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TITLE: A Phase II Study of Cabozantinib and Temozolomide in Patients with Unresectable or Metastatic Leiomyosarcoma and Other Soft Tissue Sarcomas

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A Phase II Study of Cabozantinib and Temozolomide in Patients with Unresectable or Metastatic Leiomyosarcoma and Other Soft Tissue Sarcomas

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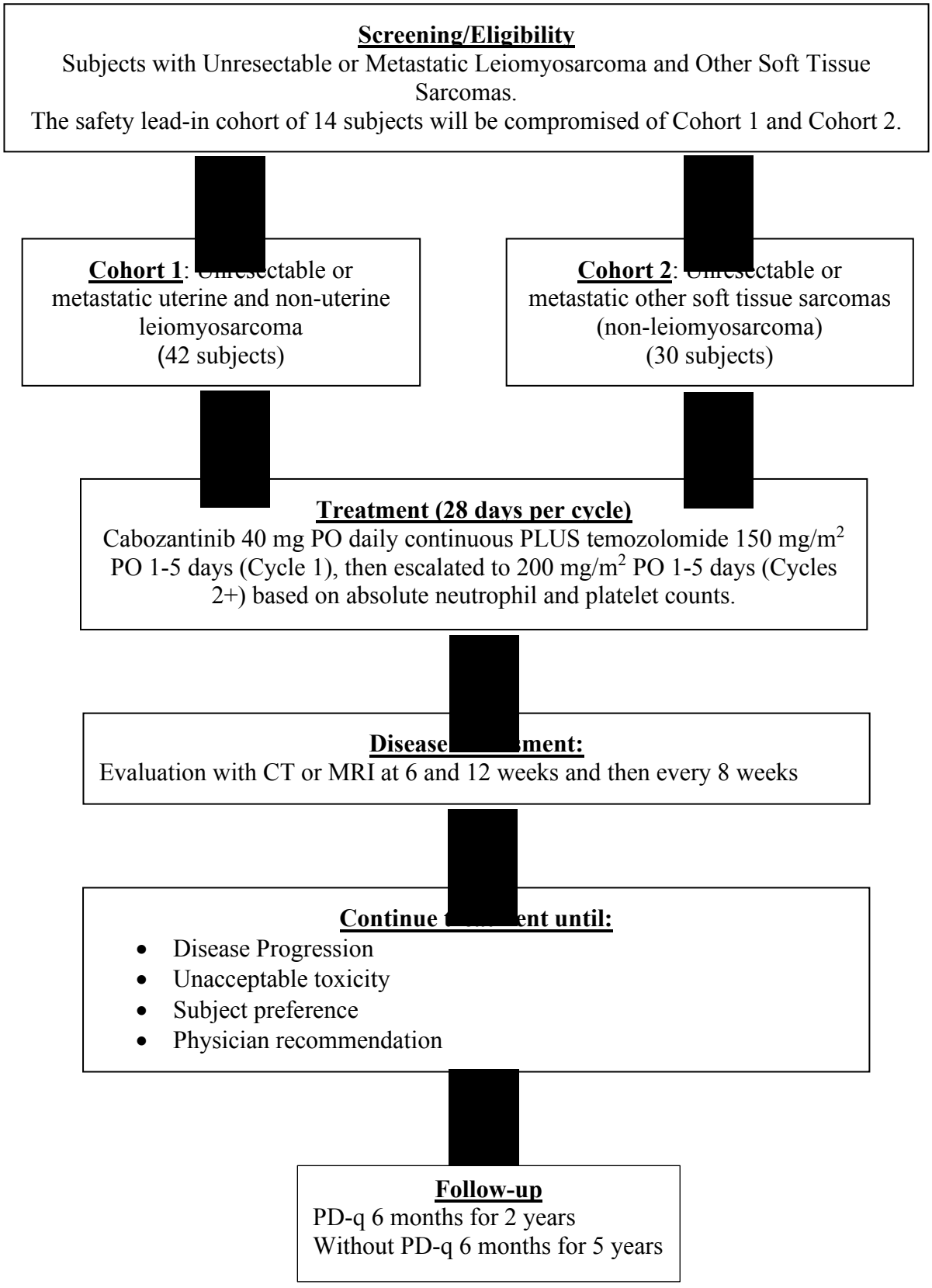
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BSA	Boday Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Clinical Trials Office
DILI	Drug-induced Liver Injury
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
EOT	End of Treatment
FDA	Food and Drug Administration
FU	Follow-up
G-CSF/GM-CSF	Granulocyte Colony-Stimulating Factors
GI	Gastrointestinal
H&PE	History & Physical Exam
IB	Investigator's Brochure
ICF	Informed Consent Form
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenously
LMWH	Low-dose Molecular Weight Heparin
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
MSTP	Midwest Sarcoma Trials Partnership
NGS	Next Generation Sequencing

