a.m. ____p.m.	
7		____a.m. ____p.m.	
8		____a.m. ____p.m.	
9		____a.m. ____p.m.	
10		____a.m. ____p.m.	
11		____a.m. ____p.m.	
12		____a.m. ____p.m.	
13		____a.m. ____p.m.	
14		____a.m. ____p.m.	
15		____a.m. ____p.m.	
16		____a.m. ____p.m.	
17		____a.m. ____p.m.	

18		____a.m. ____p.m.	
19		____a.m. ____p.m.	
20		____a.m. ____p.m.	
21		____a.m. ____p.m.	
22		____a.m. ____p.m.	
23		____a.m. ____p.m.	
24		____a.m. ____p.m.	
25		____a.m. ____p.m.	
26		____a.m. ____p.m.	
27		____a.m. ____p.m.	
28		____a.m. ____p.m.	

Physician's office will complete this section:

1. Total # of pills dispensed:_____
2. Total # of pills taken this cycle:_____
3. Total # of pills returned:_____
4. Patient's signature: _____
   Date:_____
5. Reviewer's signature:_____
   Date:_____

APPENDIX G – BLOOD PRESSURE LOG

Protocol Number _____ Institution _____

Subject Initials _____ Study ID # _____

Cycle ___	Date of assessment	Time of assessment	Systolic/Diastolic (mmHg)	Comments
Week 1				
Week 2				
Week 3				
Week 4				

Blood pressure should be recorded weekly during the treatment (+/- 3 days).

_____ _____

CRA Initials Date of Completion

Appendix H- Protocol History of Changes

Original Version Submitted to the IRB – December 02, 2014			
Amendment 1 – February 04, 2015 *Approved by SRC – February 04, 2015*			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Title Page	Sub-Investigators list	Thomas McFarland, MD and Keith Skubitz, MD removed	Administrative
Title Page	IND Number: TBD	Revised to "IND Number: EXEMPT"	Administrative
Study Schema, Study Summary, Sections 3.0, 10.1, 10.2	Up to 20 patients will be enrolled (if the first five patients are alive and continuing therapy at 12 weeks, the remaining 15 patients will be enrolled in the osteosarcoma and liposarcoma groups)	Up to 20 patients will be enrolled in the osteosarcoma and liposarcoma groups	The osteosarcoma and liposarcoma groups are exploratory and need 20 patients accrued to evaluate activity.
Section 5.0 (Study Procedures)	Footnote f includes "CMP and LFTs should include: ALT, AST."	Revised to list all tests included in the CMP and LFTs	Revised for accuracy
Amendment 2 –April 1, 2015 *Approved by Scientific Review Committee- April 15, 2015*			
Sections(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
3.1.3 (Inclusion Criteria)	"Patients must have a histologically confirmed diagnosis of : • metastatic soft tissue sarcomas (non-liposarcoma) • metastatic osteosarcoma • metastatic liposarcoma- high grade, de-differentiated, or myxoid NOTE: Pathology is not required to be reviewed at the treating institution. A copy of the pathology report is sufficient for eligibility purposes"	Revised to "Patients must have a histologically confirmed diagnosis of **metastatic or locally advanced unresectable :** • soft tissue sarcomas (non-liposarcoma) • osteosarcoma • liposarcoma- high grade, de-differentiated, or myxoid *NOTE*: *Pathology is not required to be reviewed at the treating institution. A copy of the pathology report is sufficient for eligibility purposes"*	Revised to clarify that patients must have both **metastatic or locally advanced unresectable** soft tissue sarcomas (non-liposarcoma), Osteosarcoma, or liposarcoma- high grade, de-differentiated, or myxoid

