BRAIN TUMOR TRIALS COLLABORATIVE (BTTC)

Abbreviated Title: *Ph II Pazopanib Topotecan*

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Title: A Phase II Trial of Oral Pazopanib plus Oral Topotecan Metronomic Antiangiogenic Therapy for Recurrent Glioblastoma Multiforme (A) without Prior Bevacizumab Exposure and (B) after Failing Prior Bevacizumab

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None

Commercial Agents: Pazopanib and Oral Topotecan

A DISCLAIMER STATEMENT FOR BTTC PROTOCOLS

This is a research protocol of the Brain Tumor Trials Collaborative describing an experimental treatment procedure. It is a privileged document and is not intended to be circulated or used for other purposes. The Brain Tumor Trials Collaborative assumes no responsibility for its use outside of the constraints of this research protocol or by investigators other than those approved by the Consortium.

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PRÉCIS

Background

- Glioblastoma (GBM) is the most common primary brain tumor. With optimal treatment, consisting of focal radiotherapy with concurrent chemotherapy, followed by adjuvant chemotherapy, median survival is 14.6 months. Most patients have evidence of tumor progression within one year of diagnosis despite treatment. At progression, treatment options are limited and mostly ineffective.
- Recently, bevacizumab was approved for recurrent GBM patients who fail bevacizumab indicate a short survival, on the order of 10 weeks, an approximate PFS 3 and 6 months of 0%.
- Pazopanib is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-Kit, and was recently FDA approved for advanced renal cell carcinoma.
- Topotecan is an orally bioavailable topoisomerase I and HIF-1 alpha inhibitor with reasonably high CNS/CSF penetration
- Recent pre-clinical reports have begun to argue for the clinical testing of metronomic chemotherapy administration in various cancers. The theory of improved activity of Pazopanib + Topotecan administered metronomically is based on targeting tumor vasculature (both existing capillary endothelial cells and circulating bone marrow derived endothelial cell precursors), immune modulation, as well as tumor cell HIF-1 alpha inhibition, and the induction of DNA damage. Further support for the combination comes from recent data tying drug-induced VEGF inhibition to the induction of HIF-1 alpha activity in GBM suggesting possible synergy between Pazopanib and Topotecan
- The combination of Topotecan and Pazopanib has been directly demonstrated as active in animal models

Objectives

- 6 month progression free survival rate for recurrent glioblastoma (rGBM) patients with no prior bevacizumab exposure treated with pazopanib and topotecan (Group A).
- 3 month progression free survival rate for rGBM patients with prior bevacizumab exposure treated with pazopanib and topotecan (Group B).

Eligibility

- Histologically proven intracranial glioblastoma multiforme (GBM) or gliosarcoma (GS) with evidence of progression on MRI or CT scan.
- Patient must have failed prior chemoradiation with temozolomide and any other therapies except BEV (group A), or must have failed primary chemoradiation and a BEV-incorporating treatment (group B).
- Patients must be greater than 12 weeks following completion of chemoradiation.
- Archived tumor tissue must be available for confirmation of the diagnosis
- Patients must be $\geq$ 18 years old.

- Patients must have a Karnofsky performance status of ≥ 60.
- Patients must have adequate organ function.
- No pregnancy or lactation.
- Patients must not have any significant medical illnesses that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy.
- No history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission and off of all therapy for that disease for a minimum of 3 years are eligible.
- No clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, or the absorption of the medications.
- No prior major surgery or trauma within 28 days and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major).
- No evidence of active bleeding or bleeding diathesis.
- No known endobronchial lesions and/or lesions infiltrating major pulmonary vessels.
- No serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures.
- No ongoing toxicity from prior anti-cancer therapy that is > Grade 1 and/or that is progressing in severity, except alopecia.
- No ongoing use of enzyme-inducing anti-epileptic agents (EIAEDs), unless 2 week washout has elapsed form last dose of EIAED.
- No known hypersensitivity to pazopanib or topotecan or to their excipients.
- No total daily dose of dexamethasone greater than 16 mg/day.
- No prior therapy with topotecan, pazopanib, or related drugs such as tyrosine kinase inhibitors, VEGF inhibitors (except bevacizumab). Prior treatment with TKIs that do not impact VEGFR -1, -2, or -3, PDGFR –a, -b of cKIT could be allowed.

Design

This is a 2 arm phase II trial of the combination of topotecan and pazopanib in patients with recurrent GBM or GS. Patients will be enrolled into one of the following groups: (A) Glioblastoma or gliosarcoma with no prior bevacizumab exposure: (B) Glioblastoma or gliosarcoma with prior bevacizumab exposure. Topotecan and pazopanib are administered orally daily. The primary efficacy endpoint is progression free survival (PFS) at six months from patient registration for bevacizumab naïve patients and PFS at 3 months for patients with prior bevacizumab treatment.

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1 INTRODUCTION

1.1 OBJECTIVES

1.1.1 Primary endpoint:

- 6 month progression free survival rate for recurrent glioblastoma (rGBM) patients with no prior bevacizumab exposure treated with pazopanib and topotecan (Group A).
- 3 month progression free survival rate for rGBM patients with prior bevacizumab exposure treated with pazopanib and topotecan (Group B).

1.1.2 Secondary endpoint:

- Overall survival for rGBMs (Group A and Group B) treated with pazopanib and topotecan measured from time of study enrollment.
- Objective response rate for rGBM (Group A and Group B) treated with pazopanib and topotecan.
- Patient related outcome measures.
- To evaluate the occurrence of symptoms and correlate to disease progression and tolerance to treatment using the MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) self-reporting tool. This will include:
    - To evaluate longitudinal changes in symptom measures and determine the impact of the therapy on these parameters.
    - To measure symptom burden over the course of therapy to evaluate differences between patients individual symptom severity, overall mean symptom severity, and difference in scores on the interference items between responders and non-responders.
    - To describe the variability of symptom severity longitudinally over the treatment course and follow-up period.

1.2 BACKGROUND

1.2.1 Glioblastoma (GBM)

Glioblastoma (GBM) is the most common primary brain tumor. With optimal treatment, consisting of focal radiotherapy with concurrent chemotherapy, followed by adjuvant chemotherapy, median survival is 14.6 months (Stupp et al. 987-96;Stupp et al. 459-66;Stupp et al. 459-66;Stupp et al. 987-96). Cure is exceptional and most patients have evidence of tumor progression within one year of diagnosis despite treatment. At progression, treatment options are limited and mostly ineffective; most clinical trials demonstrate six month progression free survival rate of only 9-15% and median overall survival is less than 25 weeks from time of tumor progression (Lamborn et al. 162-70). Recently, bevacizumab was approved for recurrent GBM based on data from Vredenburgh et al. and Kreisl et al. (Kreisl et al. 740-45;Vredenburgh et al. 4722-29) Data on patients who fail bevacizumab indicate a short survival, on the order of 10 weeks, an approximate PFS 3 and 6 months of 0%.

Numerous molecular changes drive the growth and pro-angiogenic behavior of GBMs (Lim et al. 158-64). Among the molecular features of GBM, Vascular Endothelial Growth Factor (VEGF)

overexpression is nearly universal and higher levels are correlated with higher tumor grade (Plate et al. 845-48;Chi et al. 621-36). Platelet Derived Growth Factor Receptor (PDGFR)-alpha is expressed in nearly all malignant gliomas and high levels of PDGFR-beta are seen on endothelial cells of capillaries adjacent to gliomas (Hermanson et al. 3213-19). Stem cell factor receptor (c-Kit) pathway activation is less well defined in malignant glioma. Reports vary widely as to its expression from as high as 75% to as low as 4% (Morris and Abrey 193-200). C-Kit amplification may be associated with the presence of PDGFR-alpha expression, and may be seen more commonly in recurrent astrocytic tumors (Puputti et al. 927-34). Intriguingly, in a small number of patients with recurrent malignant glioma whose tumors possessed c-Kit polysomy or amplification, treatment with a c-Kit inhibitor resulted in a far longer freedom from progression, as compared to those patients whose tumors contained a normal c-Kit copy number (Reardon et al. 1995-2004).

Recent work has begun to subcategorize GBM into various subgroups based on the primary molecular pathways involved (Phillips et al. 157-73;Brennan et al. e7752). One study of particular relevance to this proposal, using proteomic analysis, identified three patterns of expression and activation of proteins in glioma signaling pathways, one of which was a PDGF-pathway activation which was primarily ligand driven (Brennan et al. e7752). The other pathways were EGFR and NF1. GBM patients were evenly distributed among the three groups, suggesting up to 1/3 of GBM patients would possess the PDGF pathway activation pattern. There was a trend for tumors that had been previously treated to reside in the PDGF group ($p=0.11$). Interestingly, even though this group of tumors was defined by evidence of PDGF signaling at the protein level, none of the tumors in the class showed gene amplification of either PDGF receptors or ligands. The PDGF pathway analysis included a cluster of 17 proteins including PDGFB, phospho-PDGFRβ, and phospho-NFKB1 as well as others. This PDGF core was felt to most closely resemble the tumors recently described as “pro-neural” (Phillips et al. 157-73).

1.2.2 Pazopanib:

Pazopanib is an oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-Kit, and was recently FDA approved for advanced renal cell carcinoma. Single-agent Pazopanib at 800 mg daily was tested in a phase 2 study in recurrent GBM and was well tolerated. However, Pazopanib demonstrated a 6-month progression free survival (PFS6) of only 3% (not meeting the efficacy target), a median PFS of 12 weeks, and a median overall survival of 35 weeks. However, Pazopanib did demonstrate biological activity, in that 11 patients (31%) had a PR or a <50% reduction in tumor, indicative of Pazopanib’s effect on tumor vasculature (Iwamoto et al. 855-61). Pazopanib (in combination with lapatinib) in relapsed malignant glioma showed a clinical benefit rate (CR + PR + SD > 8 weeks) of 50-68%.

1.2.3 Topotecan:

Topotecan is an orally bioavailable topoisomerase I and HIF-1 alpha inhibitor(Rapisarda et al. 6845-48) with reasonably high CNS/CSF penetration (Baker et al. 195-202). A 1996 study of high dose IV topotecan in 31 adults with recurrent malignant gliomas demonstrated 1 CR in GBM and 1 PR in the anaplastic astrocytoma (AA) group (Macdonald et al. 205-07). More interestingly, the median time to progression was 19 weeks and the overall PFS6 was 23%, which is similar to the figure (21%) reported for temozolomide in recurrent GBM (Yung et al. 588-93) (outcomes were similar for GBMs and AAs with respect to duration of stable disease).

Additionally, a recent phase 2 study of metronomically administered single-agent oral topotecan showed some efficacy in childhood brain tumors (Minturn et al. 39-44).

1.2.4 Rationale for combination therapy:

Recent pre-clinical reports have begun to argue for the clinical testing of metronomic chemotherapy administration in various cancers. The theory of improved activity of Pazopanib + Topotecan administered metronomically is based on targeting tumor vasculature (both existing capillary endothelial cells and circulating bone marrow derived endothelial cell precursors), immune modulation, as well as tumor cell HIF-1 alpha inhibition, and the induction of DNA damage. Further support for the combination comes from recent data tying drug-induced VEGF inhibition to the induction of HIF-1 alpha activity in GBM (Keunen et al. 3749-54) suggesting possible synergy between Pazopanib and Topotecan.

The combination of Topotecan and Pazopanib has been directly demonstrated as active in animal models (Hashimoto et al. 996-1006;Merritt et al. 985-95). A mouse model of ovarian cancer showed substantially improved outcomes when both Pazopanib and Topotecan were administered in a metronomic fashion as compared to either agent alone, or when given in non-metronomic schemes (Hashimoto et al. 996-1006). Further, the combination resulted in improvements in animal survival (and decreased tumor weight), decreased tumor microvessel density, decreased tumor cell VEGFR2 phosphorylation, decreased numbers of migrating tumor cells, decreased tumor cell proliferative activity, and increased percentages of tumor cells undergoing apoptosis (Merritt et al. 985-95). These pre-clinical findings led to a phase 1 clinical trial reported at the American Society of Clinical Oncology Meeting in 2012, abstract # 5014 which showed the combination to be well tolerated, and with evidence of responses.

The single-center, open-label phase I study included 25 extensively pretreated patients (pts) with gynecologic tumors (6 cervical, 7 endometrial, 8 ovarian, 4 other) were enrolled. Mean age was 61 years; 19 Caucasian, 6 African American. This study comprised 28-day cycles of daily oral topotecan/pazopanib at dose levels of 0.50/400, 0.25/800, 0.25/600, and 0.25/400 mg. A standard 3+3 dose escalation design was used. Dose limiting toxicity (DLT) was defined as ≥ grade 3 adverse event (AE) occurring in cycle 1, noncompletion of cycle 1 at prescribed dose, or inability to start cycle 2 as scheduled due to toxicities. Imaging was conducted after every 2 cycles for response assessment. Median number of cycles received was 4 (range 1-19). DLTs occurred ≥ 2 pts for A (2/6), B (2/7), C (3/7). For level D, 1/5 had a DLT, but one dose level C pt with a DLT received level D dosing due to unavailability of pazopanib. 9/25 pts had any serious adverse event (SAE), and respiratory SAEs were most common (4/16 SAEs). Nausea, fatigue, dysgeusia, diarrhea, and vomiting were the most common conditions reported as non-serious AEs. The best overall response was 28%. The conclusions were that DLTs in dose levels C and D were effectively managed with minor dose and schedule adjustments. 4 pts with DLTs at these doses remained on treatment for 4, 5, and 6 months, with one pt still on treatment at 9 months. The overall response rate (CR + PR + SD) was 36% and 42% in the higher dosed groups.

Submitted abstract:

http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=114&abstractID=93930

Final Poster:
http://www.asco.org/ASCOv2/MultiMedia/Virtual+Meeting?&vmview=vm_session_presentations_view&confID=114&sessionID=4842

Given the initial biologically favorable signal in this heavily pretreated group and low toxicity, the investigators recommended a randomized phase II trial to define efficacy using the 0.25/600 regimen allowing for dose reduction if needed.

Thus, several lines of reasoning argue for testing the oral combination of metronomic Topotecan and Pazopanib in recurrent GBM patients: A) There is prior clinical evidence of some, albeit limited, benefit of both Topotecan and Pazopanib, individually, in glioma patients (however, Topotecan has not been previously evaluated using metronomic dosing in GBM). B) The targets of Pazopanib and Topotecan, VEGFR, PDGFR, c-Kit, HIF-1 alpha, are all relevant in recurrent GBM. C) VEGF inhibition induces HIF-1 alpha activity in GBM, creating an environment for synergy. D) Recurrent GBM after standard therapy with chemoradiation or at the time of recurrence after bevacizumab (BEV) therapy are major problems, and unmet clinical needs. E) The oral administration of these agents will allow for rapid accrual and completion of this study and determination of an efficacy signal.

1.2.5 Rationale for patient outcomes measures:

This study seeks to establish effective therapies at recurrence and improve on current clinical results in patients with glioblastoma. We hypothesize that using a combination of pazopanib and topotecan will result in improved survival. It will be important to determine whether any determined survival benefit is associated with improvements in symptoms or does a worsening of symptoms offset the increase in survival.

Precedence for measuring "non-therapeutic" endpoints exists in oncology research. For example, Gemcitabine was approved by the FDA partially as a consequence of the decrease in pain reported in pancreatic patients who were treated, not on the basis of survival improvement which was modest, at best (Siu et al. 144-51). There have been efforts in neuro-oncology to evaluate secondary endpoints using validated instruments as an additional indicator of benefit.

The M.D. Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) allows the self-reporting of symptom severity and interference with daily activities. The MDASI-BT has demonstrated reliability and validity in the adult primary brain tumor patient population (Armstrong et al. 27-35). This tool represents a modification of the widely used and validated MDASI, with particular attention to symptoms common in patients with brain tumors. The availability of validated instruments provides an opportunity to prospectively assess the impact of treatment, both positive and negative, on patients. This evaluation of symptom burden in this study will assist in finding the best possible treatment with the least toxicity.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 General Inclusion Criteria

2.1.1.1 Patients with histologically proven intracranial glioblastoma multiforme (GBM) or gliosarcoma (GS). Patients will be eligible if the original histology was low-grade glioma and a subsequent histological diagnosis of a GBM or GS is made. Patients must have evidence of progression of the

GBM or GS on MRI or CT scan. Patient must have failed prior chemoradiation with temozolomide and any other therapies except BEV (group A), or must have failed primary chemoradiation and a BEV-incorporating treatment (group B).

2.1.1.2 Patients may have had treatment for no more than 2 prior relapses. Relapse is defined as progression following initial therapy (i.e. radiation+/- chemo if that was used as initial therapy). The intent therefore is that patients had no more than 3 prior therapies (initial and treatment for 2 relapses). If the patient had a surgical resection for relapsed disease and no anti-cancer therapy was instituted for up to 12 weeks, and the patient undergoes another surgical resection, this is considered as 1 relapse. For patients who had prior therapy for a low-grade glioma, the surgical diagnosis of a high-grade glioma will be considered the first relapse.

2.1.1.3 Patients must be greater than 12 weeks following completion of chemoradiation or any additional radiation to reduce the chance of pseudoprogression.

2.1.1.4 Measurable disease is required unless patient is post-operative and in that case patient can have no evidence of disease.

2.1.1.5 All patients must sign an informed consent indicating that they are aware of the investigational nature of this study.

2.1.1.6 Archived tumor tissue must be available for all subjects for confirmation of the diagnosis before or during treatment. Samples must be provided within 4 weeks of enrollment.

2.1.1.7 Patients must be ≥ 18 years old.

2.1.1.8 Patients must have a Karnofsky performance status of ≥ 60.

2.1.1.9 At the time of registration: Patients must have recovered from the toxic effects of prior therapy: > 28 days from any investigational agent, >28 days from prior cytotoxic therapy, >14 days from vincristine, >42 days from nitrosoureas, >21 days from procarbazine administration, >21 days from bevacizumab administration and >7 days for non-cytotoxic agents, e.g., interferon, tamoxifen, thalidomide, cis-retinoic acid, etc. (radiosensitizer does not count). Any questions related to the definition of non-cytotoxic agents should be directed to Academic PI.