ONJ	Osteonecrosis of the Jaw
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFR	Progression Free Rate
PI	Principle Investigator
PPI	Proton Pump Inhibitor
PRS	Progression Free Survival
PO (or p.o.)	Per os/by mouth/orally
PPES	Hand-Foot Syndrome
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastine Time
QAM	Quality Assurance Monitor
QoL	Quality of Life
RECIST	Response Evaluation Criteria for Solid Tumors
RPLS	Reversible Posterior Leukoencephalopahy Syndrome
SAE	Serious Adverse Event
SD	Stable Disease
STS	Soft Tissue Sarcoma
TFTs	Thyroid Function Tests
TSH	Thyroid Stimulating Hormone
TIA	Transient Ischemic Attack
TMZ	Temozolomide
ULN	Upper Limit of Normal
UPCR	Urine Protein/Creatinine Ratio
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

STUDY SCHEMA



STUDY SUMMARY

Title	A Phase II Study of Cabozantinib and Temozolomide in Patients with Unresectable or Metastatic Leiomyosarcoma and Other Soft Tissue Sarcomas
Short Title	Cabozantinib and Temozolomide in Soft Tissue Sarcomas
Version	3/1/2022, Amendment 5
Study Design	Multicenter, Phase II trial designed to estimate progression-free survival (PFS) assessed at 12 weeks of combination cabozantinib and temozolomide in subjects with soft tissue sarcoma (STS). This is a single arm two-stage Simon design comparing 20% vs 39% 3-month PFS for patients enrolled in Cohort 1. If 3 or fewer out of first 14 subjects in Cohort 1 are progression free, the trial will stop early. Otherwise, additional 28 more subjects in stage 2 (total sample size 42) will be enrolled. At the end of the study a favorable outcome will be concluded if 13 or more subjects are progression-free at 3-months. . This is based on Simon's two-stage optimal design, with alpha = 0.05, and beta = 0.20. Up to 30 subjects with other types of soft tissue sarcomas will be enrolled to obtain exploratory information for subjects with these histologies. If 3 or fewer out of first 14 subjects have 3-month PFS (i.e. alive and progression-free at 3 months) the final 16 subjects will not be enrolled. The first 14 subjects enrolled to the study from either cohort will serve as a safety lead in. During the safety lead-in, any grade 5 possibly related event in this first 3 months will hold accrual pending review by the DSMC/IRB. In addition, if 2 of the first 6, or subsequently more than 30% have to stop therapy in the first cycle, the study will be put on hold pending review by the DSMC/IRB. The DSMC will also receive a report after the 14th subject is enrolled and treated for at least one cycle, to review drug-related AEs and ensure the safety to continue enrollment.
Study Center(s)	**Lead Institution**: City of Hope National Medical Center **Participating Sites**: Medical College of Wisconsin, Washington University, University of Iowa, Northwestern University

Objectives	**Primary Objective:** Determine the progression-free rate (defined as CR+PR+SD) assessed at 12 weeks for subjects in Cohort 1 treated with cabozantinib and temozolomide as defined by RECIST 1.1 **Secondary Objectives:** 1) Determine the overall response rate (defined as CR+PR) for Cohort 1 2) Determine the clinical benefit rate (CR+PR+SD) for Cohort 1 3) Determine median progression-free survival 4) Determine overall survival for Cohort 1 5) Assess safety and tolerability 6) Determine the overall response rate (defined as CR+PR) for Cohort 2 7) Assess QoL and subject reported outcomes as measured by EORTC and EQ-5D-3L **Exploratory Objective:** Estimate the correlation of PFR and OS to levels of sVEGFR2, PIGF, VEGF, HGF, sMET, VEGF-C, VEGF-D, and soluble AXL.
Sample Size	A total of 72 subjects may be enrolled including 42 in Cohort 1 (uterine and non-uterine leiomyosarcoma) and up to 30 with other soft tissue sarcomas in Cohort 2.
Diagnosis & Key Eligibility Criteria	Subjects with histologically confirmed diagnosis of unresectable or metastatic: a. uterine and non-uterine leiomyosarcoma b. other soft tissue sarcomas (non-leiomyosarcoma)- exploratory Subjects must have measurable disease within 4 weeks prior to starting the treatment by RECIST 1.1. Subjects with 0-5 chemotherapy regimens for recurrent/metastatic disease. It will be up to the investigator to determine what constitutes a "regimen" in each case. The last dose of cytotoxic therapy must have been given at least 4 weeks prior to initiation of therapy. Subjects receiving BCNU or mitomycin C must have received their last dose at least 6 weeks prior to initiation of therapy. See Section 3.0 for a full list of eligibility criteria.