5.0 (Study Procedures)	n/a	Revised to add to "X" Chemistry labs on C1D1	r advertently missed on previous amendment
Amendment 3 –June 2, 2015 *Approved by Scientific Review Committee- September 2, 2015*			
Sections(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
All	Multiple fonts	All text changed to one font	Consistency
3.1.1 Inclusion Criteria	Patients must have had a minimum of 1 and a maximum of 4 prior chemotherapy regimens for recurrent/metastatic disease. It will be up to the investigator to determine what constitutes a "regimen" in each case	**Cohort 1**: Patients must have had a minimum of 1 and a maximum of 4 prior chemotherapy regimens for recurrent/metastatic disease. It will be up to the investigator to determine what constitutes a "regimen" in each case. **Cohort 2 and 3**: Patients must have had a minimum of 1 and maximum of any number of prior chemotherapy regimens for recurrent/metastatic disease.	As cohorts 2 and 3 are exploratory only, the chemotherapy regimen maximum does not apply to these cohorts.
3.2.10 Exclusion Criteria	Patients with a history of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism, or untreated deep venous thrombosis (DVT). Patients with DVT must have received appropriate therapy for at least 6 months to be considered eligible	History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months. Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible	Updated based on previous studies using this combination of drugs.
4.3 Toxicity Management	N/A	Added clarification of how toxicity should be assessed within cycles	Clarification
5.0 Study Parameters	N/A	Removed reconsenting requirement within 30 days. Clarified T4 only needed done if TSH was abnormal. Clarified when correlative samples should be drawn.	Clarification
Amendment 4 – February 02, 2016 *Approved by Scientific Review Committee - January 5, 2016*			
Sections(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***

3.2.10 Exclusion Criteria	Rhabdomyosarcoma (embryonal, alveolar, pleomorphic)	Removed pleomorphic Rhabdomyosarcoma	Pleomorphic subtype will now be eligible
3.2.17 Exclusion Criteria	Treatment with any of the following anti-cancer therapies: • radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of therapy • chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of therapy	Removed chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of therapy.	To update that the excluded treatment categories.
4.1 Overview & 4.2 Treatment Administration sections	N/A	"Starting dose" indicated for pazopanib & topotecan, where applicable	Clarification
4.3 Toxicity Management, Dose Delays/Modifications & Supportive care	In the case that treatment has been held for 3 weeks for treatment related toxicities, the dose reduction (in the case of pazopanib) for the upcoming cycle should be based on the most severe toxicity experienced in the current cycle.	In the case that treatment has been held for 3 weeks for treatment related toxicities, the dose reduction for the upcoming cycle should be based on the most severe toxicity experienced in the current cycle.	Redundant to mention, "in the case of pazopnaib".
	Patients with stable or responding disease may be retreated at the same dose (both Topotecan and Pazopanib) or at a reduced dose level (pazopanib only), depending upon the adverse events observed in the current cycle and any adverse events present on the first day of the next cycle. If multiple toxicities are seen, the dose administered in a subsequent cycle should be based on the most severe toxicity experienced in the current cycle.	Patients with stable or responding disease may be retreated at the same dose (both Topotecan and Pazopanib) or at a reduced dose level, depending upon the adverse events observed in the current cycle and any adverse events present on the first day of the next cycle. If multiple toxicities are seen, the dose administered in a subsequent cycle should be based on the most severe toxicity experienced in the current cycle.	To update, that dose reduction will be permitted for topotecan also.

	N/A	Topotecan: Three dose reductions are permitted, based on side effects experienced, from 8 mg to 6, 6mg to 4, 4mg to 2. Further dose reduction is not allowed. Patients may be maintained on the lower dose of topotecan during treatment if deemed to be deriving benefit from the drug. Doses that are reduced for topotecan related toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose. Patients whose dose has been reduced for adverse events that are subsequently not felt to be related to topotecan may have the dose re-escalated after completion of one cycle with toxicities less than or equal to grade 1.	To update that the dose of topotecan will/can be reduced based on the adverse events.
Table I- Dose Modification Algorithms for Potential Treatment-Related Adverse Events	Topotecan can be held up to 3 weeks waiting for toxicity to resolve to <Grade 2. Topotecan may be resumed at that time at same dose. Topotecan dose will not be reduced. If toxicity does not resolve in 3 weeks, patient will be removed from treatment.	Topotecan can be held up to 3 weeks waiting for toxicity to resolve to <Grade 2. Topotecan may be resumed at that time at same dose or with a dose reduction by 1 level per physician discretion. If toxicity does not resolve in 3 weeks, patient will be removed from treatment.	To update that the dose reduction for topotecan is now permitted.
	N/A	New table added, indicating the dose levels for topotecan.	Updated based on the new amendment allowing dose reduction for topotecan.
Table III Guidelines for Management of Treatment Emergent Hepatotoxicity	For isolated total bilirubin column - Error! Reference source not found	Deleted	Hyperlink error, now deleted.
5.0 Study Procedures	N/A	Added bilirubin to the LFTs list in the footnote *'f'*	Clarification