2.1.1.10 Patients must have adequate organ function:

- Bone marrow function (WBC ≥ 3,000/µl, ANC ≥ 1,500/mm^3, platelet count of ≥ 100,000/mm^3, and hemoglobin ≥ 10 gm/dl).
    - Eligibility level for hemoglobin may be reached by transfusion.
- Liver function (alanine amino transferase (ALT) and aspartate aminotransferase (AST) < 2.5 X ULN, and total bilirubin < 1.5 X ULN), prothrombin time (PT) or international normalized ratio (INR), and activated partial thromboplastin time (aPTT) ≤ 1.2 X ULN.

- Concomitant elevations in bilirubin and AST/ALT above 1.0 x ULN (upper limit of normal) are not permitted.
- Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.

- Renal function (creatinine ≤1.5 mg/dL (133 µmol/L), or if > 1.5 mg/dL, calculated creatinine clearance ≥ 50 cc/min), and urine protein to creatinine ratio of < 1 prior to registration.

2.1.1.11 Patients must have shown unequivocal radiographic evidence for tumor progression by MRI or CT scan as defined by Section 6.4.1.4.5. A scan should be performed within 14 days prior to registration and on a steroid dose that has been stable or decreasing for at least 5 days. If the steroid dose is increased between the date of imaging and registration a new baseline MR/CT is required. The same type of scan, i.e., MRI or CT must be used throughout the period of protocol treatment for tumor measurement.

2.1.1.12 Patients having undergone recent resection of recurrent or progressive tumor will be eligible as long as all of the following conditions apply:

- They have recovered from the effects of surgery and be > 28 days from surgery.

2.1.1.13 Residual disease following resection of recurrent GBM or GS is not mandated for eligibility into the study. To best assess the extent of residual disease post-operatively, a CT/ MRI should be done no later than 96 hours in the immediate post-operative period or at least 4 weeks post-operatively, within 14 days prior to registration. If the 96-hour scan is more than 14 days before registration, the scan needs to be repeated. If the steroid dose is increased between the date of imaging and registration, a new baseline MRI/CT is required on a stable steroid dosage for at least 5 days.

2.1.1.14 Patients must have failed prior radiation therapy and must have an interval of greater than or equal to 12 weeks from the completion of radiation therapy to study entry.

2.1.1.15 Patients with prior therapy that included interstitial brachytherapy or stereotactic radiosurgery must have confirmation of true progressive disease rather than radiation necrosis based upon either PET or Thallium scanning, MR spectroscopy or surgical/pathological documentation of disease.

2.1.1.16 A female is eligible to enter and participate in this study if she is of:

2.1.1.16.1 <u>Non-childbearing potential</u> (i.e., physiologically incapable of becoming pregnant), including any female who has had:

- A hysterectomy

2.1.1.17 A bilateral oophorectomy (ovariectomy)

- A bilateral tubal ligation
- Is post-menopausal

- Subjects not using hormone replacement therapy (HRT) must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years in age, OR, in questionable cases, have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).
- Subjects using HRT must have experienced total cessation of menses for >= 1 year and be greater than 45 years of age OR have had documented evidence of menopause based on FSH and estradiol concentrations prior to initiation of HRT

2.1.1.17.1 Childbearing potential, including any female who has had a negative serum pregnancy test within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception. Novartis acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:

- Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product. Oral contraceptive, either combined or progestogen 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 subject's entry** into the study, and this male is the sole partner for that subject.
- Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository).
- Female subjects 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.

2.1.2 General Exclusion Criteria

2.1.2.1 Patients must not have any significant medical illnesses that in the investigator’s opinion cannot be adequately controlled with appropriate therapy or would compromise the patient’s ability to tolerate this therapy.

2.1.2.2 Patients with a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission and off of all therapy for that disease for a minimum of 3 years are ineligible.

2.1.2.3 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.

2.1.2.4 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.
- Presence of uncontrolled infection.
- Corrected QT interval (QTc) > 480 msecs using Bazett's formula

  Bazett's Formula:

$$QTc\ (Bazett) = \frac{QT}{\sqrt{RR}}$$

2.1.2.5 History of any one or more of the following cardiovascular conditions within the past 6 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), see appendix **15.7**
- 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. BP must be re-assessed on two occasions that are separated by a minimum of 1 hour; on each of these occasions, the mean (of 3 readings) SBP / DBP values from each BP assessment must be ≤ 140/90 mmHg in order for a subject to be eligible for the study.
- 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.

2.1.2.6 Prior major surgery or trauma within 28 days and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major).

2.1.2.7 Evidence of active bleeding or bleeding diathesis.

2.1.2.8 Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels

2.1.2.9 Hemoptysis in excess of 2.5 mL (or one half teaspoon) within 8 weeks of first dose of study drug.

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

2.1.2.11 Unable or unwilling to discontinue use of inducers and inhibitors of CYP450 listed in Appendix **15.4** and BCRP and PgP inducers and inhibitors 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. (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. Dexamethasone is acceptable although listed as a CYP3A4 inducers/inhibitors as long as the dose is 16 mg/day or lesser.

2.1.2.12 Any ongoing toxicity from prior anti-cancer therapy that is > Grade 1 and/or that is progressing in severity, except alopecia.

2.1.2.13 Ongoing use of enzyme-inducing anti-epileptic agents (EIAEDs), unless 2 week washout has elapsed form last dose of EIAED.

2.1.2.14 Patients must not have any significant medical illnesses that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy.

2.1.2.15 Patients with a known hypersensitivity to pazopanib or topotecan or to their excipients.

2.1.2.16 Patients on total daily dose of dexamethasone greater than 16 mg/day.

2.1.2.17 Patients must not have received prior therapy with topotecan, pazopanib, or related drugs such as tyrosine kinase inhibitors, VEGF inhibitors (except bevacizumab). Prior treatment with TKIs that do not impact VEGFR -1, -2, or -3, PDGFR –a, -b of cKIT could be allowed.

2.1.2.18 Patients must not have any disease that will obscure toxicity or dangerously alter drug metabolism.

2.2 PRETREATMENT EVALUATION

A complete history and neurological examination (to include documentation of the patients Karnofsky Performance Status), as well as neuro-imaging confirming tumor progression shall be performed on all patients. The scan done prior to study entry documenting progression will be

reviewed by the patient's treating physician. The baseline scan should be performed within 14 days of registration. Patients should not be on a steroid dose higher than 16 mg/day.

Prestudy laboratory tests shall include ECG, and laboratory studies including CBC, differential, platelets, ALT, AST, bilirubin, PT, PTT, INR, TSH and T4, creatinine, urinalysis with urine protein creatine (UPC) ratio microanalysis, and serum pregnancy test for women of childbearing potential. Prestudy tests (except pregnancy test) must be obtained within 14 days of registration. UPC ratio < 1.0. Pregnancy test must be obtained within 14 days prior to starting the study drugs.

All patients should be screened for hepatitis risk factors and any past illness of hepatitis B and hepatitis C (See appendix **15.8**). If patient has positive (+) response to questionnaire the Hepatitis B and C screening test should be done and recorded in the patient's chart. If liver tests are normal patient could still go on study, but the investigator would be paying close attention to the liver function test (LFT's).

2.2.1 Documentation of tumor diagnosis

Following registration, slides from the most recent pre-registration biopsy must be submitted for review15 Unstained Paraffin slides, or a paraffin tissue block, will be obtained in all study patients from original surgery or definitive surgery or the surgery closest to initiation of this clinical trial and in those patients who will be undergoing resection at time of treatment failure.

These samples should be shipped overnight mail in an appropriate container to:

Ken Aldape, M.D.
Toronto General Hospital
200 Elizabeth Street, 11th Floor
Toronto, Ontario M5G 2C4 Canada
kaldape@gmail.com

Patients will complete a baseline MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) (Appendix **15.5**) within 14 days (+ 3 working days) after enrollment on the clinical trial. The MDASI-BT will be completed only by the patient, unless changes in vision or weakness make this difficult. If this occurs, then the caregiver or research assistant may read the questions to the patient or assist with marking the severity number or score as described by the patient. A patient caregiver may complete the questionnaires as a patient-preference proxy if the patient's deficits preclude self-report.

2.3 REGISTRATION PROCEDURES

Patients who are candidates for the study will first be evaluated for eligibility by the local investigator. All patients must be registered both locally and centrally with BTTC.

BTTC patients will be registered with the BTTC Coordinating Center. All eligibility requirements will be checked prior to registration. The status of all regulatory documents will be checked prior to registration. No patient will be entered on protocol if they do not satisfy all regulatory document and eligibility requirements.

2.3.1 Informed Consent/Authorization

Prior to protocol enrollment and initiation of treatment, subjects must sign and date an Institutional Review Board (IRB) approved consent form.

Registrations must be completed after the patient has signed the informed consent and has been determined to be eligible by the local investigator.

At the time of registration, the following information will be requested by the BTTC Coordinating Center:

- A copy of a completed and signed, protocol specific, Eligibility Checklist form
- One copy of the signed and dated Informed Consent/Authorization.
- Copies of all source documents to support protocol specific eligibility. Please refer to the Operations Manual for specific source documents required.

2.3.2 Registration at the NCI

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent for patients enrolling at the lead institution. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and faxed to 301-480-0757. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.3.3 Participating Site Registration

All patients must be registered through the NCI Central Registration Office (CRO). A protocol registration form and cover memo will be supplied by the Coordinating Center, NCI CCR and updates will be provided as needed. Subject eligibility and demographic information is required for registration. To initially register a subject, after the participant has signed consent, complete the top portion of the form and send to Coordinating Center's Research Nurse, Melanie Herrin, RN; fax: 301-451-5429, Melanie.Herrin@nih.gov. Once eligibility is confirmed, send the completed eligibility checklist with the attached supporting source documents to Melanie Herrin, RN. If patient is not eligible, please notify Melanie Herrin, RN. The CRO will notify you either by e-mail or fax that the protocol registration form has been received. Questions about eligibility should be directed to the Coordinating Center's Research Nurse, Melanie Herrin, RN; 301-451-5979; fax: 301-451-5429, Melanie.Herrin@nih.gov.

2.3.3.1 Patient Number for Participating Institutions

Once eligibility has been confirmed by the Coordinating Center, the patient from the participating institution will be registered through the Central Registration Office. A Verification of Registration will be received from the Central Registration Office with the assigned patient ID number. The patient ID number is unique to the patient and must be written on all data and correspondence for the patient and used to enter data into the C3D database. The participating site will receive the Verification of Registration via fax or email within one working day of registration.

2.3.4 Initiation of Therapy

Treatment may not be initiated until the participating institution receives a faxed or emailed copy of the patient's Registration Verification Letter from the Central Registration Office.

All Patients that are eligible to receive therapy must initiate treatment <u>within 96 hours</u> after the registration.

The BTTC Coordinating Center must be notified in writing of any exceptions to this policy.

2.3.5 Eligibility Exceptions

Eligibility Exceptions will not be granted.

2.4 DESCRIPTIVE FACTORS

Patients with recurrent GBM or GS will be enrolled into one of the following groups: (A) Glioblastoma or gliosarcoma with no prior bevacizumab exposure: (B) Glioblastoma or gliosarcoma with prior bevacizumab exposure. Accrual goals and endpoints for each group are determined separately as described in the statistical section.

There will be a total accrual of approximately 66 eligible patients to this 2-arm Phase II study (34 recurrent GBM/GS patients with no prior exposure to bevacizumab, and 32 GBM/GS patients with prior exposure to bevacizumab).

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a 2 arm phase II trial of the combination of topotecan and pazopanib in patients with recurrent GBM or GS. Patients will be enrolled into one of the following groups: (A) Glioblastoma or gliosarcoma with no prior bevacizumab exposure: (B) Glioblastoma or gliosarcoma with prior bevacizumab exposure. Topotecan and pazopanib are administered orally daily. The primary efficacy endpoint is progression free survival (PFS) at six months from patient registration for bevacizumab naïve patients and PFS at 3 months for patients with prior bevacizumab treatment.

3.2 DRUG ADMINISTRATION

Patients will be treated with the combination of topotecan and pazopanib at the following doses:

3.2.1.1 Pazopanib: Starting dose is 600 mg (3x200mg) per day to be taken orally, daily, continuous, without food at least one hour before or two hours after a meal.

Pazopanib should be taken whole with water and must not be broken or crushed.

If a dose of pazopanib is missed, it should not be taken if it is less than 12 hours until the next dose.

3.2.1.2 Topotecan: Starting dose of topotecan is 0.25 mg orally, daily, continuous.

3.3 DOSE MODIFICATIONS:

3.3.1 For treatment or dose modification related questions, please contact the Academic PI or the BTTC Coordinating Center's Research Nurse Melanie Herrin, RN; 301-451-5979;

fax: 301-451-5429, Melanie.Herrin@nih.gov. Topotecan length of treatment is until progression, up to one year. Drug may be held up to 3 weeks waiting from toxicities to resolve. Drug dose will not be reduced.

3.3.2 Pazopanib length of treatment is until progression, up to one year. Dose of Pazopanib may be held up to 3 weeks waiting from toxicities to resolve and reduced to 400 mg or to 200 mg daily based on side effects. Patient may be maintained on the lower dose of pazopanib during protocol if deemed to be deriving benefit from the drug.

If a patient is felt to be deriving benefit for the agent(s) and is stable at the one year time point, based on discussion with the PI and sponsor it may be possible to continue treatment at that point.

3.3.3 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.

Dose modifications or delays should be made based upon whether toxicities occur within a 4-week treatment cycle or at the expected start of the next treatment cycle.

3.3.4 Within Treatment Cycles:

3.3.4.1 Topotecan:

For patients who experience Grade 3 or 4 diarrhea, or other non-hematologic toxicities, the topotecan dose can be held up to 3 weeks waiting for toxicity to resolve to < Grade 2. Drug may be resumed at that time at same dose. If toxicity does not resolve in 3 weeks, patient will be taken off study. Patients with Grade 2 diarrhea may need to follow the same dose modification guidelines.

Topotecan should not be re-administered unless the neutrophil count is more than or equal to 1.5 x 10^9/L, the platelet count is more than or equal to 75 x 10^9/L, and the hemoglobin level is more than or equal to 9 g/dL (after transfusion if necessary).

Standard oncology practice for the management of neutropenia is either to administer topotecan with other medications (e.g. G-CSF) or to dose reduce to maintain neutrophil counts. Please refer to section 4.1 for protocol guideline regarding G-CSF administration.

3.3.4.2 Pazopanib:

For Pazopanib, two dose reductions are permitted, from 600 to 400 or 200 mg daily or from 400 to 200 mg daily. Further dose reduction is not allowed. Patients may be maintained on the lower dose of pazopanib during protocol 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. Patients whose dose has been reduced for adverse events that are subsequently not felt to be related to pazopanib may have the dose re-escalated after completion of one cycle with toxicities less than or equal to grade 1.

3.3.5 Hematologic Toxicity:

Dose Modifications Based on ANC and Platelet Counts **(topotecan):**

ANC (/mL)		Platelets (/mL)	% of Planned topotecan
> 1500	and	> 75,000	100%
< 750	or	< 50,000	hold*

*Topotecan should be held. Upon recovery to ANC ≥ 1,500/mL and platelets to >75,000/mL, the same dose level will be administered.

3.3.6 Non-hematologic Toxicity:

Dose Modifications Based on **topotecan- or pazopanib**-Related Non-Hematologic Toxicities:

NCI Grade	% of Planned Dose
0-2+	100%+
3*	hold**
4	hold***

+For symptomatic Grade 2 toxicity, the suspect drug dose may be held at the discretion of the investigator until recovery to CTC Grade 0-1, then resume at same dose for topotecan or one dose lower for pazopanib.

*Except nausea/vomiting (unless patients are on optimal antiemetic therapy).

**Hold suspect drug until recovery to CTC Grade 0-1 (or to within 1 grade of starting values for pre-existing laboratory abnormalities), and then resume at same dose for topotecan or one dose level lower for pazopanib.

***Hold suspect drug until recovery to CTC Grade 0-1 (or to within 1 grade of starting values for pre-existing laboratory abnormalities), and then resume at same dose for topotecan or two dose levels lower for pazopanib.

3.3.6.1 Management of other drug related complications:

3.3.6.1.1.1 Management of Hepatic effects:

Cases of hepatic failure (including fatalities) have been reported during the use of pazopanib. In clinical trials with pazopanib, increase in serum transaminases (ALT, AST) and bilirubin were observed. In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin. The vast majority (92.5%) of all transaminase elevations of any grade occurred in the first 18 weeks.

Monitor serum liver tests before initiation of treatment with pazopanib and at least once every 4 weeks for at least the first 4 months of treatment, and as clinically indicated. Periodic monitoring should then continue after this time period.

The following guidelines are provided for patients with baseline values of total bilirubin ≤1.5 X ULN and AST and ALT ≤2 X ULN.

- Patients with isolated ALT elevations between 3 X ULN and 8 X ULN may be continued on pazopanib with weekly monitoring of liver function until ALT return to Grade 1 (NCI CTCAE) or baseline.
- Patients with ALT of >8 X ULN should have pazopanib interrupted until they return to Grade 1 (NCI CTCAE) or baseline. 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 once daily and measure serum

liver tests weekly for 8 weeks. Following reintroduction of pazopanib, if ALT elevations >3 X ULN recur, then pazopanib should be permanently discontinued.

- If ALT elevations >3 X ULN occur concurrently with bilirubin elevations >2 X ULN pazopanib should be permanently discontinued. Patients should be monitored until return to Grade 1 (NCI CTCAE) or baseline. Pazopanib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinaemia, known or suspected Gilbert's syndrome, and elevation in ALT >3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations.

Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring.