	N/A	Added a new footnote *'o'* for toxicity management	To update that the patient has to call-in weekly to report toxicities.
Amendment 5 – March 16, 2016 *Approved by Scientific Review Committee – March 16, 2016*			
Sections(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Title page	One sub-PI from NU Funding Source: Glaxo Smith Kline	***Added*** one more sub-I from NU: Valerie Nelson Funding Source: changed to Novartis	***Per PI*** As of March 2016, Votrient (Pazopanib) commercial supply with auxiliary label will also be available for the study, provided by Novartis. There is no set date when commercial supply will take over the clinical supply. It will depend on when the clinical supply will be exhausted at each site As of Oct 2015, Novartis has taken over all pharmacovigilance activities
Section 3.1.6 Inclusion criteria	The last dose of systemic therapy much have been given at least 4 weeks prior to initiation of therapy	**Wash-out period changed to 28 days:** "The last dose of systemic therapy much have been given ***at least 28 days*** prior to initiation of therapy"	***Per PI***
Section 3.2.16 Exclusion criteria	BCRP and PgP inducers and inhibitors will also be prohibited (Appendix A and B)	BCRP and PgP inducers and inhibitors should be used with caution if another alternative drug is not able to be used (Appendix A and B)	***Per PI and QA (to correct conflicting information within the protocol)***

Section 3.2.16 Exclusion criteria	Unable or unwilling to discontinue use of inducers and inhibitors of CYP450 listed in Appendix for at least 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of study drug and for the duration of the study (Appendix).	Unable or unwilling to discontinue use of inducers and inhibitors of CYP450 listed in Appendix for at least 14 days prior to the first dose of study drug and for the duration of the study (Appendix A).	***Per PI***
Section 3.2.17 Exclusion criteria	Treatment with any of the following anti-cancer therapies: radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of therapy	**Wash-out period changed to 28 days:** "Treatment with any of the following anti-cancer therapies: radiation therapy, surgery or tumor embolization ***within 28 days*** prior to the first dose of therapy"	***Per PI***
Section 3.2.18 Exclusion criteria	Administration of any <u>non-oncologic</u> investigational drug within 30 days or 5 half-lives whichever is longer prior to receiving the first dose of study treatment	**Wash-out period changed to 28 days:** "Administration of any investigational drug within 28 days prior to receiving the first dose of study treatment"	***Per PI***
Exclusion Criteria Section 3.2.7	Corrected QT interval (QTc) > 480 msecs using Bazett's formula (QTc= QT/√RR),	***Added:*** EKG for screening must be ≤ 4 weeks before registration	***Per PI***
Section 4.4.4.	BCRP and PgP inducers and inhibitors will be also prohibited, listed in the Appendix B	BCRP and PgP inducers and inhibitors should be used with caution if another alternative drug is not able to be used (listed in the Appendix B).	***Per PI and QA (to correct conflicting information within the protocol)***
Section 5.0 Study procedures table	**Footnote d:** EKG: Cycle 2 day 1 and then day 1 of every even cycle until end of treatment (+/-3 days)	***Added:*** EKG for screening must be ≤ 4 weeks before registration	***Per PI***
Section 7.0 Adverse events	Reference to appendix for the NU DSMP	***Removed:*** Reference to DSMP ***Inserted:*** DSMP link inserted in text.	***Per NU template***
Section 7.3.3.2 Reporting to the NU IRB	Previous information	***Added:*** "Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is	***Per NU IRB***

	Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within **10 working days** of notification	possibly related to study treatment)" Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within **5 working days** of notification.	
Section 7.3.3.4 Reporting to sponsor	**Instructions about reporting to GlaxoSmithkline**	***Removed:*** GlaxoSmithKline reporting instructions ***Added:*** Instructions about reporting to Novartis	***Per sponsor. As of Oct 2015, Novartis has taken over all pharmacovigilance activities***
Section 8.1.9 Drug Availability and Supply	Drug(Topotecan) ordering and shipment information inserted	***Removed****:* Drug shipment information ***Added*****:** "Please complete the drug order form located on the protocol page in NOTIS. This form includes directions for ordering"	***Per PI and QA***
Section 8.2.9 Drug Availability and Supply	Drug (Pazopanib) ordering and shipment information inserted	***Removed****:* Drug shipment information ***Added:*** "Please complete the drug order form located on the protocol page in NOTIS. This form includes directions for ordering" ***Inserted:*** Currently all sites are using Pazopanib clinical supply that is provided by GlaxoSmithKline (GSK).As each site uses up this supply , they will I transition to the commercial Pazopanib supply provided by Novartis.	***Per PI, QA And sponsor***

		As of March 2016, Votrient (Pazopanib) commercial supply with auxiliary label will also be available for the study, provided by Novartis. This commercial supply study drug should be administrated and stored according to the instructions specified on the drug labels. There is no set date when commercial supply will take over the clinical supply. It will depend on when the clinical supply will be exhausted at each site.	
11.4 Data submission	Data submission guidelines available as Appendix D	***Removed*:** Appendix D details Inserted: New section on Data Submission. (Rest of the sub-sections under 11.0 have been re-numbered accordingly)	***Per NU QA***
Appendix D	Data Collection and Submission Guidelines	***Removed:*** Data Collection and Submission Guidelines ***Inserted:*** "Please see the data submission guidelines located on the protocol page in NOTIS"	***Per NU QA***
Appendix E	DSMP details	***Removed: details*** ***Added:*** Link inserted in appropriate sections	***Per NU QA***
Amendment 6 – July 27, 2016			
Sections(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
Study Schema	Patients with recurrent or metastatic and unresectable or bone or soft tissue sarcoma who failed at least 1 prior therapy	The 'or' has been removed	***Correction of error***

Inclusion criteria Section 3.1.6	Cohort 2 and 3 requirements were stated together Cohort 1: Patients must have had a minimum of 1 and a maximum of 4 prior chemotherapy regimens for recurrent/metastatic disease. Cohort 2: Patients must have had a minimum of 1 and maximum of any number of prior chemotherapy regimens for recurrent/metastatic disease	**Cohort 2 and 3 have been separated.** **Cohort 3:** Patients may have had any number of prior therapies for recurrent/metastatic or locally advanced/unresectable disease. There are no restrictions. Cohort 1: Patients must have had a minimum of 1 and a maximum of 4 prior chemotherapy regimens for recurrent/metastatic ***or locally advanced/unresectable*** disease. Cohort2: Patients must have had a minimum of 1 and maximum of any number of prior chemotherapy regimens for recurrent/metastatic ***or locally advanced/unresectable*** disease.	***Improve clarity, since all 3 cohorts have different requirements.***
Inclusion criteria Section 3.1.8	Patients must have adequate organ function within **7 days** prior to registration. Serum creatinine and creatinine clearance tests were both listed as part of organ function tests. Urine protein to creatinine ratio and 24 hr urine tests were both listed as part of organ function tests.	Patients must have adequate organ function within **14 days** prior to registration. Now, either Serum creatinine 'OR' creatinine clearance listed as part of organ function tests. Clarified that function tests. 24- hour urine protein test is to be done only when UPC≥1. Mention of 'reference of appropriate appendix' has been removed, since the protocol does not have such appendix listed.	***Increase accrual by making criteria less restrictive***. ***Clarification***

Exclusion criteria Section 3.2.7	Corrected QT interval (QTc) > 480 msecs using Bazett's formula (QTc= QT/√RR). EKG for screening must be before registration	Modified to: Corrected QT interval (QTc) > 480 msecs using Bazett's formula (QTc= QT/√RR). EKG for screening must be *within 28 days prior to registration.*	***For clarity, specifying the screening period***.
Exclusion criteria Section 3.2.8	History of Cardiovascular events did not include Left ventricular ejection fraction	Added : Left ventricular ejection fraction < 45% in patients with prior anthracycline use or otherwise at risk for left ventricular systolic dysfunction	***Added for safety purposes***.
Exclusion criteria Section 3.2.10 Section 3.2.11 section 3.2.17	Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible Major surgery or trauma within 28 days prior to first dose of investigational product and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major surgery). radiation therapy, surgery or tumor embolization within 28 days prior to the *first dose of therapy*	Modified: The time periods in these three criteria are specified to be prior to first dose of study treatment	***For clarity***