Beyond recommending that patients with mild hepatic impairment are treated with 800 mg pazopanib once daily (600 mg daily for this study) and reducing the initial starting dose to 200 mg per day for patients with moderate impairment, no further dose modification guidelines based on results of serum liver tests during therapy have been established for patients with preexisting hepatic impairment.

3.3.6.2 Monitoring and management of hypertension

In clinical studies with pazopanib, events of hypertension including hypertensive crisis have occurred. Hypertension (systolic blood pressure ≥ 150 or diastolic blood pressure ≥ 100 mm Hg) occurs early in the course of treatment (39% of cases occurred by Day 9 and 88% of cases occurred in the first 18 weeks).

Blood pressure should be well controlled prior to initiating pazopanib (see 2.1.2.5)

3.3.6.2.1 BP MONITORING:

- Check BP twice weekly for the first 2 months of therapy, then weekly for 2 months, and then once per month thereafter. On days that the patient is not scheduled for clinic visits, BP can be taken at home, local Pharmacy or local Physician's office.
- BP should be taken preferably in the morning and after resting for at least 5 minutes.
- If BP is ≥140/90, then it should be repeated twice (30 and 60 minutes after the first reading). The lowest of these 3 readings will be the one considered for grading and management purposes.
- If BP measured outside the clinic visits is ≥140/90, the result should be immediately reported to the Research Nurse and/or treating physician to take appropriate action as outlined below.

BP MANAGEMENT BASED ON GRADE (CTCAE 4.02):

Hypertension- Adverse Event Grade	**Management**
Grade 1 (systolic 120-139, diastolic 80-89)	• no need to modify or add anti BP meds; if the patient is already taking BP meds, reinforce need for compliance. • continue pazopanib and topotecan at same doses.
Grade 2 (systolic BP 140-159 or	• add or increase dose of BP meds (at the discretion of

diastolic 90-99)*	the treating physician); • continue topotecan; • HOLD pazopanib at the discretion of the treating physician until AE recovers to grade 0-1, then restart same dose.
Grade 3 (systolic ≥160 or diastolic ≥100)	• add or increase dose of BP meds (at the discretion of the treating physician); • continue topotecan; • HOLD pazopanib until AE recovers to grade 0-1, then restart pazopanib reducing 1 dose level.
Grade 4 (malignant hypertension; transient or permanent neurologic deficit, hypertensive crisis)	• DISCONTINUE pazopanib; • patient finishes trial participation.

*Note: for elevated BP to be considered grade 2 or 3 the patient should be previously normotensive or should be taking BP medication/s regularly.

3.3.6.2.2 IF THE PATIENT IS NOT COMPLIANT:

- REINFORCE need for strict compliance with current BP medication/s,
- HOLD pazopanib AND CONTINUE BP monitoring at least once a day until BP returns to grade 0-1,
- Then resume pazopanib at same dose.

THIS ELEVATED BP WILL NOT BE CONSIDERED AN AE UNLESS THERE IS A SECOND OCCURRENCE WHILE TAKING BP MEDICATIONS REGULARLY.

3.3.6.3 Management of QT Prolongation and Torsade de Pointes:

In clinical studies with pazopanib, events of QT prolongation or Torsade de Pointes have occurred. Pazopanib should be used with caution in patients with a history of QT interval prolongation, patients taking antiarrythmics or other medications that may potentially prolong QT interval, or those with relevant pre-existing cardiac disease. When using pazopanib, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (calcium, magnesium, potassium) within normal range is recommended.

3.3.6.4 Management of Arterial Thrombotic Events:

In clinical studies with pazopanib, myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed. Fatal events have been observed. Pazopanib should be used with caution in patients who are at increased risk of thrombotic events or who have had a history of thrombotic events. Pazopanib has not been studied in patients who have had an event within the previous 6 months. A treatment decision should be made based upon the assessment of individual patient's benefit/risk.

3.3.6.5 Management of Hemorrhagic Events:

In clinical studies with pazopanib hemorrhagic events have been reported. Fatal hemorrhagic events have occurred. Pazopanib has not been studied in patients who had a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months. Pazopanib should be used with caution in patients with significant risk of hemorrhage.

3.3.6.6 Management of Gastrointestinal Perforations and Fistula:

In clinical studies with pazopanib, events of gastrointestinal (GI) perforation or fistula have occurred. Fatal perforation events have occurred. Pazopanib should be used with caution in patients at risk for GI perforation or fistula.

3.3.6.7 Wound Healing issues:

No formal studies on the effect of pazopanib on wound healing have been conducted. Since Vascular Endothelial Growth Factor (VEGF) inhibitors may impair wound healing, treatment with pazopanib should be stopped at least 7 days prior to scheduled surgery. The decision to resume pazopanib after surgery should be based on clinical judgment of adequate wound healing. Pazopanib should be discontinued in patients with wound dehiscence.

3.3.6.8 Hypothyroidism:

In clinical studies with pazopanib, events of hypothyroidism have occurred. Proactive monitoring of thyroid function tests is recommended.

3.3.6.9 Proteinuria:

In clinical studies with pazopanib, proteinuria has been reported. Baseline and periodic urinalyses during treatment are recommended and patients should be monitored for worsening of proteinuria. Pazopanib should be discontinued if the patient develops nephrotic syndrome.

3.3.6.10 Pregnancy:

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.

3.3.6.11 Topotecan-induced neutropenic colitis:

Topotecan-induced neutropenia can cause neutropenic colitis. Fatalities due to neutropenic colitis have been reported in clinical trials with topotecan. In patients presenting with fever, neutropenia, and a compatible pattern of abdominal pain, the possibility of neutropenic colitis should be considered.

3.3.6.12 Interstitial lung disease:

Topotecan has been associated with reports of interstitial lung disease (ILD), some of which have been fatal. Underlying risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic exposure to radiation and use of pneumotoxic drugs and/or colony stimulating factors. Patients should be monitored for pulmonary symptoms indicative of ILD (e.g. cough, fever, dyspnea and/or hypoxia), and topotecan should be discontinued if a new diagnosis of ILD is confirmed.

3.3.6.13 Diarrhea

Diarrhea, including severe diarrhea requiring hospitalization, has been reported during treatment with oral topotecan. The incidence of diarrhea has been reported to be greater in patients receiving oral topotecan compared to those receiving topotecan i.v. Additionally, in patients with relapsing small cell lung cancer, greater than 65 years of age, there is substantially higher risk of

severe diarrhea and subsequent hospitalization than in patients less than 65 years of age. Communication with patients prior to drug administration regarding diarrhea and proactive management of all signs of diarrhea is important. Physicians are advised to follow guidelines that describe the aggressive management of this event. This includes use of anti-diarrheal agents, administration of fluids and electrolytes and interruption or discontinuation of therapy with oral topotecan.

Diarrhea related to oral topotecan can occur at the same time as drug-related neutropenia and its sequelae.

3.3.6.14 At the Start of the Next Treatment Cycle:

A new course of treatment may begin when the ANC is at least 1500/mm^3 and the platelet count is at least 75,000/mm^3 and any other treatment-related toxicities are less than or equal to grade 1. If after a one-week delay, all treatment related toxicities are less than or equal to grade 1, then proceed with treatment at the dose level dictated by the modifications outlined above. If treatment related toxicities have not resolved to less than or equal to grade 1 after a one-week delay, then treatment will be held again, and the patient will be evaluated weekly. If treatment will be held for 2 weeks for treatment related toxicities, then reduce the pazopanib dose by one dose level beyond that indicated by whether or not the patient had DLT in the prior cycle. If re-treatment must be held for more than 2 weeks the investigator should be notified. If a patient develops another DLT at the reduced dose or if they experience a life-threatening toxicity at any time, they will be removed from study.

3.4 ON STUDY EVALUATION

3.4.1 General Requirements

3.4.1.1 CBC with differential and platelets and serum chemistries and LFTs (ALT, AST and bilirubin) will be performed every two weeks X 2, (+/- 3 days) then every 4 weeks (+/- 3 days) prior to each cycle during treatment. UPC (+/- 3 days) will be done monthly prior to each cycle.

3.4.1.2 A brain MRI/CT for group B will be done monthly until 3 months then every other month thereafter, for group A scan will be obtained every other month prior to initiation of odd numbered 28 days treatment cycles (+/- 3 days).

3.4.1.3 All relevant information regarding drug doses, concomitant medications, and doses, measurable lesions with measurements, tumor response, laboratory examinations, and treatment-related toxicities shall be documented in the patient's medical record and flow sheets.

3.4.2 A complete Neurologic exam (to include documentation of the patients Karnofsky Performance Status) will be performed prior to every evaluation where an MRI is scheduled. The MDASI-BT (Appendix **15.5**) will be completed at baseline and at the time of each evaluation that includes an imaging study.

3.4.3 The patient will complete the MDASI-BT (see Appendix **15.5**) at the time of clinical evaluation with MRI as long as the clinical therapy is being administered, unless clinical deterioration makes self-report not possible before that time. The time when patients are unable to complete the self-report questionnaires will be used as part of the study analysis. The MDASI-BT will be completed only by the patient, unless changes in vision

or weakness make this difficult. If this occurs, then the caregiver or research assistant may read the questions to the patient or assist with marking the severity number or score as described by the patient. A patient caregiver may complete the questionnaires as a patient-preference proxy if the patient's deficits preclude self-report.

3.4.3.1 A measurement of BP should be taken twice weekly for the first 2 months of therapy, then weekly for 2 months, and then once per month thereafter as detailed in 3.3.5.2. BP can be assessed by any method (i.e., at home or by another physician) as long as the treating physician is informed of the measurement, verifies any measurement that is not normal and takes appropriate action.

3.4.3.2 Thyroid function test (T4 and TSH) (+/- 3 days) are to be monitored every 8 weeks (+/- 3 days)

3.4.3.3 EKG before treatment and week 4 and then every 8 weeks until end of treatment (+/- 3 days)

3.4.4 Follow-up

Patients will be evaluated for adverse events at the end of each cycle. In addition, all serious adverse events will be reported to the NCI BTTC as in section **8.6**.

All patients will be followed for overall survival, when possible.

Patients who discontinue treatment due to progression will be followed for survival every 3 months.

Patients who come off therapy for reasons other than progression should be followed until progression or institution of new anti-tumor therapy. They should then be followed for survival.

3.5 QUESTIONNAIRES

The MDASI-BT will be utilized for this portion of the study. Full instruments are provided in the Appendix **15.5** In addition, information regarding demographics and treatment history will be collected as part of the larger study and used in this analysis.

The MDASI-BT consists of 23 symptoms rated on an 11-point scale (0 to 10) to indicate the presence and severity of the symptom, with 0 being "not present" and 10 being "as bad as you can imagine." Each symptom is rated at its worst in the last 24 hours. Symptoms included on the instrument include those commonly associated with cancer therapies, those associated with increased intracranial pressure, and those related to focal deficits. The questionnaire also includes ratings of how much symptoms interfered with different aspects of a patient's life in the last 24 hours. These interference items include: general activity, mood, work (includes both work outside the home and housework), relations with other people, walking, and enjoyment of life. The interference items are also measured on 0 - 10 scales. The average time to complete these instruments is 5 minutes. The MDASI-BT has been translated into 18 languages [17, 20]

3.6 STUDY CALENDAR

	Screening	Week One	Week Two	Every 4 wks	Every 8 wks	End of tx	F/U^{m}
Informed Consent	X						

	Screening	Week One	Week Two	Every 4 wks	Every 8 wks	End of tx	F/U[m]
History/Physical Exam	X			X		X	
NeuroExam[k]	X				X		
Concomitant Meds/Adverse Events				X			
Vitals signs	X	X[a]	X[a]	X		X	
Performance Status	X			X		X	
Treatment Toxicity				X		X	
CBC [g]	X		X	X		X	
Chemistries, LFTs[b]	X		X[b]	X[b]		X	
Pregnancy test [j]	X					X	
UPC ratio	X			X			
UA	X						
Thyroid function test	X				X[c]		
Coagulation test	X						
EKG[d]	X				X[d]		
MRI or CT brain	X			X[e]	X[f]		
MDASI-BT[l]	X			X	X		
Tumor tissue	X[i]						
Hepatitis Questionnaire	X						
Hepatitis B and C	X[n]						

[a] Monitoring of BP only: A measurement of BP should be taken twice weekly for the first 2 months of therapy, then weekly for 2 months, and then once per month thereafter. BP can be assessed by any method (i.e., at home or by another physician) as long as the treating physician is informed of the measurement, verifies any measurement that is not normal and takes appropriate action.
[b] Monitoring of LFTs: LFTs (AST, ALT, Bili) every 2 weeks X 2, (+/- 3 days) then every 4 weeks prior to each cycle during treatment. (+/- 3 days)
[c] Thyroid function test (T4 and TSH) are monitored every 8 weeks (+/- 3 days)
[d] EKG: Week 4 and then every 8 weeks until end of treatment (+/-3 days)
[e] MRI: Group B only: Every 4 weeks until 3 months, then every 8 weeks thereafter (+/- 3 days)
[f] MRI: Group A only: Scan will be obtained every other month prior to initiation of odd numbered 28 day treatment cycles (+/- 3 days)
[g] CBC: Performed every 2 weeks X 2 (+/- 3 days) then every 4 weeks (+/3 days) prior to each cycle. For patients experiencing significant drop in WBCs or platelets felt 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] Tumor tissue blocks or 15 unstained paraffin slides to be obtained from institutions where surgery performed and provided to collaborating neuro-pathologist for confirmatory tumor diagnosis. Patient may be enrolled prior to acquisition of tumor tissue block.
[J] Only for women of childbearing potential; must be tested within 14 days prior to starting study drugs

[k] Complete Neurologic exam will be performed prior to every evaluation where an MRI is scheduled.
[l] MDASI-BT should be completed by patient at the time of clinical evaluation with MRI.
[m] Patient will be followed for overall survival when possible
[n] If positive (+) response to Hepatitis questionnaire Hepatitis B and C screening test should be done.

3.7 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.7.1 Criteria for Removal from Protocol Therapy

3.7.1.1 After administration of 12 28-day cycles of treatment, unless further treatment is felt to be in the best interest of the patient by the treating physician.

3.7.1.2 Progression of disease (as defined in Section **6.4.1**).

Patients must be followed by the same type of brain scan, as was used for baseline tumor measurements, and will be removed from study if progression is documented after any cycle of treatment. Patients with stable disease, partial or complete response will continue on therapy.

3.7.1.3 Unacceptable toxicity (see Section **3.3**).

3.7.1.4 The patient may withdraw from the study at any time for any reason.

3.7.1.5 Medical or psychiatric illness which in the investigator's judgment renders the patient incapable of further therapy.

3.7.1.6 Treatment delay due to toxicity greater than 21 days measured from the start of the preceding cycle.

3.7.1.7 All reasons for discontinuation of treatment must be documented in the flow sheets

3.7.2 Off Study Criteria

All patients will be followed for overall survival, when possible.

Patients who discontinue treatment due to progression will be followed for survival every 3 months.

Patients who come off therapy for reasons other than progression should be followed until progression or institution of new anti-tumor therapy. They should then be followed for survival.

3.7.3 Off Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and faxed to 301-480-0757.

All subjects must be registered through the NCI Central Registration Office (CRO). An off-study form will be supplied by the Coordinating Center, NCI CCR. Send the completed off-study form to the Coordinating Center's Research Nurse; Melanie Herrin, RN; fax: 301-451-5429, Melanie.Herrin@nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 G-CSF ADMINISTRATION

4.1.1.1 If neutrophil count < 1500/mm^3 or platelet count < 75,000/mm^3, hold topotecan until counts resolve to < grade 2 CTC grade toxicity. If neutrophil count remains < 1500/mm^3 x 1 week or more, granulocyte colony stimulating factor may be used to support. If neutrophil count achieves level > 1500/mm^3, 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 study.

4.2 CORTICOSTEROIDS

Corticosteroids should be used in the smallest dose to control symptoms of cerebral edema and mass effect, and discontinued if possible. Patients must not be on a dexamethasone dose of greater than 16 mg/day.

4.3 ANTI-SEIZURE MEDICATIONS

Anti-seizure medications should be used as indicated. If for unavoidable clinical reasons (severe allergies, toxicities, etc.) a patients AED is switched to the alternate AED group the following guidelines must be followed:

4.3.1.1 Patients are to be maintained on non-EIAEDS

4.3.1.1.1 Patients who were previously on an EIAED and need to change anticonvulsants, should first be started on a non-EIAED. Two weeks washout after this change are required before starting treatment on study.

4.3.1.1.2 Patients who were previously on a non- EIAED and were inadvertently and temporarily changed to an EIAED, should immediately be started on another non-EIAED. The patient may continue the current treatment dose while a non- EIAED is re-started.

4.3.1.2 Patients who were previously on a non-EIAED and need to permanently change anticonvulsant, but who cannot change to another non-EIAED need to be removed from the study due to drug-drug interactions

4.3.1.3 Patients who were previously on a non-EIAED and need to change anticonvulsants, should be started on another non-EIAED if at all possible. No delays in treatment would be required.

4.4 FEBRILE NEUTROPENIA

Febrile neutropenia may be managed according to the local institution's Infectious Disease Guidelines. Measures may include appropriate laboratory testing, including blood and urine cultures and the institution of broad-spectrum antibiotics. If a source for the fever is not

identified or the fever resolves when the neutrophil count recovers, antibiotics may be discontinued and the patient observed.

4.5 ANTI-EMETICS

The use of anti-emetics will be left to the investigators' discretion.

4.6 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.

4.7 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.

4.8 SURGERY

If neurosurgical management is required for reasons not due to tumor progression, these procedures must be documented, including the indications for surgery, the surgical operative note and pathology report. If possible defer surgery for 4 weeks from last dose of therapy. Patients who undergo resection for presumed tumor progression but are shown to only have treatment associated changes (treatment effect or necrosis) can resume treatment once they have recovered from the surgical procedure. Pazopanib treatment can only resume > 28 days after surgery.

5 BIOSPECIMEN COLLECTION

5.1 PATHOLOGY REVIEW

Following registration, slides from the most recent pre-registration biopsy must be submitted for review. The purpose of this review is to verify the histologic diagnosis.