Exclusion criteria 3.2.16	Unable or unwilling to discontinue use of inducers and inhibitors of CYP450 listed in Appendix.	Unable or unwilling to discontinue use of **strong** inducers and inhibitors of CYP450 listed in Appendix. ***ADDED:*** *Note: As this list is constantly evolving, if a medication is incorrectly documented as prohibited in this protocol, documentation from the site pharmacist to the contrary will be acceptable for the purposes of registration.*	***Added for clarity. It provides for specificity.***

Section 4.3 Toxicity Management, Dose Delays/Modifications & Supportive care	After cycle 1, defined as 4 weeks of therapy, additional cycles of therapy may be administered provided the patient meets the following criteria.	**Modified:** "After cycle 1 day 1 of therapy, defined as 4 weeks of therapy, cycle 1 day 15, cycle 2 day 1, cycle 2 day 15, cycle 3 day 1, and day one of all subsequent cycles may be administered provided the patient meets the following criteria." **Other language** added or modified to include details about lab assessment timelines and delayed/held doses. **Deleted:** **Table 1:** Dose Modification Algorithms for potential treatment-related adverse events for Topotecan **Modified:** Table II which had dose modification algorithms for Pazopanib has been changed to Table 1 and details about "continue Topotecan at current dose" has been added to this table wherever appropriate. Other information added per current IB **Other updates** **Table II** updated according to current Pazopanib Investigator's brochure(IB). **Table III** containing 'Guidelines for management of Treatment Emergent Hepatotoxicity has been reanmed Table II and has been updated according to current Pazopanib IB	For clarity clarifications were added for safety monitoring purposes and to align with current version of Pazopanib IB

Section 4.4.3	No section on Palliative care	**Added section on Palliative Care.** Palliative radiation and surgery are allowed on this trial IF they are not being used to address a target lesion. Parameters to be used have been stated.	***Clarification added to enhance patient care.***
Section 4.4.5 Concomitant medications discouraged while on study	"inducers and inhibitors of Cyp450 listed in appendix A"	***"strong*** inducers and inhibitors of Cyp450 listed in appendix A" **Added:** Note: As this list is constantly evolving, if a medication is incorrectly documented as prohibited in this protocol, documentation from the site pharmacist to the contrary will be acceptable.	Added for clarity. It provides for specificity.
Section 5.0 Study Procedures	**Footnote a** Informed consent must be signed within 30 days of registration. **Footnote b:** Contains timelines for labs and radiologic evaluations **Footnote c:** Information about 'vitals' **Footnote K:** "Radiology assessment by CT or MRI will be done at Week 6, Week 12, Week 20 and every 8 weeks thereafter." N/A	**Footnote 'a' modified to** ***"***Pre-study procedures done within 7 days of C1D1 do not need to be repeated on C1D1. ***Footnote b:*** Added timeline for EKG as well. **Footnote c:** Language regarding vitals modified for clarity. Added statement that 'Blood pressure log to be updated in NOTIS each cycle for duration of treatment.' **Footnote k modified:** "Radiology assessment by CT or MRI will be done at Week 6, Week 12, Week 20 and every 8 weeks (+/- 7 days) thereafter. After 1 year of protocol treatment, patient may be switched to scans every 12 weeks (+/- 7 days) at the discretion of the patient and treating physician." **Footnote p added** in relation to **new row added in table** '**MUGA or ECHO'** Footnote p states that 'ONLY required for patient's with prior anthracycline use OR otherwise at risk for left ventricular systolic dysfunction. Can be assessed by MUGA or echocardiogram."	***Improve clarity and safety monitoring***

	N/A	**Footnote q added in relation to Pazopanib and Topotecan administration schedule added as new rows in the table**: Footnote q states "Day 1 of each cycle should be every 28 days. In the event that this day falls on a holiday or other such event, study team should use +/- 3 day window to complete pre-treatment procedures, and dispense protocol agents to patients with instructions to commence treatment on day 1 as usual. Similarly, any missed doses will not be made up and should be skipped to maintain 28 day cycle."	
Section 6.3 Evaluable for Objective response	Language stating different categories in which patients will be allocated depending on response.	**This language has been removed.** **Added statement:** **"**However, if a patient is removed from treatment prior to their 12 week assessment for reasons other than disease progression or death, they will be considered non-evaluable for response if approved by the DMC. "	***Clarification regarding evaluable patients.***
Section 7.3.3.4 Reporting to Novartis	The date was stated as 19th of October 2015 The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.	The date has been updated to 2nd March 2015. Language modified to say that these will be kept per local standard operating procedures.	***Per update from the sponsor Novartis*** ***Clarification***
Section 8.2.10 Pazopanib side-effects	Some side effects listed	Inserted sentence: 'Please refer to current IB for more details and a complete list of side-effects'	***Added for safety purposes, and to be in alignment with IB updates***

Section 8.1.12 and 8.2.12	language to notify GSK about destruction of unused/defective drug	GSK replaced with Sponsor Novartis	***Study take-over by Novartis from GSK. Sites will start using Novartis drug supply when they exhaust local GSK supplies.***
Section 9.2 Sample processing, storage, shipment	Dr. Brian Van Tine's address listed	Dr.Tine's address has been updated.	***Administrative***
Appendix A1	List of CYP3A4 Inhibitors List of CYP3A4 inducers	The word 'strong' has been added to both indicating strong inducers and inhibitors.	***Increase clarity and specificity. Maintain consistency with rest of the protocol.***
Appendix E	Reference to DSMP	DSMP link inserted here as well	***Administrative***
Appendix F and G	Patient Medication Diary Blood pressure Log	***Both modified with appropriate details***	***For clarity and to be in alignment with current template***
Amendment 7 – January 24th , 2017			
Section(s) Affected	***Prior Version***	***Amendment 7 Changes***	***Rationale***
Study summary and Section 10.2(statistics)	Original statistical details and sample size.	Added language: The DMC reviewed the interim analysis data on 1/11/2017, and has approved cohort 1 to reopen to 96 total patients(to obtain 92 evaluable patients). In addition, based on the percentage of non-evaluable patients during the interim analysis, it was determined that a total of 108 patients would most likely need to be enrolled in	***Changes made following review by DMC on 1/11/17.***

		order to obtain 92 evaluable patients. The remaining slots have been equally divided in 5 ways among the sites, with an expiration date of May 12, 2017. Status of accrual will be reassessed at that time, and the remaining slots will be divided accordingly.	
Study summary and section 3.0	A total of 136 patients may be enrolled including 96 patients with STS (to acquire 92 evaluable patients)	The number 136 has been updated to 148 and 96 has been updated to 108.	***Based on the percentage of non-evaluable patients during the interim analysis by DMC, it was determined that a total of 108 patients would most likely need to be enrolled in order to obtain 92 evaluable patients.***
Throughout	96 STS patients to get 92 evaluable patients	Updated to 108 STS patients to get 92 evaluable patients	***Based on the percentage of non- evaluable patients during the interim analysis by DMC, it was determined that a total of 108 patients would most likely need to be enrolled in order to obtain 92 evaluable patients.***
Section 3.1.8 Inclusion criteria	Creatinine clearance (Cl_{CR}): ≥30 mL/min to ≥50 mL/min	Modified to : Creatinine clearance (Cl_{CR}): ≥50 mL/min	***For clarity, and to be consistent with other current related studies***.

Section 4.3 Table 1 Dose Modification Algorithms for Potential Treatment-Related Adverse Events (for Pazopanib)	***For Proteinuria:*** UPC ≥3 or 24-h urine protein ≥3g Step 3. If UPC ≥3 or 24-h urine protein ≥3g **recurs**, repeat steps 1 and 2. Step 4. If UPC ≥3 or 24-hr urine protein ≥3 **recurs** and the pazopanib dose can no longer be reduced, discontinue protocol treatment and continue follow-up per protocol. ***For thrombocytopenia:*** If no recovery to ≤ Grade 1 or recurrent Grade 3 or 4 thrombocytopenia, discontinue protocol treatment and follow-up per protocol. **For palmar-plantar erythrodysesthesia syndrome**: If recurrent consider a further dose reduction to 200mg or discontinuation	Language modified to state: " recurs at current dose" Similarly, language added to state: "If no recovery to ≤ Grade 1 or recurrent Grade 3 or 4 thrombocytopenia **at current dose**" Similarly, language added to state: "If recurrent at the current dose"	***For clarity***
Amendment 8 – May 25th, 2017			
Sections(s) Affected	***Prior Version***	***Amendment 8 Changes***	***Rationale***
Section 3.1.9 and 3.1.10	Two exclusionary criteria were clubbed together in section 3.1.9	Exclusionary criterion pertaining to 'hypertension' was separated from the 'ejection fraction' exclusionary criterion. Section 3.1.10 was designated for the criterion related to hypertension. The subsequent criteria were re-numbered accordingly.	***Correction of formatting error***