The materials are to be submitted after registration step 1 to:

Ken Aldape, MD
Toronto General Hospital
200 Elizabeth Street, 11th Floor
Toronto, Ontario M5G 2C4 Canada
kaldape@gmail.com

Pathology Materials Required for Review:

1. One to two representative H&E stained slides from a pre-registration biopsy demonstrating lesion.
2. A copy of the pathology report and the operative report.
3. The Tissue Collection Shipping Form (see **15.3**).
4. The submitting institution is responsible for the costs of shipping and handling.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.. Designated research staff from the registering institution will enter the data via remote electronic data entry. The protocol specific electronic forms are to be used by the participating sites. All investigators will utilize these forms for Baseline, Treatment, Adverse Events, Tumor Evaluation, Off Treatment, Survival, and Off-study data.

All data will be kept secure. Personal identifiers will not be used when collecting and storing data. An enrollment log will be maintained in the regulatory binder/file which is the only location of personal identifiers with unique subject identification number.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.1.1 Source Documentation Timeframes

The following information will be entered into C3D within the indicated timeframes. In addition, the source documents should be provided to the NCI BTTC coordinating center research nurse within the indicated timeframe.

Data Set / Source Documents	Schedule for Submission
Regulatory Documents (as described in the BTTC Operations Manual)	Prior to Patient Registration
Eligibility Checklist	Prior to Patient Registration
Copy of signed & dated Informed Consent w/ HIPAA Authorization	Prior to Patient Registration
Pathology Report (from the most recent pre-registration diagnostic biopsy or surgery)	Prior to registration
Baseline Data (To include prior disease/treatment history, and baseline clinical evaluation information)	Within 14 days after the registration date
Baseline MDASI – BT Questionnaire	Within 14 days after the registration date
Baseline Source Documents	Within 14 days after the registration date

6.1.2 Database Entry Timeframes

The following data should be entered into C3D within the specified timeframes. Source documentation will be kept at the participating site.

Treatment (Cycle) Data (To include treatment, response, AE, and clinical evaluation information)	Within 40 days after the first day of each treatment cycle.
Off Treatment Data	Within 10 days after the last date of any modality of protocol treatment.
Follow-up (Survival) Data	Within 52 days after the last treatment date and then every 90 days until Off Study (unless otherwise specified by the protocol).
Non-Treatment Data (May include Quality of Life questionnaires (MDASI-BT), Specimen Tracking information, Pathology Specimen Submission, etc.)	Within 10 days after each scheduled assessment, event, or activity.
Off Study Data	Within 10 days after the date the patient is removed from the study.

6.1.3 Confidentiality

All documents, investigative reports, or information relating to the patient are strictly confidential. Any patient specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the NCI BTTC Coordinating Center must have the patient's full name & social security number "blacked out" and the assigned patient ID number and protocol number written in. Patient initials may be included or retained for cross verification of identification.

6.1.4 Safety Data

All patients receiving study agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, CNS observations, physical examination findings, and spontaneous reports of adverse events reported to the investigator by patients. All toxicities encountered during the study will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and recorded prior to each course of therapy. Life-threatening toxicities that are unexpected and assessed to be possibly related to the study agent/s should be reported immediately as per section **7.2.**

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Case Report Form and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded on the Baseline Evaluations Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are also recorded on the Adverse Events Case Report Form.

6.1.5 Data Sharing with Pharmaceutical Collaborator, Novartis

NCI may share data from this study with its pharmaceutical collaborator, Novartis, pursuant to the NCI CDA with Novartis. Specifically, Novartis may access and review analytical results and primary quantitative and empirical data including identifiable private information in accordance with the terms of the CDA.

6.2 DATA MONITORING

All submitted data will be monitored by the BTTC Protocol Manager specifically assigned to this protocol. Requests for correction of data deficiencies will be sent via mail to the Institutional Coordinator. Any major deficiencies will be corrected by telephone communication. All data will be monitored for completeness. Key parameters such as drug dosages including attenuations and escalations, toxicity documentation and tumor measurements will be analyzed. All data deficiencies will be corrected within two weeks.

6.3 DATA SHARING PLAN

6.3.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows (check all that apply):

X Coded, Linked data in an NIH-funded or approved public repository.

__ Coded, Linked data in another public repository.

X Identified data in BTRIS (automatic for activities in the Clinical Center)

X Identified or coded, linked data with approved outside collaborators under appropriate agreements.

___ I will not share human data generated in this research for future research. If checked, explain:

How and where will the data be shared?

Data will be shared through (check all that apply):

X An NIH-funded or approved public repository. Insert name or names: clinicaltrials.gov

__ Another public repository. Insert name or names: _____.

X BTRIS (automatic for activities in the Clinical Center)

X Approved outside collaborators under appropriate individual agreements.

X Publication and/or public presentations.

When will the data be shared? (check all that apply)

X Before publication.

X At the time of publication or shortly thereafter.

6.4 RESPONSE CRITERIA

The primary efficacy endpoint is progression free survival (PFS) at six months from patient registration for bevacizumab naïve patients and PFS at 3 months for patients with prior bevacizumab treatment. However, objective response status should be measured and recorded.

6.4.1 Definitions of Response

6.4.1.1 Measurable Disease: Bidimensionally measurable lesions with clearly defined margins by CT or MRI scan.

6.4.1.2 Evaluable Disease: Unidimensionally measurable lesions, masses with margins not clearly defined.

6.4.1.3 Non-Evaluable Disease: Not Applicable for response evaluation

6.4.1.4 Objective Status, To Be Recorded at Each Evaluation: If there are too many measurable lesions to measure at each evaluation, choose the largest two to be followed before a patient is entered on study. The remaining lesions will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL measurable and evaluable sites and lesions are assessed.

6.4.1.4.1 Complete Response (CR): Complete disappearance of all measurable and evaluable disease. No new lesions. No evidence of non-evaluable disease. All measurable, evaluable and non-evaluable lesions and sites must be assessed using the same techniques as baseline. Patients must be on no steroids.

6.4.1.4.2 Partial Response (PR): Greater than or equal to 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline. *The steroid dose at the time of the scan evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy.*

6.4.1.4.3 Partial Response, Non-Measurable (PRNM): Not applicable.

6.4.1.4.4 Stable/No Response: Does not qualify for CR, PR, or progression. All measurable and evaluable sites must be assessed using the same techniques as baseline. The steroid dose at the time of the scan

evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy.

6.4.1.4.5 Progression: 25% increase in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, OR clear worsening of any evaluable disease, OR appearance of any new lesion/site, OR clear clinical worsening or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer). Patients will also be considered to have progressive disease if there is significant increase in T2/FLAIR non-enhancing lesions AND clinical progression. (See section 6.4.1 and 6.3.7 for definitions). To be considered progressive disease, increase in T2/FLAIR should occur on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy, and should not be due to co-morbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).

6.4.1.4.6 Unknown: Progression has not been documented and one or more measurable or evaluable sites have not been assessed.

6.4.2 Best Response: This will be calculated from the sequence of objective statuses.

For patients with all disease sites assessed every evaluation period, the best response will be defined as the best objective status as measured according to Section 6.4.1. If the response does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, e. g. still present on the subsequent MRI, it will be recorded as a sustained response, lasting until the time of tumor progression. Best response is unknown if the patient does not qualify for a best response or increasing disease and if all objective status determinations before progression are unknown.

6.4.3 Neurological Exam: Although not used for determining response, it is useful to evaluate improvement in the neurologic exam, (as compared to the baseline assessment), that should coincide with objective measurement of tumor size.

+1	Better
0	Unchanged
-1	Worse
B	Baseline

6.4.4 Performance Status: Patients will be graded according to Karnofsky Performance Status (See Appendix **15.1**). Clinical progression can be declared if there is a decrease in 100 or 90 to 70 or less, at least 20 from 80 or less, or decline in KPS from any baseline to 50 or less, for at least 7 days and not attributable to comorbid events or change in steroid dose.

6.4.5 Time to Treatment Failure: From date of registration to the date of first observation of progressive disease (as defined in Section 6.4 .1.4.5), non-reversible neurologic progression or permanently increased steroid requirement (applies to stable disease only), death due to any cause, or early discontinuation of treatment.

6.4.6 Time to Death: From date of registration to date of death due to any cause.

6.4.7 Documenting FLAIR: investigators will be asked to measure tumor related changes on FLAIR sequence as best as possible, as non-enhancing patterns of recurrence can occur. If this occurs within the setting of clinical progression not caused by seizures or other identifiable cause, the patient will be considered to have progressive disease. Please see section 6.4.1 for definition of clinical progression.

Presumed non-enhancing tumor without clinical progression should be observed. The time of progression if eventual clinical deterioration occurs can be back dated to the time of the increase in non-enhancing tumor. Investigators will also be asked to document if recurrence of disease is multifocal.

6.5 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2.3 Multi-Institutional Guidelines

7.2.3.1 IRB Approvals

The Administrative PI will provide the NIH Intramural IRB with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NIH Intramural IRB.

7.3 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.3.1 Principal Investigator/Research Team

The clinical research team will have a teleconference every other week when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the Principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using eIRB system.

The Principal Investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The Principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.3.2 NCI BTTC Coordinating Center Monitoring Plan

This trial will be monitored by personnel employed by Harris Technical Services on contract to the NCI, NIH. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

At least 25% of enrolled patients will be randomly selected and monitored at least biannually or as needed, based on accrual rate. The patients selected will have 100% source document verification done. Additional monitoring activities will include: adherence to protocol specified study eligibility, treatment plans, data collection for safety and efficacy, reporting and time frames of adverse events to the NIH Intramural IRB and FDA, and informed consent requirements. Written reports will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

7.3.3 Safety Monitoring Committee (SMC)

This protocol will require oversight from the Safety Monitoring Committee (SMC). Initial review will occur as soon as possible after the annual NIH Intramural IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC. For initial and subsequent

reviews, protocols will not be reviewed if there is no accrual within the review period. Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

8 SAFETY REPORTING TO BTTC

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 4.0.

8.2 ASSESSING CAUSALITY

Investigators are required to assess whether there is a reasonable possibility that the study agent/s caused or contributed to an adverse event. The following general guidance may be used.

Yes: If the temporal relationship of the clinical event to the study agent/s administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: If the temporal relationship of the clinical event to the study agent/s administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

8.3 PROTOCOL SPECIFIC DEFINITIONS

Events *not* considered to be serious adverse events are hospitalizations for the purposes of this protocol and include:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on an emergency, outpatient basis for an event *not* fulfilling any of the definitions of serious given above and *not* resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

8.4 GUIDELINES & PROCEDURES FOR REPORTING DEVIATIONS AND UNANTICIPATED PROBLEMS

Neither the FDA nor the ICH GCP guidelines define the term "protocol deviation." The definition is often left to the Lead Institution IRB. Accordingly, since NCI, Center for Cancer Research is the Coordinating Center and the Administrative PI must adhere to those policies set by the NIH Intramural IRB, the definitions for unanticipated problem and protocol deviation as described in Policy 801 will be applied for reporting purposes for all institutions participating in the NCI Center for Cancer Research Multi-center Project.

Protocol Deviations or Unanticipated problems occurring at a participating institution will be submitted to that institution's own IRB in accordance with local policies and procedures. However, the participating institution must submit a report to the BTTC Coordinating Center even in instances where the local IRB does not require a report.

Deviations or Unanticipated problems must be submitted to the NCI BTTC Coordinating Center within 5 working days after becoming aware of the event (if not reportable to the local IRB). When Deviations or Unanticipated Problems are reported to BTTC, but, the local IRB does not require a report, the report that is submitted to the NCI BTTC Coordinating Center must be accompanied by a formal memo explaining the local policy and the rationale for not reporting the event to the local IRB.

Deviation or Unanticipated problem Reports and any accompanying documentation (to include the local IRB acknowledgement of the event when applicable) are to be submitted to the NCI BTTC Coordinating Center using the problem report form in Appendix **15.9** via fax at: 301-451-5429.

NCI Center for Cancer Research Coordinating Center: Upon receipt of the deviation/unanticipated problem report from the participating institution, the NCI BTTC Coordinating Center will submit the report to the Academic PI for review.

8.5 REPORTING TO THE STUDY DRUG MANUFACTURER (NOVARTIS)

The NCI BTTC Coordinating Center will forward all SAE reports to the lead IRB via the lead investigator, FDA (when applicable), and Novartis:

Novartis Pharmaceuticals Corporation
FAX: 888-299-4565

SAEs will be forwarded to Novartis via the NCI BTTC Coordinating Center in accordance with the following:

All serious adverse events should be reported to Novartis within 24 hours. In the event of an SAE, the investigator should refer to the Pharmacovigilance section of the contract for reporting procedures. In brief:

> **The Investigator/Sponsor may report serious adverse drug reactions (SADRs) using either:**
>
> An ADEERS form (Adverse Event Expedited Reporting System) available at http://ctep.cancer.gov/reporting/adeers.html
>
> OR
>
> A MedWatch form available at http://www.fda.gov/medwatch/

Occasionally BTTC may contact the reporter for additional information, clarification, or current status of the subject for whom an adverse event was reported.

8.6 GUIDELINES FOR REPORTING SERIOUS ADVERSE EVENTS TO BTTC

What to Report?	When to Report?
1. All Deaths, except that due to progressive disease, occurring from the time the consent is signed through 30 days after the last day of active treatment	Within 1 **working** day (24 hours) from the time the **research team** becomes aware of event

What to Report?	When to Report?
2. Other Serious Unexpected Suspected Adverse Reactions (that did not result in death) occurring from the time the consent is signed through 30 days after the last day of active treatment	Within 5 **working** days from the time the **research team** becomes aware of event
3. All protocol deviations, non-compliance and unanticipated problems	Within 5 **working** days from the time the **research team** becomes aware of event
4. Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.	Within 5 **working** days from the time the **research team** becomes aware of event

The CCR problem report form will be used to submit adverse events to BTTC. See Appendix **15.9.** Participating centers must also submit the report to their IRB in accordance with their institutional policies.

The BTTC Coordinating Center will maintain documentation of all Serious Adverse Events from each institution. The BTTC Coordinating Center will notify all investigators of any serious and unexpected adverse experiences that are possibly related to the study agent/s. The investigators are to file a copy with their protocol file and send a copy to their IRB according to their local IRB's policies and procedures.

9 STATISTICAL CONSIDERATIONS

For this study, since there is experience with the drug combination a formal DSMB review will not be necessary.

Time to progression and overall survival will be evaluated using the Kaplan-Meier product-limit survival curve methodology. Six-month Progression Free Survival (PFS) will be estimated using Kaplan-Meier estimates and associated two-sided 95% confidence intervals.

Recurrent glioblastoma with <u>no</u> prior exposure to bevacizumab cohort (Group A): A maximum of 34 patients will be observed in a two-stage Simon optimum design. In the first stage, 9 patients will be accrued. If two or more patients are progression-free at 6 months (PFS6), an additional 25 patients will be accrued. We halt registering patients after 9 patients until we have at least 2 patients are progression free at six months. If 9 or more out of 34 have PFS6, then the study will be declared promising. This study has a 5% chance of declaring promise if the PFS6 rate is at most 15%. It has an 80% chance of declaring promise if the PFS rate is at least 35%.

Recurrent glioblastoma <u>with</u> prior exposure to bevacizumab cohort (Group B): In the group that failed bevacizumab, a maximum of 32 patients will be observed in a two-stage Simon

optimum design. In the first stage, 14 patients will be accrued. If one or more patients is progression-free at 3 months (PFS3), an additional 18 patients will be accrued. We will halt registration after 14 patients until at least 1 patient is progression free at 3-months. If 2 or more out of 32 have PFS3, then the study will be declared promising. This study has a 5% chance of declaring promise if the PFS3 rate is at most 1%. It has an 80% chance of declaring promise if the PFS rate is at least 12%.

In both patient cohorts, for patients who drop out for reasons other than PD or toxicity, we will replace them. We expect the dropout rate to be not more than 10%, therefore in general it is not an issue to implement the design. The patients who drop out due to toxicity will be counted as treatment failure when implementing the Simon's two stage design and assessing the 6-month PFS rate in either cohort.

The trial will be monitored by the Academic PI, Morris D. Groves, MD, and the study statistician, Yuan Ying, PhD.

We will monitor the toxicity based on the combined data from the above two cohorts with a total sample size of 66. All grade 3 or greater toxicities attributable to the study treatment will be counted. Accrual will be temporarily suspended for analysis after each of the following interim accrual goals. We will monitor the toxicity when the accrual is 5, 10, 20, 35, and 50 based on using the following stopping rule: if the posterior probability of toxicity greater than 0.3 is greater than 0.95 (i.e., Pr (toxicity>0.3|data) >0.95), we terminate the study for toxicity. Assuming the beta prior Beta (0.6, 1.4) for the toxicity, we have the following operating characteristics.

Operating characteristics of the proposed stopping rule

True toxicity probability	0.2	0.3	0.4	0.5
Stopping Probability	1.3%	12.4%	55.0%	92.7%
Average number of patients treated	65.3	60.3	43.9	24.2

We obtain the following stopping boundary: the study will be terminated if we observe >= 4/5, 6/10, 10/20, 16/35, 21/50 (# of patients experienced DLTs/# of patients treated). Note that our safety monitoring starts with a small cohort size of 5, and then gradually increases to 15. Therefore, if the treatment agents are overly toxic, the trial will stop before exposing many patients to toxicities.

Patient-reported outcomes: The sample size for this trial was based on the primary endpoint of the study.

Received MDASI-BT forms will be checked versus the timing schedule and considered as valid if they fall within ten days of the scheduled assessment. Compliance rates will be calculated as the number of received valid forms over the number of expected forms. Differences between groups in compliance will be tested by use of Fisher's exact test at every time point.