Section 3.1.18	Washout period for anti-cancer therapies-radiation, surgery or tumor embolization was 28 days	Washout period for anti-cancer therapies-radiation, surgery or tumor embolization changed to 14 days	***For ease of enrollment.*** ***(14 day washout period adequate for safety).***
Section 5.0 Study Procedures table	Footnote n:End of treatment must occur 30 days following the last day of treatment Footnote o: patient required to call in weekly to report toxicities.	Footnote n modified to state : " End of treatment visit must occur within 30 days following the last day of treatment, particularly prior to patient starting new treatment." Footnote o modified to state: Toxicities should be followed for 30 days after last dose of study treatment, however, new toxicities that arise within the 30 day period definitely related to new anti-cancer treatment and NOT related to study treatment do not need to be reported.	***For added clarity***
Section 6.3	Details about evaluation of Objective response. Stated that all conclusion and main analysis would be based on all *eligible* patients. Conditions for sub analyses defined.	Language modified to increase clarity. Modified to state that conclusion and main analysis will be based on all *enrolled* patients. Treatment of' ineligible patients' added to examples of protocol deviations and these will not be included for sub analyses of different subsets of patients.	***For increased clarity***
Section 7.3.2 Determining if Expedited Reporting is Required	Expedited reporting is required for all events that occur within 30 days of the last dose of protocol treatment.	Added language to this to state that the event need not be reported if it is definitely attributable to new anti-cancer treatment and is NOT related to study treatment .	***For added clarity and to be in alignment with update made to the procedures table footnote o***
Section 5.0 Footnote L and Section 9.1	Peripheral blood samples to be collected for correlative studies	Removed the word 'peripheral'to just state that blood samples will be collected for correlative studies	***For convenience***

Section 10.1	A total of 108 patients required to obtain 92 evaluable patients	Modified to state: 'A total of 108 **STS** patients needed to obtain 92 evaluable patients'. Term STS(soft tissue sarcoma) added in other appropriate sentences.	***For clarity***
Amendment 9: February 2nd , 2018			
Sections(s) Affected	***Prior Version***	***Amendment 9 Changes***	***Rationale***
Study schema and Study summary and section 3.0	Cohort 2 osteosarcoma patients was 20.	The accrual number for osteosarcoma has been expanded to 36. To accommodate this, the total accrual limit has been increased to 164.	***Original 20 osteosarcoma patients were evaluated. Now, expansion to 36 patients is being done to evaluate efficacy of the regimen.***
Section 1.8	Previous rationale language	Added rationale for increasing accrual for osteosarcoma patients.	***Rationale to support the expansion of osteosarcoma cohort from 20 to 36.***
Section 10.2	Originally 20 osteosarcoma patients were listed.	Expansion to 36 patients in the osteosarcoma cohort. The 16 additional osteosarcoma slots will only be available at (NMH).	***Originally, 20 osteosarcoma patients were evaluated. Now, expansion to 36 patients is being done to evaluate efficacy of the regimen.***
Amendment 10 dated 3.28.19			
Sections(s) Affected	**Prior Version**	**Amendment 10 Changes**	***Rationale***
Study summary, Section 2.3 and Section 6.7 Exploratory objectives and endpoints	Exploratory objective was to evaluate the correlation of PFR and OS to levels of sVEGFR2 and PIGF.	Added new exploratory objective for Cohort 1 and 3 : "Quantify Cell-free circulating tumor DNA (ctDNA) at each time point, and correlate these results with demographic, diagnostic, treatment, and outcomes data". These 2 cohorts are closed to accrual.	***Cohort 1 and 3 samples have been collected and is closed to accrual. Decision made by PI to use these samples for said exploratory analysis.***

Section 9.0 Correlative/Special studies	Details regarding original exploratory objective as stated above.	Updated with details regarding new exploratory objective for Cohort 1 and 3. The details for Cohort 2 remains the same.	***To align with updates made to the exploratory objectives of this study.***
Section 5.0 Study procedures table Footnote h	Day 1 of each cycle was stated to have a window of (+/3days).	The window has been updated to (+/-3 days). Footnote 'm' already states this.	***Correction of discrepancy***
Section 9.2 Sample shipment	Address listed for Dr.Van Tine's lab	Address presented in the correct manner, as listed in the lab manual. Address remains the same.	***For consistency***
References	List of references used in the body of the protocol	Added list of references used for adding new exploratory objective. Details reflected in Section 9	***To align with updates made to the exploratory objectives of this study.***
Amendment 11 dated 12.02.19			
Sections(s) Affected	**Prior Version**	**Amendment 11 Changes**	***Rationale***
Coverpage	Lists Alfred W. Rademaker as statistician	Updates to list Hui Zhang as the statistician	***Administrative update***
Study Summary	Patients must have had a minimum of 1 and a maximum of 4 prior chemotherapy regimens for recurrent/metastatic disease. It will be up to the investigator to determine what constitutes a "regimen" in each case.	Patients must have had a minimum of **0** and a maximum of 4 prior chemotherapy regimens for recurrent/metastatic disease **determined by cohort assignment**. It will be up to the investigator to determine what constitutes a "regimen" in each case.	***Updated to reflection more accurate inclusion criteria for cohorts***

Inclusion criteria Section 3.1.6	**Cohort 2**: Patients must have had a minimum of 1 and maximum of any number of prior chemotherapy regimens for recurrent/metastatic ***or locally advanced/ unresectable*** disease. **Cohort 3:** Patients may have had any number of prior therapies for recurrent/metastatic or locally advanced/unresectable disease. There are no restrictions.	**Inclusion criteria for Cohort 2 and 3 have been switched:** **Cohort 2:** Patients may have had any number of prior therapies for recurrent/metastatic or locally advanced/unresectable disease. There are no restrictions. **Cohort 3**: Patients must have had a minimum of 1 and maximum of any number of prior chemotherapy regimens for recurrent/metastatic ***or locally advanced/ unresectable*** disease.	***Correction of error from amendment 6***
Amendment 12 dated 02.13.20			
Sections(s) Affected	**Prior Version**	**Amendment 12 Changes**	***Rationale***
8.2.10 (Side effects of pazopanib)	Following side effects are listed under "*Likely (occurring in more than 20% of patients)"* decreased albumin, hypomagnesemia, hypophosphatemia, hair loss, painful blisters and/or rash on palms and soles, tumor pain, dysgeusia, headache, gastrointestinal pain, musculoskeletal pain, weight loss, myalgia.	These side effects were moved to "*Common (occurring in 3-20% of patients)"*	***Administrative update to match these side effects to current frequencies experienced with pazopanib as listed in IB.***
Amendment 12.1 dated 05.14.20 (Updates to Amendment 12 prior to IRB approval of Amendment 12)			
Sections(s) Affected	**Prior Version**	**Amendment 12.1 Changes**	***Rationale***
8.1.10 (Side effects of topotecan) 8.2.10 (Side effects of pazopanib)	Provided information from the IB on current side effects and frequencies experienced.	Removed language of all side effects and frequencies and incorporated the sentence into these sections: "*Please refer to current IB for details and a complete list of side-effects."*	***Administrative update to match current interventional protocol template to prevent further protocol amendments due to risk updates and in response to IRB questions.***
Amendment 12.2 dated 06.10.20			
Sections(s) Affected	**Prior Version**	**Amendment 12.2 changes**	***Rationale***

11.1 (Institutional Review Board (IRB) Approval and Consent)	N/A	Adds language for the process of consenting patients with limited English proficiency	***IRB requested update***
Amendment 13 dated 06.26.20			
Sections(s) Affected	**Prior Version**	**Amendment 13 changes**	***Rationale***
Coverpage	Lists Mark Agulnik as the PI for the study	Updates to list Mary Mulcahy as the PI and provides her contact details	Change due to PI leaving Northwestern.
	Lists the IND holder as Mark Agulnik	Updates to "IND-EXEMPT"	Correction of error
	Lists the previous statisticians email address	Updates the email to current statisticians email address	
3.0 (Patient Eligibility); 3.4 (Population and Accrual Overview)	Lists the PI by name with phone number	PI name and phone number removed	Change due to PI leaving Northwestern and the study is closed to further accrual.