We will use descriptive statistics to describe how patients rate symptom severity and interference with function at each time point. Error bar graphs for each of the symptoms will be constructed at each time point. The proportion of patients rating their symptoms to be 7 or greater (on a 0-10 scale) will also be reported. We will construct individual patient profiles for each of the selected symptoms to describe the individual patients' patterns of change over time. We will calculate the

mean core symptom severity, mean severity of the MDASI-BT and mean symptom interference at the time of clinical evaluation. Estimates of differences in the mean symptom severity and mean symptom interference between responders and non-responders will be estimated in the intent to treat population. All patients with at least one valid questionnaire will be included in the analyses. Questionnaires completed at study registration will be considered baseline. All questionnaire data received after randomization will be used in the primary analyses.

Differences of at least 2 points will be classified as the minimum clinically meaningful change in the symptom severity and symptom interference measures. For example, an increase of 2 points or more would mean a moderate improvement, whereas a decrease of 2 points or more would be interpreted as moderate worsening. For individual symptoms, a rise in a symptom score means deterioration, whereas a reduced score means improvement of the specific symptom.

10 COLLABORATIVE AGREEMENTS

10.1 AGREEMENT TYPE

There is a BTTC consortia agreement in place between all of the participating institutions listed on the title page of this study. In addition, there is a CDA (13618-17) in place with Novartis. Other agreements are found in Appendix **15.13**, Technology Transfer Agreements.

11 HUMAN SUBJECTS PROTECTIONS

11.1 RATIONALE FOR SUBJECT SELECTION

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. Males and females will be recruited with no preference to sex. No exclusion to this study will be based on race. Minorities will actively be recruited to participate. High grade gliomas occur in patients of all races and although there is a slight predominance in men, this is a disease that is also common in women. The molecular targets of pazopanib and topotecan within the tumor are not known to be different among patients based on sex or race; hence this study will be open to all adults.

11.2 PARTICIPATION OF CHILDREN

Individuals under the age of 18 will not be eligible to participate in this study because they are unlikely to have glioblastoma, and because of unknown toxicities of the study agents in the pediatric patient. Furthermore, the targets of the pazopanib and topotecan are not as prevalent in pediatric malignant gliomas and therefore, the efficacy of this regimen will be initially determined in the adult population before consideration of its use in pediatrics.

11.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The primary risk to patients participating in this research study is from the toxicity of pazopanib and topotecan, or both drugs. Both are investigational agents in the treatment of gliomas, although bevacizumab is an FDA-approved drug for the treatment of colorectal carcinoma. The protocol provides for detailed and careful monitoring of all patients to assess for toxicity. Toxicity data from the current dose level will be collected and reviewed to ensure that there were no severe toxicities that would preclude further patient enrollment. Patients will be treated with therapeutic intent and response to the therapy will be closely monitored.

11.4 RISKS/BENEFITS ANALYSIS

11.4.1 Benefits

The potential benefit to a patient on this study is a reduction in the bulk of their tumor and improvement in cancer lesions, which may or may not have favorable impact on symptoms and/or survival.

11.4.2 Risks

Risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document or this protocol document. Frequent monitoring for adverse effects will help to minimize the risks associated with administration of the study agents.

11.4.3 Risks/Benefits Analysis

The potential benefits from this therapy are disease stabilization or shrinkage and a reduction in symptoms caused by the brain tumor such as neurological deficits and headache. Given the efforts to minimize risk with the administration of this combination, this protocol involves greater than minimal risk, but presents the potential for direct benefit to individual subjects.

11.5 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

All patients who are being considered for this trial will undergo informed consent prior to being enrolled on the trial. The PI or associate investigator will perform the consenting process. Patients and family members when applicable will be asked to read the consent and will be encouraged to ask questions. It will be stated clearly that participation in the research study is voluntary and that participants can withdraw from the study without losing benefits they would otherwise be entitled to. Patients will be enrolled after the consent document has been signed. Separate consents will be obtained for any surgical procedures performed. The informed consent process will be documented in the patient's medical record and on the informed consent document. This process will be performed by the local Principal Investigator or designee.

If new safety information results in significant changes in the risk/ benefit assessment, the consent form will be reviewed and updated as necessary. All subjects (including those already being treated) will be informed of the new information, be given a copy of the revised form, and be asked give their consent to continue in the study.

12 REGULATORY AND OPERATIONAL CONSIDERATIONS

12.1 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for

Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12.2 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NCI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

12.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NCI CCR

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or

local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

13 PHARMACEUTICAL INFORMATION

There will be no IND obtained for the use of Topotecan or Pazopanib for this study.

This study meets the criteria for exemption for an IND as this investigation is not intended to support a new indication for use or any other significant change to the labeling; the drugs are already approved and marketed and the investigation is not intended to support a significant change in advertising; and the investigation does not involve a route of administration or dosage level in use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

13.1 DRUG NAME: HYCAMTIN (TOPOTECAN HYDROCHLORIDE)

13.1.1 **Chemical Name**:(*S*)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione monohydrochloride

13.1.2 **Molecular Formula**: $\mathbf{C_{23}H_{23}N_3O_5}$ •HCl

13.1.3 **Molecular Weight**: 457.9 g/mol

13.1.4 **Appearance**: Topotecan hard capsule, 0.25 mg: Opaque white to yellowish white, imprinted with HYCAMTIN 0.25 mg. Each hard capsule contains topotecan hydrochloride equivalent to 0.25 mg topotecan free base.

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

13.1.6 **Mechanism 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.

13.1.7 **Pharmacology**

The pharmacokinetics of topotecan after oral administration have been evaluated in cancer patients following doses of 1.2 to 3.1 mg/m^2 and 4 mg/dose administered daily for 5 days.

13.1.7.1 Absorption

Topotecan is rapidly absorbed with peak plasma concentrations occurring between 1 to 2 hours following oral administration. Following co-administration of the ABCG2 (BCRP) and ABCB1 (P-gp) inhibitor, elacridar (GF120918) at 100 to 1000 mg with oral topotecan, the $AUC_{0\text{-}inf}$ of

topotecan lactone and total topotecan increased approximately 2.5-fold. Administration of oral cyclosporin A (15 mg/kg), an inhibitor of transporters ABCB1 (P-gp) and ABCC1 (MRP-1) as well as the metabolizing enzyme CYP3A4, within 4 hours of oral topotecan increased the dose-normalized $AUC_{0\text{-}24h}$ of topotecan lactone and total topotecan approximately 2.0- and 2.5-fold, respectively. Following a high-fat meal, the extent of exposure was similar in the fed and fasted state while t_{max} was delayed from 1.5 to 3 hours (topotecan lactone) and from 3 to 4 hours (total topotecan).

13.1.7.2 Distribution

The binding of topotecan to plasma proteins was low (35%) and its distribution between blood cells and plasma was homogeneous.

13.1.7.3 Metabolism

A major route of inactivation of topotecan is a reversible pH-dependent ring opening to the inactive carboxylate form. Metabolism accounts for less than 10% of the elimination of topotecan. An N-desmethyl metabolite was found in urine, plasma, and feces. Following oral administration the mean metabolite: parent AUC ratio was less than 10% for both total topotecan and topotecan lactone. An O-glucuronide of topotecan and N-desmethyl topotecan has been identified in the urine. *In vitro*, topotecan did not inhibit human cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A nor did it inhibit the human cytosolic enzymes dihydropyrimidine dehydrogenase or xanthine oxidase.

13.1.7.4 Elimination

Following oral administration, the plasma concentrations decline bi-exponentially. The pharmacokinetics of oral topotecan are approximately dose proportional. There is little or no accumulation of either formulation of topotecan with repeated daily dosing, and there is no evidence of a change in the pharmacokinetics with multiple dosing. The pharmacokinetics of topotecan after oral administration have been evaluated in cancer patients following doses of 1.2 to 3.1 mg/m^2 and 4 mg/dose administered daily for 5 days. Oral topotecan exhibits a mean terminal half-life of approximately 3.0 to 6.0 hours. Overall recovery of drug-related material following five daily doses of topotecan was 49% to 71% of the administered oral dose. Approximately 20% was excreted as total topotecan and 2% was excreted as N-desmethyl topotecan in the urine. Fecal elimination of total topotecan accounted for 33% while fecal elimination of N-desmethyl topotecan was 1.5%. Overall, the N-desmethyl metabolite contributed a mean of less than 6% (range 4–8%) of the total drug related material accounted for in the urine and feces.

13.1.8 Special Patient Populations

A cross-study analysis in 217 patients with advanced solid tumors indicated that age and sex did not significantly affect the pharmacokinetics of oral topotecan.

13.1.8.1 Renal impairment

Patients with small cell lung carcinoma who participated in oral topotecan clinical trials had a serum creatinine less than or equal to 1.5 mg/dL (133umol/L) or a creatinine clearance (CrCl) of greater than or equal to 60 mL/min. Dosing recommendations for patients receiving oral topotecan with CrCl less than 60 mL/min have not been established.

13.1.8.2 Hepatic impairment

Pharmacokinetics of oral topotecan has not been specifically studied in patients with impaired hepatic function.

13.1.9 Pre-clinical Toxicology:

13.1.9.1 Carcinogenesis, mutagenesis

The carcinogenic potential of topotecan has not been studied. In common with a number of other cytotoxic agents, and resulting from its mechanism of action, topotecan is genotoxic to mammalian cells (mouse lymphoma cells and human lymphocytes) *in vitro* and mouse bone marrow cells *in vivo*.

13.1.9.2 Reproductive toxicology

As with other cytotoxics, topotecan was also shown to cause embryo-fetal toxicity when given to rats (0.59 mg/m^2/day) and rabbits (1.25 mg/m^2/day) at doses less than the clinical i.v. dose in humans (1.5 mg/m^2/day). A dose of 0.59 mg/m^2 was teratogenic in rats (predominantly effects of the eye, brain, skull and vertebrae).

13.1.10 Human Toxicity:

13.1.10.1 Adverse Reactions

13.1.10.1.1 Infections and infestations

Very Common	Infection
Common	Sepsis

13.1.10.1.2 Blood and lymphatic system disorders

Very Common	Anaemia, febrile neutropenia, leucopenia, neutropenia , thrombocytopenia
Common	Pancytopenia
Not Known	Severe bleeding (associated with thrombocytopenia)

13.1.10.1.3 Immune system disorders

Common	Hypersensitivity, including rash

13.1.10.1.4 Metabolism and nutrition disorders

Very Common	Anorexia (which may be severe)

13.1.10.1.5 Respiratory, thoracic and mediastinal disorders

Rare	Interstitial lung disease

13.1.10.1.6 Gastrointestinal disorders

Very Common	Diarrhea (see Warnings and Precautions), nausea and vomiting (all of which may be severe), abdominal pain*, constipation and stomatitis.

With oral topotecan, the overall incidence of drug-related diarrhea was 22%, including 4% with Grade 3 and 0.4% with Grade 4. With oral topotecan, drug-related diarrhea was more frequent in patients greater than or equal to 65 years of age (28%) compared to those less than 65 years of

age (19%). After i.v. topotecan, drug-related diarrhea in patients greater than 65 years of age was 10%.

*Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia.

13.1.10.1.7 Hepatobiliary disorders

Common	Hyperbilirubinaemia

13.1.10.1.8 Skin and subcutaneous disorders

Very Common	Alopecia

13.1.10.1.9 General disorders and administrative site conditions

Very Common	Asthenia, fatigue, pyrexia
Common	Malaise
Very Rare	Extravasation (i.v. formulation only)

13.1.10.2 Integrated safety data

Safety data is presented on an integrated data set of 682 patients with relapsed lung cancer administered 2536 courses of oral topotecan monotherapy (275 patients with relapsed SCLC and 407 with relapsed non-SCLC) (*see Adverse Reactions*).

13.1.10.2.1 Hematological

13.1.10.2.1.1 Neutropenia: Severe neutropenia (Grade 4 - neutrophil count less than 0.5 x 109/L) occurred in 32% of patients in 13% of courses. Median time to onset of severe neutropenia was Day 12 with a median duration of 7 days. In 34% of courses with severe neutropenia, the duration was greater than 7 days. In course 1 the incidence was 20%, by course 4 the incidence was 8%. Infection, sepsis and febrile neutropenia occurred in 17%, 2%, and 4% of patients respectively. Death due to sepsis occurred in 1% of patients. Growth factors were administered to 19% of patients in 8% of courses.

13.1.10.2.1.2 Thrombocytopenia: Severe thrombocytopenia (Grade 4 - platelets less than 10 x 109/L (as defined by v2 of CTC criteria)) occurred in 6% of patients in 2% of courses. Median time to onset of severe thrombocytopenia was Day 15 with a median duration of 2.5 days. In 18% of courses with severe thrombocytopenia the duration was greater than 7 days. Moderate thrombocytopenia (Grade 3 - platelets between greater than or equal to 10 and less than 50 x 109/L) occurred in 29% of patients in 14% of courses. Platelet transfusions were given to 10% of patients in 4 % of courses. Reports of significant sequelae associated with thrombocytopenia including fatalities due to tumor bleeds have been infrequent.

13.1.10.2.1.3 Anemia: Moderate to severe anemia (Grade 3 and 4 - Hb less than 8.0 g/dl) occurred in 25% of patients (12% of courses). Median time to onset of moderate to severe anemia was Day 12 with a median duration of 7 days. In 46% of courses with moderate to severe anemia the duration was greater than 7 days. Red blood cell transfusions were given in 30% of patients (13% of courses). Erythropoietin was administered to 10% of patients in 8% of courses.

13.1.10.2.2 Non-hematological

The most frequently reported non-hematological adverse reactions, all cases irrespective of associated causality were nausea (37%), diarrhea (29%), fatigue (26%), vomiting (24%), alopecia (21%) and anorexia (18%). For severe cases (CTC grade 3/4) reported as related/possibly related to topotecan administration the incidence was diarrhea 5%, fatigue 4%, vomiting 3%, nausea 3% and anorexia 2%.

The overall incidence of drug-related diarrhea was 22%, including 4% with Grade 3 and 0.4% with Grade 4. Drug-related diarrhea was more frequent in patients greater than or equal to 65 years of age (28%) compared to those less than 65 years of age (19%). Loperamide was administered to 13% of patients in 5% of courses. The median time to onset of grade 2 or worse diarrhea was 9 days.

Complete alopecia related/possibly related to topotecan administration was observed in 9% of patients and partial alopecia related/possibly related to topotecan administration in 11% of patients.

13.1.10.3 Special Warnings and Precautions for Use

Topotecan is approved for treatment of patients with ovarian, cervical cancers and small cell lung cancer. There is less experience in treating primary brain tumor patient, thus there is always potential for unexpected adverse events.

13.1.10.3.1 Pregnancy: Topotecan is contraindicated during pregnancy and during breast-feeding.

Women of childbearing potential must be apprised of the potential hazard to the fetus, which includes severe malformation (teratogenicity), failure to thrive and fetal death (embryotoxicity).

Topotecan has been shown to be both embryotoxic and fetotoxic in preclinical studies. As with other cytotoxic drugs, topotecan may cause fetal harm when administered to pregnant women and therefore is contraindicated during pregnancy. Women should be advised to avoid becoming pregnant during therapy with topotecan and to inform the treating physician immediately should this occur.

Topotecan is contraindicated during breast-feeding. Topotecan should not be used during pregnancy.

13.1.10.3.2 **Effects on ability to drive and use machines:** Caution should be observed when driving or operating machinery if fatigue and asthenia persist.

13.1.10.3.3 **Patients with Hepatic Impairment:** Pharmacokinetics of oral topotecan have not been specifically studied in patients with impaired hepatic function.

13.1.10.3.4 **Patients with Renal Impairment:** Patients with small cell lung carcinoma who participated in oral topotecan clinical trials had a serum creatinine less than or equal to 1.5 mg/dL (133umol/L) or a creatinine clearance (CrCl) of greater than or equal to 60 mL/min. Dosing recommendations for patients receiving oral topotecan with CrCl less than 60 mL/min have not been established.

13.1.10.3.5 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** The carcinogenic potential of topotecan has not been studied. In common with a number of other cytotoxic agents, and resulting from its mechanism of action, topotecan is genotoxic to mammalian cells (mouse lymphoma cells and human lymphocytes) *in vitro* and mouse bone marrow cells *in vivo*. As with other cytotoxics, topotecan was also shown to cause embryo-fetal toxicity when given to rats (0.59 mg/m^2/day) and rabbits (1.25 mg/m^2/day) at doses less than the clinical i.v. dose in humans (1.5 mg/m^2/day). A dose of 0.59 mg/m^2 was teratogenic in rats (predominantly effects of the eye, brain, skull and vertebrae).

13.1.10.3.6 **Pediatric Use:** Use in children is not recommended as only limited data are available.

13.1.10.3.7 **Geriatric Use:** No overall differences in effectiveness were observed between patients over 65 years and younger adult patients. However, it has been reported that patients older than 65 years old receiving topotecan experienced an increase in drug related diarrhea compared to those younger than 65 years of age.

13.1.10.3.8 Capsules:

Interaction with Other Medications: 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/m^2/day for 5 consecutive days) and cisplatin (60 mg/m^2/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 C_{max}, 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/m^2/day for 3 consecutive days) and cisplatin (50 mg/m^2/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/m^2/d for 5 days) with i.v. cisplatin (60 mg/m^2 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.

Table of oral topotecan drug interactions is below. This table is also included in Appendix **15.6**

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

13.1.10.3.9 Pregnancy and Lactation

Pregnancy

Topotecan is contraindicated during pregnancy.

Lactation

Topotecan is contraindicated during breast-feeding.

Topotecan has been shown to be both embryotoxic and fetotoxic in preclinical studies. As with other cytotoxic drugs, topotecan may cause fetal harm when administered to pregnant women and therefore is contraindicated during pregnancy. Women should be advised to avoid becoming pregnant during therapy with topotecan and to inform the treating physician immediately should this occur.

Topotecan is contraindicated during breast-feeding.

13.1.10.4 Frequency of adverse reactions to oral topotecan:

Likely adverse reactions (occurring in more than 20% of patients)

Diarrhea, Nausea, Vomiting, Fatigue, Anemia, Leukopenia, neutropenia, thrombocytopenia, pain, dyspnea, infection, alopecia

Common adverse reactions (occurring in 3 – 20% of Patients)

Anorexia, Stomatitis, asthenia, cough, fever, febrile neutropenia

Rare but Serious adverse reactions (occurring in fewer than 3% of patients)

Interstitial lung disease, sepsis

13.1.11 Clinical Pharmacokinetic Properties:

The pharmacokinetics of topotecan after oral administration have been evaluated in cancer patients following doses of 1.2 to 3.1 mg/m^2 and 4 mg/dose administered daily for 5 days.

13.1.11.1 Absorption and Distribution

Absorption

Topotecan is rapidly absorbed with peak plasma concentrations occurring between 1 to 2 hours following oral administration. Following co-administration of the ABCG2 (BCRP) and ABCB1 (P-gp) inhibitor, elacridar (GF120918) at 100 to 1000 mg with oral topotecan, the AUC (0-inf) of topotecan lactone and total topotecan increased approximately 2.5-fold. Administration of oral cyclosporin A (15 mg/kg), an inhibitor of transporters ABCB1 (P-gp) and ABCC1 (MRP-1) as well as the metabolising enzyme CYP3A4, within 4 hours of oral topotecan increased the dose-normalized AUC (0-24h) of topotecan lactone and total topotecan approximately 2.0- and 2.5-fold, respectively.

Following a high-fat meal, the extent of exposure was similar in the fed and fasted state while t_{max} was delayed from 1.5 to 3 hours (topotecan lactone) and from 3 to 4 hours (total topotecan).

Distribution

The binding of topotecan to plasma proteins was low (35%) and its distribution between blood cells and plasma was homogeneous.

13.1.11.2 Metabolism and Elimination

Metabolism

A major route of inactivation of topotecan is a reversible pH-dependent ring opening to the inactive carboxylate form. Metabolism accounts for less than 10% of the elimination of topotecan. An N-desmethyl metabolite was found in urine, plasma, and feces**.** Following oral administration the mean metabolite: parent AUC ratio was less than 10% for both total topotecan

and topotecan lactone. An O-glucuronide of topotecan and N-desmethyl topotecan has been identified in the urine. *In vitro*, topotecan did not inhibit human cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A nor did it inhibit the human cytosolic enzymes dihydropyrimidine dehydrogenase or xanthine oxidase.

Elimination

Following oral administration, the plasma concentrations decline bi-exponentially. The pharmacokinetics of oral topotecan are approximately dose proportional. There is little or no accumulation of either formulation of topotecan with repeated daily dosing, and there is no evidence of a change in the pharmacokinetics with multiple dosing. The pharmacokinetics of topotecan after oral administration have been evaluated in cancer patients following doses of 1.2 to 3.1 mg/m^2 and 4 mg/dose administered daily for 5 days. Oral topotecan exhibits a mean terminal half-life of approximately 3.0 to 6.0 hours. Overall recovery of drug-related material following five daily doses of topotecan was 49% to 71% of the administered oral dose. Approximately 20% was excreted as total topotecan and 2% was excreted as N-desmethyl topotecan in the urine. Fecal elimination of total topotecan accounted for 33% while fecal elimination of N-desmethyl topotecan was 1.5%. Overall, the N-desmethyl metabolite contributed a mean of less than 6% (range 4–8%) of the total drug related material accounted for in the urine and feces.

13.1.11.3 Special Populations

A cross-study analysis in 217 patients with advanced solid tumors indicated that age and sex did not significantly affect the pharmacokinetics of oral topotecan.

13.1.11.3.1 **Pediatric:** Use in children is not recommended as only limited data are available.

13.1.11.3.2 **Hepatic Impairment:** Pharmacokinetics of oral topotecan has not been specifically studied in patients with impaired hepatic function.

13.1.11.3.3 **Renal Impairment:** Patients with small cell lung carcinoma who participated in oral topotecan clinical trials had a serum creatinine less than or equal to 1.5 mg/dL (133umol/L) or a creatinine clearance (CrCl) of greater than or equal to 60 mL/min. Dosing recommendations for patients receiving oral topotecan with CrCl less than 60 mL/min have not been established.

13.1.12 **Administration**: 0.25 mg (1 capsule) orally daily with or without food.

13.1.13 **Supplier**: Novartis

13.1.14 **Ordering Study Agent/s**:

Study Agent/s may be requested by the Principal Investigator (or their authorized designees) at each participating institution. All regulatory document requirements (including a Pharmacy Initiation Worksheet), as described in the BTTC Operations Manual, must be current and up to date in the BTTC Coordinating Center. The participating institution must have received an Activation memo from the BTTC Coordinating Center prior to requesting study agents. A study drug order form and Pharmacy Initiation Worksheet will be provided to the sites by BTTC Coordinating Center.

Signed and Dated Drug requests should be emailed to:

Uintavision
Attn: Michelle DuBoise
Email: mdubois@uintavision.com

When a number of investigators are participating on a clinical study at the same institution, one investigator should be considered or designated the Principal or lead investigator under whom all investigational agents for that protocol should be ordered.

13.1.15 Agent Storage and Accountability:

The investigator is responsible for the proper and secure physical storage and record keeping of investigational agents received for BTTC protocols. Specifically, the investigator must:

- Maintain a careful record of the receipt, use and final disposition of all investigational agents received, using the NCI Agent Accountability Record Form (DARF), http://ctep.cancer.gov/forms/index.html.
- Store the agent in a secure location, accessible to only authorized personnel, preferably in the pharmacy.
- Maintain appropriate storage of the investigational agent to ensure the stability and integrity of the agent.
- Return or destroy any unused investigational agents at the completion of the study or upon notification that an agent is being withdrawn.

The intent of the agent accountability procedures described in this section is to assist the investigator in making certain that agents received from BTTC are used only for patients entered onto an approved protocol. The record keeping described in this section is required under FDA regulation. Investigators are responsible for the use of investigational agents shipped in their name. Even if a pharmacist or chemotherapy nurse has the actual task of handling these agents upon receipt, the investigator is the responsible individual and has agreed to accept this responsibility by signing the FDA 1572, http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.doc.

13.1.16 BTTC Procedures for Agent Accountability and Storage

- Each investigational agent should be stored separately by protocol. If an agent is used for more than one protocol, there should be separate physical storage for each protocol. Remember that agents are provided and accounted for on a protocol-by-protocol basis.
- Each agent should be accounted for separately by protocol. If an agent is used for more than one protocol, there should be a separate Drug Accountability Record Form (DARF) for each protocol, http://ctep.cancer.gov/forms/index.html. There should be a separate DARF for each agent in a multi-agent protocol.
- Separate accountability forms should be maintained for each different strength or dosage form of a particular agent (e.g., an agent with a 1-mg vial and a 5-

mg vial would require a different DARF for the 1-mg vial than for the 5-mg vial).

- The DARF has been designed for use at each location where agents are stored, e.g., main pharmacy, satellite pharmacy, physician's office, or other dispensing areas.
- The DARF is also designed to accommodate both dispensing records and other agent transaction documentation (e.g., receipt of agent, returns, broken vials, etc.). A copy of the DARF may be found at http://ctep.cancer.gov/forms/index.html.
- Unauthorized inter-institutional transfer of BTTC investigational agents from one **participating** institution to another is not permitted. For some protocols the **lead** institution may enter into contractual agreements to forward agents to participating institutions (see BTTC Operations Manual).
- BTTC Supplied agents must not be repackaged and forwarded to patients on a routine basis. Refer to the BTTC Operations Manual for BTTC polices on forwarding BTTC supplied agents under certain limited circumstances.

Verification of Compliance

Investigators are reminded that compliance with procedures to ensure proper agent usage will be reviewed during site visits conducted under the monitoring program. Specifically, site visitors will check that the agent accountability system is being maintained, and will spot-check the agent accountability records by comparing them with the patients' medical records to verify that the agents were administered to a patient entered in the recorded protocol

13.1.17 Returning or destroying unused and/or defective Agent:

Investigators/Designees should make every effort to minimize the amount of agent ordered and returned or destroyed unused, (e.g. limit inventories to an 8 week supply or less).
Investigators/Designees must return/or destroy unused supplied agent when:

- The agent is no longer required because the study is completed.
- Agent is outdated.
- The agent is damaged or unfit for use.

General Guidelines

- Regulations require that all agents received be returned to the supplier for accountability and disposition or destroyed on-site in accordance with local procedures for agent destruction. On-site agent destruction must be documented in the protocol specific accountability records.
- Return only unused vials/bottles. Do **NOT** return opened or partially used vials/bottles unless specifically requested otherwise in the protocol.
- Return only supplied agents. Do **NOT** ship agents received from other sources to the supplier.

Procedure

Unused, expired or defective study drug should be destroyed by the site's pharmacy in accordance with their drug disposal policy or standard operating procedure. The destruction of the study will be documented in the DARF. Submit copy of the destruction record (DARF) to Novartis only if study is closing.

13.1.18 **Handling of study medication: Store refrigerated 2º to 8ºC (36º to 46ºF).** Store the bottles protected from light in the original outer cartons. Topotecan capsules must not be opened or crushed. If the capsules are punctured or leaking, you should immediately wash your hands thoroughly with soap and water. If you get it in your eyes, wash them immediately with gently flowing water for at least 15 minutes. Consult your doctor/healthcare provider after eye contact or if you experience a skin reaction. Pharmacists should use appropriate precautions in handling and disposal of hazardous agents.

13.2 **DRUG NAME: PAZOPANIB**

13.2.1 **Chemical Name:** 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzolsulfonamide monohydrochloride.

13.2.2 **Molecular formula:** $C_{21}H_{23}N_7O_2S \bullet HCl$

13.2.3 **Molecular Weight:** 473.99 g/mol (monohydrochloride salt)

437.53 g/mol (free base)

13.2.4 **Appearance:** White to slightly colored solid. The 50 mg and 100 mg tablets are round, the 200 mg and 400 mg tablets are oval shaped or capsule-shaped, and the 500 mg tablets are capsule shaped. The 50 mg, 100 mg, and 500 mg tablets are white to slightly colored, while the oval-shaped 200 mg and 400 mg tablets are white. Additionally, the capsule-shaped 200 mg tablets can be gray or pink and may be debossed, and the capsule-shaped 400 mg tablets can be white or yellow and may be debossed

13.2.5 **How Supplied:** GW786034B Tablets are supplied as 50 mg, 100 mg, 200 mg, 400 mg and 500 mg (as free base) tablets for oral administration to support oncology indications. Tablets are packaged in white high density polyethylene (HDPE) bottles with white plastic, induction seal, child-resistant caps.

13.2.6 **Formulation:** Pazopanib is supplied as tablets for oral administration containing pazopanib together with magnesium stearate, microcrystralline cellulose, povidone sodium starch glycolate, magnesium stearate and a film coat containing: hypromellose, macrogol/polyethylene glycol 400, polysorbate 80, titanium dioxide and may contain Iron Oxide Yellow, Red, or Black depending on tablet color, all as inactive ingredients.

13.2.7 **Storage and Stability:** Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

13.2.8 **Mechanism 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. In preclinical experiments, pazopanib dose dependently inhibited ligand-induced auto-phosphorylation of VEGFR-2, c-Kit and PDGFR-β receptors in cells. *In vivo*, pazopanib inhibited VEGF-

induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in various animal models, and the growth of multiple human tumor xenografts in mice.

13.2.9 Pharmacology

DRUG INTERACTIONS

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 C_{max} 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 co-administered 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 C_{max} 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/m^2 (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26 % and 31 % in paclitaxel AUC and C_{max}, 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 Food on Pazopanib

Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, pazopanib should be administered at least 1 hour before or 2 hours after a meal.

13.2.10 Pre-clinical Toxicology

The toxicity profile of pazopanib has been defined in single dose studies in the rat and dog and repeat dose toxicity studies of up to 13 weeks in mice, 26 weeks in rats and 52 weeks in monkeys. The genetic toxicity has been assessed in vitro and in vivo. Embryo fetal development has been assessed in rats and rabbits, and effects on fertility have been assessed in male and female rats. Juvenile toxicity studies are in progress. Dermal and ocular irritation, in vitro phototoxicity and mouse local lymph node assays have also been conducted. Definitive studies were conducted with the monohydrochloride salt which is used in the clinic and with batches having a similar impurity profile. The toxicokinetic profile of pazopanib was evaluated in all definitive repeat dose studies, and comparison of systemic exposure to pazopanib achieved in key toxicology studies is presented in Table 4 in the investigator's Brochure. Exposure margins are presented based upon comparison of the animal systemic exposure with that reported for cancer patients receiving an oral therapeutic dose of 800 mg/day pazopanib (AUC of 1037 μg.h/mL and a C_{max} of 58.1 μg/mL).

The principal nonclinical toxicology findings associated with pazopanib treatment are believed to be directly associated with VEGFR-2 inhibition, or secondary consequences to this inhibition, and in rodents reflect the responsive nature of these species to inhibition of VEGF receptors (Patyna et al. 905-16). These include effects on bone, bone marrow, incisor teeth, ovary, kidney, pancreas, nails, testes, adrenal, pituitary, trachea, hematological tissues, salivary glands and developing embryo/fetus. Some effects occurred at doses of 3 mg/kg/day. Other effects have been noted in liver, small intestine and mesenteric lymph nodes (mice, rats, monkey). Toxicities observed in rodents in teeth, bone, pancreas, nails, bone marrow, kidney and liver were assessed clinically and/or via serum chemistries in the clinic, or in the case of other pre-clinical targets such as adrenal, pituitary, trachea and spleen, were of minimal severity and unlikely to result in adverse clinical events.

13.2.11 Human Toxicity

WARNINGS AND PRECAUTIONS

13.2.11.1 Hepatic Effects:

Cases of hepatic failure (including fatalities) have been reported during the use of pazopanib. In clinical trials with pazopanib, increase in serum transaminases (ALT, AST) and bilirubin were observed. In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin. The vast majority (92.5%) of all transaminase elevations of any grade occurred in the first 18 weeks. Grades are based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3 (NCI CTCAE).

Monitor serum liver tests before initiation of treatment with pazopanib and at least once every 4 weeks for at least the first 4 months of treatment, and as clinically indicated. Periodic monitoring should then continue after this time period.

The following guidelines are provided for patients with baseline values of total bilirubin ≤1.5 X ULN and AST and ALT ≤2 X ULN.

- Patients with isolated ALT elevations between 3 X ULN and 8 X ULN may be continued on pazopanib with weekly monitoring of liver function until ALT return to Grade 1 (NCI CTCAE) or baseline.
- Patients with ALT of >8 X ULN should have pazopanib interrupted until they return to Grade 1 (NCI CTCAE) or baseline. 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 once daily and measure serum liver tests weekly for 8 weeks. Following reintroduction of pazopanib, if ALT elevations >3 X ULN recur, then pazopanib should be permanently discontinued.
- If ALT elevations >3 X ULN occur concurrently with bilirubin elevations >2 X ULN pazopanib should be permanently discontinued. Patients should be monitored until return to Grade 1 (NCI CTCAE) or baseline. Pazopanib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinaemia, known or suspected Gilbert's syndrome, and elevation in ALT >3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations.

Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring. Beyond recommending that patients with mild hepatic impairment are treated with 800 mg pazopanib once daily and reducing the initial starting dose to 200 mg per day for patients with moderate impairment, no further dose modification guidelines based on results of serum liver tests during therapy have been established for patients with preexisting hepatic impairment.

13.2.11.2 Hypertension:

In clinical studies with pazopanib, events of hypertension including hypertensive crisis have occurred. Blood pressure should be well controlled prior to initiating pazopanib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. Hypertension (systolic blood pressure ≥ 150 or diastolic blood pressure ≥ 100 mm Hg) occurs early in the course of treatment (39% of cases occurred by Day 9 and 88% of cases occurred in the first 18 weeks). In the case of persistent hypertension despite anti-hypertensive therapy, the

pazopanib dose may be reduced. Pazopanib should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persists despite anti-hypertensive therapy and pazopanib dose reduction (see specific guidelines for BP monitoring and management in Section 3.3.6.2)

13.2.11.3 QT Prolongation and Torsade de Pointes:

In clinical studies with pazopanib, events of QT prolongation or Torsade de Pointes have occurred. Pazopanib should be used with caution in patients with a history of QT interval prolongation, patients taking antiarrythmics or other medications that may potentially prolong QT interval, or those with relevant pre-existing cardiac disease. When using pazopanib, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (calcium, magnesium, potassium) within normal range is recommended.

13.2.11.4 Arterial Thrombotic Events:

In clinical studies with pazopanib, myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed. Fatal events have been observed. Pazopanib should be used with caution in patients who are at increased risk of thrombotic events or who have had a history of thrombotic events. Pazopanib has not been studied in patients who have had an event within the previous 6 months. A treatment decision should be made based upon the assessment of individual patient's benefit/risk.

13.2.11.5 Hemorrhagic Events:

In clinical studies with pazopanib hemorrhagic events have been reported. Fatal hemorrhagic events have occurred. Pazopanib has not been studied in patients who had a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months. Pazopanib should be used with caution in patients with significant risk of hemorrhage.

13.2.11.6 Gastrointestinal Perforations and Fistula:

In clinical studies with pazopanib, events of gastrointestinal (GI) perforation or fistula have occurred. Fatal perforation events have occurred. Pazopanib should be used with caution in patients at risk for GI perforation or fistula.

13.2.11.7 Wound Healing:

No formal studies on the effect of pazopanib on wound healing have been conducted. Since Vascular Endothelial Growth Factor (VEGF) inhibitors may impair wound healing, treatment with pazopanib should be stopped at least 7 days prior to scheduled surgery. The decision to resume pazopanib after surgery should be based on clinical judgment of adequate wound healing. Pazopanib should be discontinued in patients with wound dehiscence.

13.2.11.8 Hypothyroidism:

In clinical studies with pazopanib, events of hypothyroidism have occurred. Proactive monitoring of thyroid function tests is recommended.

13.2.11.9 Proteinuria:

In clinical studies with pazopanib, proteinuria has been reported. Baseline and periodic urinalyses during treatment are recommended and patients should be monitored for worsening of proteinuria. Pazopanib should be discontinued if the patient develops nephrotic syndrome.

13.2.11.10 Pregnancy:

Pre-clinical studies in animals have shown reproductive toxicity. If pazopanib is used during pregnancy, or if the patient becomes pregnant while receiving pazopanib, 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.

13.2.12 Interactions

13.2.12.1.1 Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes

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.

13.2.12.1.1.1 *CYP3A4 Inhibitors:* Concurrent administration of a single dose pazopanib eye drops with the strong CYP3A4 inhibitor, ketoconazole, in healthy volunteers resulted in 220 % and 150 % increase in mean AUC(0-t) and C_{max} values, respectively. 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 C_{max} 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.

13.2.12.1.1.2 *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.

13.2.12.2 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 C_{max} 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/m^2

(CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26 % and 31 % in paclitaxel AUC and C_{max}, respectively.

13.2.12.3 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.

13.2.12.4 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.

13.2.12.5 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 C_{max}. Therefore, pazopanib should be administered at least 1 hour before or 2 hours after a meal.

13.2.12.5.1 Medication that raise gastric pH

Concomitant use of pazopanib with esomeprazole decreases the bioavailability of pazopanib by approximately 40% (AUC and C_{max}), and co-administration of pazopanib with medicines that increase gastric pH should be avoided.

13.2.13 Pregnancy and Lactation

13.2.13.1 Fertility

Pazopanib may impair fertility in human males and females. In female reproductive toxicity studies in rats, reduced female fertility has been observed.

13.2.13.2 Pregnancy

There are no adequate data from the use of pazopanib in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Pazopanib should not be used during pregnancy unless the clinical condition of the woman requires treatment with pazopanib. If pazopanib is used during pregnancy, or if the patient becomes pregnant while receiving pazopanib, the potential hazard to the fetus should be explained to the patient. Women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with pazopanib.

13.2.13.3 Lactation

The safe use of pazopanib during lactation has not been established. It is not known whether pazopanib is excreted in human milk. Breast feeding should be discontinued during treatment with pazopanib.

13.2.14 Ability to perform tasks that require judgment, motor or cognitive skills

There have been no studies to investigate the effect of pazopanib on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of pazopanib. The clinical status of the patient and the adverse event profile of pazopanib should be borne in mind when considering the patient's ability to perform task that require judgment, motor and cognitive skills.

13.2.15Adverse Reactions

The safety and efficacy of pazopanib in renal cell carcinoma (RCC) were evaluated in a randomized, double-blind, placebo-controlled multi-centre study. Patients with locally advanced and/or metastatic RCC were randomized to receive pazopanib 800 mg once daily (N=290) or placebo (N=145). The median duration of treatment was 7.4 months for the pazopanib arm and 3.8 months for the placebo arm.

Adverse reactions are listed below by MedDRA body system organ class.

The following convention has been utilized for the classification of frequency:

Very common ≥ 1 in 10

Common ≥ 1 in 100 and < 1 in 10

Uncommon ≥ 1 in 1,000 and < 1 in 100

Categories have been assigned based on absolute frequencies in the clinical trial data. *Note: Updated to about 6000 patients as of February 9, 2012.*

13.2.15.1 Blood and lymphatic system disorders

Common	Thrombocytopenia Neutropenia

13.2.15.2 Endocrine disorders

Very common	Changes in blood sugar
Common	Hypothyroidism*****

13.2.15.3 Metabolism and nutrition disorders

Very common	Anorexia, weight loss

13.2.15.4 Nervous system disorders

Very common	Headache, dysgeusia
Common	Transient ischaemic attack*****
Uncommon	Ischaemic stroke*****

13.2.15.5 Cardiac disorders

Very common	slow heart beat (<60 beats per minute)
Common	Myocardial ischaemia***** QT prolongation***** Cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure), Myocardial infarction*****
Uncommon	Torsade de Pointes*****

13.2.15.6 Vascular disorders

Very common	Hypertension*****

13.2.15.7 Hemorrhages*****

Common	Epistaxis, Haematuria, blood clots, Pulmonary haemorrhage
Uncommon	Gastrointestinal haemorrhage, Cerebral haemorrhage

13.2.15.8 Gastrointestinal disorders

Very common	Diarrhea, Nausea, Vomiting, Abdominal pain
Common	Dyspepsia, Lipase elevations, abdominal gas
Uncommon	Gastrointestinal perforation***,** Gastrointestinal fistula*****

13.2.15.9 Hepatobiliary disorders*

Very common	Alanine aminotransferase increased, Aspartate aminotransferase increased
Common	Hepatic function abnormal, Hyperbilirubinaemia

13.2.15.10 Skin and subcutaneous tissue disorders

Very common	Hair depigmentation, hair loss, exfoliative rash, Palmar-plantar erythrodysaesthesia syndrome, lightening of skin color
Common	Rash, dry skin, nail disorder

13.2.15.11 Renal and urinary disorders

Common	Proteinuria*****

13.2.15.12 General disorders and administration site conditions

Very common	Fatigue, Asthenia, dyspnea, cough, peripheral edema, dizziness, mouth sores, muscle pain or cramps, chest pain*
Common	Chills

*******See Warnings and Precautions in Investigator's Brochure for additional information.*

13.2.15.13 Overdosage

Pazopanib doses up to 2,000 mg have been evaluated in clinical trials. Grade 3 fatigue (dose limiting toxicity) and Grade 3 hypertension were each observed in 1 of 3 patients dosed at 2,000 mg and 1,000 mg daily, respectively.

13.2.15.14 Symptoms and Signs

There is currently limited experience with overdosage in pazopanib.

13.2.15.15 Treatment

Further management should be as clinically indicated or as recommended by the national poisons centre, where available. Haemodialysis is not expected to enhance the elimination of pazopanib because pazopanib is not significantly renally excreted and is highly bound to plasma proteins.

13.2.16Frequency of adverse reactions to pazopanib:

13.2.16.1 Likely (occurring in more than 20% of patients)

Diarrhea, hypertension, hair color changes, hair loss, painful blisters and/or rash on palms and soles, nausea, anorexia, vomiting, fatigue, weight loss, tumor pain, dysgeusia, headache, gastrointestinal pain, musculoskeletal pain, myalgia, decreased albumin, hypomagnesemia, hypophosphatemia, increased glucose level, leucopenia, neutropenia, thrombocytopenia, ALT increased, AST increased, bilirubin increased, tumor pain

13.2.16.2 Common (occurring in 3 – 20% of Patients)

Asthenia, abdominal pain, exfoliative rash, cough, constipation, peripheral edema, abnormal ear nose and throat examination, skin disorder or hypopigmentation, dizziness, stomatitis, chest pain, pyrexia, dyspnea, hypertensive crisis, hypothyroidism, lymphopenia, slow heart beat, chills, dry skin, nail disorder

13.2.16.3 Rare but Serious (occurring in fewer than 3% of patients)

Hepatotoxicity, congestive heart failure, myocardial infarction, prolonged QT interval, Torsades de pointes, bleeding from anus, bleeding from mouth, gastroinstinal fistula, pancreatitis, rectal hemorrhage, venous thromboembolism, stroke, reversible posterior leukoencephalopathy syndrome, transient ischemic attack, pneumothorax, pulmonary embolism, pulmonary hemorrhage

13.2.17Clinical Pharmacokinetic Properties

13.2.17.1 Absorption

Pazopanib is absorbed orally with median time to achieve peak concentrations of 2.0 to 4.0 hours after the dose. Daily dosing results in 1.23- to 4-fold increase in AUC. There was no consistent increase in AUC and C_{max} when the pazopanib dose increased above 800 mg.

Systemic exposure to pazopanib is increased when administered with food. Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, pazopanib should be administered at least 1 hour before or 2 hours after a meal.

Administration of a single pazopanib 400 mg crushed tablet increased AUC(0-72) by 46% and C_{max} by approximately 2 fold and decreased t_{max} by approximately 1.5 hours compared to administration of the whole tablet. These results indicate that the bioavailability and the rate of pazopanib oral absorption are increased after administration of the crushed tablet relative to administration of the whole tablet. Therefore, due to this potential for increased exposure, tablets should not be crushed.

13.2.17.2 Distribution

Binding of pazopanib to human plasma protein in vivo was greater than 99 % with no concentration dependence over the range of 10-100 μg/ml. *In vitro* studies suggest that pazopanib is a substrate for P-glycoprotein (Pgp) and breast cancer resistant protein (BCRP).

13.2.17.3 Metabolism

Results from *in vitro* studies demonstrated that the metabolism of pazopanib is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8.

13.2.17.4 Elimination

Pazopanib is eliminated slowly with mean half-life of 30.9 hours after administration of the recommended dose of 800 mg. Elimination is primarily via feces with renal elimination accounting for < 4 % of the administered dose.

13.2.18Special Populations

13.2.18.1 Renal Impairment

In a population pharmacokinetic analysis using 408 subjects with various cancers, creatinine clearance (30-150 ml/min) did not influence clearance of pazopanib. Renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatinine clearance ≥ 30 ml/min.

13.2.18.2 Hepatic Impairment

The median steady-state pazopanib C_{max} and AUC(0-24) in patients with mild hepatic impairment (defined as either normal bilirubin and any degree of ALT elevations or as an elevation of bilirubin up to 1.5 x ULN regardless of the ALT value) after a once daily dose of 800 mg/day (30.9 µg/ml, range 12.5-47.3 and 841.8 µg.hr/ml, range 600.4-1078) are similar to the median in patients with no hepatic impairment (49.4 µg/ml, range 17.1-85.7 and 888.2 µg.hr/ml, range 345.5-1482).

The maximally tolerated pazopanib dose (MTD) in patients with moderate hepatic impairment (defined as an elevation of bilirubin > 1.5 x to 3 x ULN regardless of the ALT values) was 200 mg once daily. The median steady-state values of C_{max} (22.4 µg/ml, range 6.4-32.9) and AUC(0-24) (350.0 µg.hr/ml, range 131.8-487.7) after administration of 200 mg pazopanib once daily in subjects with moderate hepatic impairment were approximately 45% and 39%, respectively, that of the corresponding median values after administration of 800 mg once daily in subjects with normal hepatic function. There are insufficient data in patients with severe hepatic impairment (total bilirubin >3x ULN regardless of any level of ALT); therefore, use of pazopanib is not recommended in these patients.

13.2.19 Administration

Pazopanib (GW786034) is an orally administered multi-targeted tyrosine kinase inhibitor (TKI) currently under development by Novartis for the treatment of a variety of human cancers in adults. Currently, pazopanib is administered orally at 800 mg daily in Phase II and Phase III monotherapy studies.

13.2.19.1 Combination therapy

Doses ranged from 200 to 800 mg daily in a Phase I combination dose-ranging study (VEG10006) in which pazopanib was administered in combination with the Novartis compound lapatinib (GW572016). Pazopanib 200 to 800 mg daily is being investigated in combination with multiple cytotoxic chemotherapy regimens.

13.2.19.2 Dosing information from recent studies combining Pazopanib and oral topotecan

Recent investigations of the combination, relevant to this study found safe and effective dosing of pazopanib using a starting dose of 600 mg (3x200mg) Pazopanib per day taken orally without food at least one hour before or two hours after a meal. The dose of Pazopanib may be held up to

3 weeks and reduced to 400 mg or to 200 mg daily based on side effects. Patient may be maintained on the lower dose of pazopanib during protocol if deemed to be deriving benefit from the drug. Length of treatment will be until progression, up to one year.

13.2.20 **Supplier:** Novartis

13.2.20.1 Ordering Study Agent/s:

Study Agent/s may be requested by the Principal investigator (or their authorized designees) at each participating institution. All regulatory document requirements (including a Pharmacy Initiation Worksheet), as described in the BTTC Operations Manual, must be current and up to date in the BTTC Coordinating Center. The participating institution must have received an Activation memo from the BTTC Coordinating Center prior to requesting study agents. A study drug order form will be provided to the sites by BTTC Coordinating Center.

Signed and Dated Drug requests should be emailed to:

Uintavision
Attn: Michelle Dubois
Email: mdubois@uintavision.com

When a number of investigators are participating on a clinical study at the same institution, one investigator should be considered or designated the Principal or lead investigator under whom all investigational agents for that protocol should be ordered.

13.2.20.2 Agent Storage and Accountability

The investigator is responsible for the proper and secure physical storage and record keeping of investigational agents received for BTTC protocols. Specifically, the investigator must:

- Maintain a careful record of the receipt, use and final disposition of all investigational agents received, using the NCI Agent Accountability Record Form (DARF), http://ctep.cancer.gov/forms/index.html.
- Store the agent in a secure location, accessible to only authorized personnel, preferably in the pharmacy.
- Maintain appropriate storage of the investigational agent to ensure the stability and integrity of the agent.
- Return or destroy any unused investigational agents at the completion of the study or upon notification that an agent is being withdrawn.

The intent of the agent accountability procedures described in this section is to assist the investigator in making certain that agents received from BTTC are used only for patients entered onto an approved protocol. The record keeping described in this section is required under FDA regulation. Investigators are responsible for the use of investigational agents shipped in their name. Even if a pharmacist or chemotherapy nurse has the actual task of handling these agents upon receipt, the investigator is the responsible individual and has agreed to accept this responsibility by signing the FDA 1572, http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.doc.

13.2.21BTTC Procedures for Agent Accountability and Storage

- Each investigational agent should be stored separately by protocol. If an agent is used for more than one protocol, there should be separate physical storage for each protocol. Remember that agents are provided and accounted for on a protocol-by-protocol basis.
- Each agent should be accounted for separately by protocol. If an agent is used for more than one protocol, there should be a separate Drug Accountability Record Form (DARF) for each protocol, http://ctep.cancer.gov/forms/index.html. There should be a separate DARF for each agent in a multi-agent protocol.
- Separate accountability forms should be maintained for each different strength or dosage form of a particular agent (e.g., an agent with a 1-mg vial and a 5-mg vial would require a different DARF for the 1-mg vial than for the 5-mg vial).
- The DARF has been designed for use at each location where agents are stored, e.g., main pharmacy, satellite pharmacy, physician's office, or other dispensing areas.
- The DARF is also designed to accommodate both dispensing records and other agent transaction documentation (e.g., receipt of agent, returns, broken vials, etc.). A copy of the DARF may be found at http://ctep.cancer.gov/forms/index.html.
- Unauthorized inter-institutional transfer of BTTC investigational agents from one **participating** institution to another is not permitted. For some protocols the **lead** institution may enter into contractual agreements to forward agents to participating institutions (see BTTC Operations Manual).
- BTTC Supplied agents must not be repackaged and forwarded to patients on a routine basis. Refer to the BTTC Operations Manual for BTTC polices on forwarding BTTC supplied agents under certain limited circumstances.

Verification of Compliance

Investigators are reminded that compliance with procedures to ensure proper agent usage will be reviewed during site visits conducted under the monitoring program. Specifically, site visitors will check that the agent accountability system is being maintained, and will spot-check the agent accountability records by comparing them with the patients' medical records to verify that the agents were administered to a patient entered in the recorded protocol.

13.2.22 Returning or Destroying unused or defective Agent

Investigators/Designees should make every effort to minimize the amount of agent ordered and returned or destroyed unused, (e.g. limit inventories to an 8 week supply or less).
Investigators/Designees must return/or destroy unused supplied agent when:

- The agent is no longer required because the study is completed.
- Agent is outdated.

- The agent is damaged or unfit for use.

General Guidelines

- Regulations require that all agents received be returned to the supplier for accountability and disposition or destroyed on-site in accordance with local procedures for agent destruction. On-site agent destruction must be documented in the protocol specific accountability records.
- Return only unused vials/bottles. Do **NOT** return opened or partially used vials/bottles unless specifically requested otherwise in the protocol.
- Return only supplied agents. Do **NOT** ship agents received from other sources to the supplier.

Procedure

Unused or defective drug will be destroyed. Novartis should be notified of this action.

13.2.23 **Handling of Study medication:** Pharmacists should use appropriate precautions in handling and disposal of hazardous agents. Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)

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15 APPENDICES

15.1 KARNOFSKY PERFORMANCE STATUS AND NEUROLOGIC FUNCTION

Karnofsky Performance Status

Patient's performance status and Neurologic Functions will be graded according to the following scales:

KPS 100 Normal; no complaints; no evidence of disease

KPS 90 Able to carry on normal activity; minor signs or symptoms of disease

KPS 80 Normal activity with effort; some sign or symptoms of disease

KPS 70 Cares for self; unable to carry on normal activity or do active work

KPS 60 Requires occasional assistance, but is able to care for most personal needs

KPS 50 Requires considerable assistance and frequent medical care

KPS 40 Disabled; requires special care and assistance

KPS 30 Severely disabled; hospitalization is indicated, although death no imminent

KPS 20 Very sick; hospitalization necessary; active support treatment is necessary

KPS 10 Moribund; fatal processes progressing rapidly

KPS 0 Dead

Neurologic Function

☐	+1	Better
☐	0	Unchanged
☐	-1	Worse
☐	B	Baseline

15.2 EIAEDs AND NON-EIAEDs

EIAEDs:

Carbamazipine (Tegretol, Tegretol XR, Carbatrol)

Oxcarbazepine(Trileptal)

Phenytoin (Dilantin, Phenytek)

Fosphenytoin (Cerebyx)

Phenobarbital

Primidone (Mysoline)

Non-EIAEDs:

Valproic acid (Depakote, Depakene)

Gabapentin (Neurontin)

Lamotrigine (Lamictil)

Topriamate (Topamax)

Tiagabine (Gabatril)

Zonisamide (Zonegran)

Levatriacetam (Keppra)

Clonazepam (Klonopin)

Clonozam (Frisium)

15.3 TUMOR TISSUE HANDLING INSTRUCTIONS AND TISSUE COLLECTION SHIPPING FORM

General Information: Tissue evaluation is highly recommended for this study. The evaluation will consist of confirmation that the histologic features meet WHO criteria for GBM or GS. All blocks for review will be sent directly to Dr. Aldape.

Rationale

The purpose of analyzing the tissue samples is to confirm the diagnosis of GBM

Specimen Collection: Tissue specimens should be taken from pre-study diagnostic open biopsy or surgical resection.

To be eligible for this study, the patient must have a GBM, or GS, WHO grade IV. Features of a high-grade astrocytic neoplasm with tumor necrosis and/or microvascular proliferation must be present.

The following materials will be required for tissue evaluation:

Representative tissue blocks or 15 unstained paraffin slides that contain diagnostic tumor. **A block that, when sectioned, yields at least 1 square centimeter of viable tumor must be present on the H&E slide.** Blocks obtained via the CUSA methodology are not adequate for tissue analysis. Do not send blocks with tissue obtained by this method.

An accompanying H&E is encouraged for rapid diagnosis but not required. If an H&E is included, Dr. Aldape will use this for the review. If not included, Dr. Aldape will cut a section from the paraffin block, stain this with H&E, and use that slide for the review.

A Pathology Report documenting that the submitted material contains tumor; the report must include the protocol number, patient case number, and the patient's initials. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

A Tissue Collection Shipping Form (below) listing pathology materials being submitted for Tissue Evaluation completed by the local pathologist must be included in the pathology submission. These forms must include the protocol number, patient case number, and the patient's initials.

Tissue evaluation is highly recommended for every case. Send pathology material by overnight mail directly to:

Ken Aldape, M.D.
Toronto General Hospital
200 Elizabeth Street, 11th Floor
Toronto, Ontario M5G 2C4 Canada
kaldape@gmail.com

- Include on the form the name, telephone number, and fax number of the person to notify with the results of the tissue evaluation.
- Shipments must be made Monday through Thursday.
- Notify Dr. Aldape by email on or before the day of submission: (1) that a case is being submitted for review; (2) the name of the contact person; (3) when to expect the sample; and (4) the overnight shipping carrier and tracking number.

- Dr. Aldape will email the appropriate contact person from the submitting institution with the results and will fax a copy of the completed form to the institution.

When Dr. Aldape has completed testing of the tumor tissue, the remaining tissue will be sent back to the submitting institution.

Submission of frozen tissue is strongly encouraged in order to maximize the information gained from this trial. When available, frozen tissue should be sent in dry ice to Dr. Aldape at the above address.

Upon receipt, the specimen is labeled with the protocol number and the patient's case number only.

The specimens will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use the specimens, the material will be returned to the institution that submitted it.

Tissue Collection Shipping Form **PLEASE USE ONE FORM PER PATIENT**

BTTC12-01: PHASE II Trial of Oral Pazopanib plus Oral Topotecan Metronomic Antiangiogenic Therapy for Recurrent Glioblastoma Multiforme (A) without Prior Bevacizumab Exposure and (B) after Failing prior Bevacizumab

DATE SHIPPED:

SITE NAME:

INVESTIGATOR'S NAME:

PATIENT'S INITIALS:

PATIENT'S ID NUMBER:

Tissue sample:

Collection Date:

Number of paraffin blocks:

Number of unstained slides (15 slides preferred if block is not available):

Please remember all samples for a patient must be shipped within 28 days of collection and to label samples as instructed in the protocol. See section 5.1 of the protocol for shipment and labeling instructions.

Name of person completing this form:

Telephone number:

Signature:

Date:

SHIP TO: Ken Aldape, M.D.
Toronto General Hospital
200 Elizabeth Street, 11th Floor
Toronto, Ontario M5G 2C4 Canada
kaldape@gmail.com

Note: Prior to shipping the samples, please contact Dr. Aldape by email on or before the day of to ensure appropriate tracking and receipt of the sample. Shipment must be made Mondays through Thursdays by overnight shipment to ensure timely arrival of samples during working days. **s

15.4 DRUGS KNOWN TO BE METABOLIZED BY CYP450 ISOENZYMES 2D6 AND 3A4

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 Exemestene Dofetilide (minor) Felodipine Fentanyl Fexotenadine Finaxteride Fluoxetine Flutamide Glyburide Granisetron Halofantrine Hydrocortixone Hydroxyarginine lfosfamide lmipramine lndinavir lsradipine ltraconazole Ketoconazole Lansoprazole (minor) Letrozole Levobupivicaine Lidocaine Loratadine Losartan Lovastatin Methadone Mibefradil Miconazole Midazolam Mifepristone Mirtazapine (N-demethylation) Montelukast Navelbine Toremifene Trazodone Tretinoin Triazolam Troglitazone Troleandomycin Venlafaxine (N-demethylation) Verapamil Vinblastine	Pimozide Pioglitazone Pravastatin Prednisone Progesterone Proguanil Propafenone Quercetin Quetiapine Quinidine Quinine Repaglinide Retinoic acid Rifampin Risperidone Ritonavir Salmeterol Saquinavir Sertindole Sertraline Sibutramine Sildenafil citrate Simvastatin Sirolimus Sufentanil Tacrolimus Tamoxifen Temazepam Teniposide Terfenadine Testosterone Tetrahydrocannabinol Theophylline Tiagabine Tolterodine Vincristine Warfarin (R-warfarin) Yohimbine Zaleplon (minor pathway) Zatoestron Zileuton Ziprasidone Zolpidem 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	Metronidazole
Anastrozole	Mibefradil
Atazanavir	Miconazole (moderate)
Azithromycin	Nefazodone
Cannabinoids	Nelfinavir
Cimetidine	Nevirapine
Clarithromycin	Norfloxacin
Clotrimazole	Norfluoxetine
Cyclosporine	Omeprazole (weak)
Danazol	Oxiconazole
Delavirdine	Paroxetine (weak)
Dexamethasone	Propoxyphene
Diethyldithiocarbamate	Quinidine
Diltiazem	Quinine
Dirithromycin	Quinupristin and dalfopristin
Disulfiram	Ranitidine
Entacapone (high dose)	Ritonavir
Erythromycin	Saquinavir
Ethinyl estradiol	Sertindole
Fluconazole (weak)	Sertraline
Fluoxetine	Telithromycin
Fluvoxamine	Troglitazone
Gestodene	Troleandomycin
Grapefruit juice	Valproic acid (weak)
lndinavir	Verapamil
lsoniazid	Voriconazole
ltraconazole	Zafirlukast
Ketoconazole	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)

15.5 MD ANDERSON SYMPTOM INVENTORY FOR BRAIN TUMORS (MDASI – BT)

38755

Date: ☐☐ / ☐☐ / ☐☐☐☐ (month) (day) (Year)

MDASI-BT

Participant's Initials: ☐☐☐

PLEASE USE A BLACK INK PEN

Patient #: ☐☐☐☐☐☐

Protocol Acc #: ☐☐☐☐

M.D. Anderson Symptom Inventory (MDASI - BT)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You can Imagine 10
1. Your pain at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your fatigue (tiredness) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your nausea at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your disturbed sleep at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being distressed (upset) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your shortness of breath at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with remembering things at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with lack of apetite at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling drowsy (sleepy) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a dry mouth at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling sad at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your vomiting at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your numbness or tingling at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your weakness on one side of the body at its WORST	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty understanding at its WORST	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty speaking (finding the words) at its WORST	○	○	○	○	○	○	○	○	○	○	○

38755

Date: ☐☐ / ☐☐ / ☐☐☐☐ (month) (Day) (Year)

MDASI-BT

Participant's Initials: ☐☐☐

Patient #: ☐☐☐☐☐☐

Protocol Acc # : ☐☐☐☐

PLEASE USE A BLACK INK PEN

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You can Imagine 10
17. Your seizures at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty concentrating at its WORST	○	○	○	○	○	○	○	○	○	○	○
19. Your vision at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in appearance at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in bowel pattern (diarrhea or constpation) at its WORST	○	○	○	○	○	○	○	○	○	○	○
22. Your irritability at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interefere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did not interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. General activity ?	○	○	○	○	○	○	○	○	○	○	○
24. Mood ?	○	○	○	○	○	○	○	○	○	○	○
25. Work (including work around the house) ?	○	○	○	○	○	○	○	○	○	○	○
26. Relations with other people?	○	○	○	○	○	○	○	○	○	○	○
27. Walking?	○	○	○	○	○	○	○	○	○	○	○
28. Enjoyment of life ?	○	○	○	○	○	○	○	○	○	○	○

38755

Date: ☐☐ / ☐☐ / ☐☐☐☐ **MDASI-BT**

Participant's Initials: ☐☐☐

PLEASE USE A BLACK INK PEN

Patient #: ☐☐☐☐☐☐

Protocol Acc #: ☐☐☐☐

M.D. Anderson Symptom Inventory (MDASI - BT)

Participant Signature		**Date**	
Clinician Signature		**Date**	

Collection of this information is authorized under 42 USC 285. The primary use of the information you provide is to assess the severity of your symptoms. The information may be disclosed to clinicians and researchers for research purposes, to HHS personnel offices for determination of fitness for duty, and to monitor personnel to assure that safety standards are maintained. Submission of this information is voluntary.

15.6 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

15.7 THE 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

15.8 HEPATITIS RISK FACTORS

Note: The site cannot use the form attached in the protocol (Appendix 13.8). The site will need to copy the form with their own site letterhead. The form need to be signed and dated by the research staff after discussion with the patient.

Hepatitis A Risk factors

1. Travel or work in regions with high rates of hepatitis A
2. Are a man who has sexual contact with other men
3. Are HIV positive
4. Use injected or noninjected illicit drugs
5. Live with another person who has hepatitis A
6. Receive clotting-factor concentrates for hemophilia or another medical condition

Hepatitis B risk factors

1. A history of having unprotected sex with more than one partner
2. If you have had unprotected sex with someone who's infected with HBV
3. If you have a sexually transmitted infection such as gonorrhea or chlamydia
4. If you are a man who has sexual contact with other men
5. If you share needles during intravenous (IV) drug use
6. If you share a household with someone who has a chronic HBV infection
7. If you have a job that exposes you to human blood

Hepatitis C Risk factors

1. Health care worker who has been exposed to infected blood
2. Have ever injected illicit drugs
3. Are HIV positive
4. Received a piercing or tattoo in an unclean environment using unsterile equipment
5. Received a blood transfusion or organ transplant before 1992
6. Received clotting factor concentrates before 1987
7. Received hemodialysis treatments for a long period of time
8. Were born to a woman with a hepatitis C infection

15.9 CCR PROBLEM REPORT FORM

CCR PROBLEM REPORT FORM

<table>
<tr><td>NCI Protocol #:</td><td colspan="2">Protocol Title:</td></tr>
<tr><td></td><td colspan="2">Report version: (select one)
____Initial Report
____Revised Report
____Follow-up</td></tr>
<tr><td>Site Principal Investigator:</td><td colspan="2"></td></tr>
<tr><td>Date of problem:</td><td colspan="2">Location of problem: (e.g., patient’s home, doctor’s office)</td></tr>
<tr><td colspan="3">Who identified the problem? (provide role (not name of person): nurse, investigator, monitor, etc…)</td></tr>
<tr><td>Brief Description of Subject (if applicable)
(Do NOT include personal identifiers)</td><td colspan="2">Sex: ___ Male ___ Female Age:
___ Not applicable (more than subject is involved)</td></tr>
<tr><td colspan="3">Diagnosis under study:</td></tr>
<tr><td colspan="3">Name the problem: (select all that apply)
[ ] Adverse drug reaction
[ ] Abnormal lab value
[ ] Death
[ ] Cardiac Arrest/ code
[ ] Anaphylaxis
[ ] Sepsis/Infection
[ ] Blood product reaction
[ ] Unanticipated surgery/procedure
[ ] Change in status (e.g. increased level of care required)
[ ] Allergy (non-medication)
[ ] Fall
[ ] Injury/Accident (not fall)
[ ] Specimen collection issue
[ ] Informed consent issue
[ ] Ineligible for enrollment
[ ] Breach of PII
[ ] Tests/procedures not performed on schedule
[ ] Other, brief 1-2 word description: _____

Detailed Description of the problem: (Include any relevant treatment, outcomes or pertinent history):</td></tr>
</table>

***Is this problem unexpected?** *(see the definition of unexpected in the protocol))* __YES __NO **Please explain:**
***Is this problem related or possibly related to participation in the research?** __YES __NO **Please explain:**
***Does the problem <u>suggest</u> the research places subjects or others at a greater risk of harm than was previously known or recognized?** __YES __NO **Please explain:**
Is this problem? (*select all that apply*) [ ] An Unanticipated Problem* that is: [ ] Serious [ ] Not Serious [ ] A Protocol Deviation that is: [ ] Serious [ ] Not Serious [ ] Non-compliance **Note if the 3 criteria starred above are answered, "YES", then this event is also a UP.*
Is the problem also *(select one)* [ ] AE [ ] Non-AE
Have similar problems occurred on this protocol at your site? __YES __NO **If "Yes", how many? ____ Please describe:**
Describe what steps you have already taken as a result of this problem:
In addition to the NCI IRB, this problem is also being reported to: (*select all that apply*) [ ] Local IRB [ ] Study Sponsor [ ] Manufacturer : _____ [ ] Institutional Biosafety Committee [ ] Data Safety Monitoring Board [ ] Other: _____ [ ] None of the above, not applicable

INVESTIGATOR'S SIGNATURE:	**DATE:**

15.10 PILL DIARY

[redacted] PILL DIARY [redacted]

Patient Name/Initials:_____ **Patient ID#:**_____ **Phase/Cycle #:**____ _

This calendar is for you to indicate that you took the drug(s) according to the instructions. Please put a check mark or your initials after each dose. Please sign this calendar at the end of the cycle and bring the calendar and all study drug bottle(s) back to your next clinic visit.

PAZOPANIB **Dose:** _____**mg (_ Tablets)** **Route:** *Oral* **Frequency:** ***DAILY***				**TOPOTECAN** **Dose:** _____**mg (__ Tablets)** **Route:** ***Oral*** **Frequency:** ***Daily***			
Day #	Date	Time	Patient's Initials	Day #	Date	Time	Patient's Initials
1							
2							
2							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
25							
26							
27							
28							

[redacted]

Patient Name/Initials:_____**Patient ID#:**_____ **Phase/Cycle #:** ____ __

This calendar is for you to indicate that you took the drug(s) according to the instructions. Please put a check mark or your initials after each dose. Please sign this calendar at the end of the cycle and bring the calendar and all study drug bottle(s) back to your next clinic visit.

My signature signifies that the study drug(s) have been taken as indicated:

Patient's Signature: _____ **Date:** _____

PATIENT'S NOTES:

15.11 PILL COUNT DOCUMENTATION FOR PAZOPANIB

TO BE COMPLETED BY CLINICAL RESEARCH STAFF

PATIENT INITIALS: _____ BTTC ID #: __ CYCLE#: ___

DOSE OF PAZOPANIB PRESCRIBED:__mg PO Daily for 28 days EVERY cycle

(Pazopanib is supplied in Tablet strength(s) mg

DATE DISPENSED: _____

(mm/dd/yyyy)

QUANTITY OF BOTTLES DISPENSED: _

QUANTITY OF____MG TABLETS DISPENSED: _____

NUMBER OF MG TABLETS PER DAY REQUIRED TO ACHIEVE PRESCRIBED DOSE: __

************DO NOT RETURN UNUSED TABLETS TO THE PATIENT**************

RETURN PILL COUNT DATE: ___

(mm/dd/yyyy)

Has the patient taken the dose scheduled for this date? YES NO

QUANTITY OF BOTTLES RETURNED: _

QUANTITY OF TABLETS RETURNED: _

QUANTITY OF TABLETS DESTROYED: _____

_____

SIGNATURE OF PHARMACY OR RESEARCH STAFF: **DATE**: _____

SITE: _____ **PHONE #** _____

15.12 PILL COUNT DOCUMENTATION FOR TOPOTECAN

PATIENT INITIALS: _____ BTTC ID #: _____ CYCLE#: _____

DOSE OF TOPOTECAN PRESCRIBED:__mg PO Daily for 28 days EVERY cycle

(Topotecan is supplied in Capsule strength(s)_____mg

DATE DISPENSED: _____

(mm/dd/yyyy)

QUANTITY OF BOTTLES DISPENSED: _

QUANTITY OF____MG TABLETS DISPENSED: _____

NUMBER OF_____MG TABLETS PER DAY REQUIRED TO ACHIEVE PRESCRIBED DOSE: _____

************DO NOT RETURN UNUSED TABLETS TO THE PATIENT**************

RETURN PILL COUNT DATE: ___

mm/dd/yyyy)

Has the patient taken the dose scheduled for this date? YES NO

QUANTITY OF BOTTLES RETURNED: _____

QUANTITY OF TABLETS RETURNED: _____

QUANTITY OF TABLETS DESTROYED: ____

_____

SIGNATURE OF PHARMACY OR RESEARCH STAFF: **DATE**: _____

SITE: _____ **PHONE #** _____

15.13 TECHNOLOGY TRANSFER AGREEMENTS

Agreement	Party	Number	Date Executed
DTA Amendment 1	Baylor	13855-18	5/7/2018
CDA	Baylor	13855-18	11/7/2017
DTA	Cleveland Clinic	14084-18	7/11/2018
DTA	Henry Ford	13837-18	10/30/2017
DTA Amendment 1	Henry Ford	13837-18	5/21/2018
DTA	MDACC	14085-18	4/13/2018
DTA	NorthShore	14167	4/30/2018
DTA	Northwestern	14168-18	6/18/2018
CDA	Texas Oncology	13754-17	10/24/2017
CDA Amendment 1	Texas Oncology	13754-17	6/22/2018
DTA	UTSW	14169-18	6/6/2018
DTA	Utah	14083-18	5/28/2018
CDA	MDACC	13471-17	7/3/2017
DTA	Texas Oncology	14403-18	8/8/2018
CDA	Novartis	13618-17	9/6/2017