Treatment Plan	Subjects will be treated with cabozantinib 40 mg oral daily, plus temozolomide 150 mg/m^2 oral Days 1-5 (Cycle 1), then escalated to 200 mg/m^2 oral Days 1-5 (Cycles 2+), based on absolute neutrophil and platelet counts, until disease progression or unacceptable toxicity occurs, or until discontinuation per subject preference or physician recommendation.
Statistical Methodology	PFS and OS will be estimated using Kaplan-Meier methods for each histologic group. Response rates will be summarized by the observed proportion of subjects with response, along with a 95% confidence interval. Toxicities will be tabulated and summarized by the number of subjects experiencing each toxicity. A formal hypothesis test for the median PFS of the STS subjects is planned; no formal hypothesis test is planned for Cohort 2.

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Disease Background, and Current Treatment Strategies

Soft Tissue Sarcomas (STS) are malignant tumors that arise from mesenchymal tissue. In 2018, there were estimated to be approximately 13000 cases of STS in the United States.[1] Within STS, leiomyosarcoma, a tumor derived from smooth muscle, is one of the most common. In sum, it represents approximately 10-20% of newly diagnosed soft tissue sarcomas. Surgical resection remains the preferred treatment modality for individuals diagnosed with localized soft tissue sarcomas, including leiomyosarcomas. [2] Perhaps compounding this, survival outcomes in patients with locally advanced, unresectable, or metastatic disease are poor. 5 year OS for stage III, and IV disease is 35, and 16%, respectively.[3] Treatment options for patients in these situations are not only scarce, but also often ineffective. [4] Current chemotherapy options consist of single agent or combination gemcitabine, docetaxel, doxorubicin, ifosfamide, decarbazine, and temozolomide.[5–8] Not only is complete response rare, but therapy may also be limited by substantial toxicity. Furthermore, responsiveness to chemotherapy does not always correlate with overall survival.[9] Given the limited options available, and their substantial toxicities, new, and novel therapeutic strategies are needed in the area of leiomyosarcoma, and soft tissue sarcoma.

1.2 Intervention Background & Overview

1.2.1 The Role of VEGF in Soft Tissue Sarcoma

Angiogenesis is an established mechanism of tumor growth, invasion, and development of metastasis. [10] What's more, it has more recently been recognized as an important factor for the development and progression of STS, and leiomyosarcoma. Vascular endothelial growth factor (VEGF) has been a target in the treatment of many cancers, as it plays an important role in angiogenesis. In particular, VEGFR-2 is significantly associated with low survival rates in patients with sarcomas. [11] In order to maintain growth beyond a certain diameter, neovascularization of tumors is required. [12] Angiogenesis within tumors, including STS, is largely driven

by VEGF.[13] The VEGF pathway involves three receptors, VEGFR 1, 2, and 3, as well as seven ligands (VEGF A, B, C, D, E, PIGF-1, 2). [14] Expression of VEGF has been demonstrated in numerous subtypes of STS, and is associated with higher tumor grade, and decreased survival. [15,16] In leiomyosarcoma, higher VEGF serum levels were associated with a worse prognosis, and shorter survival. Agents that disrupt tumor angiogenesis have become of interest in STS, and numerous trials have shown the effectiveness of these treatments.[17] However, no trials have been conducted with cabozantinib.

1.2.2 The Role of Hepatocyte Growth Factor, and Met in STS

In addition to VEGF, *met* protooncogene tyrosine kinase receptor (MET), and its ligand, hepatocyte growth factor have been shown to be associated with sarcoma tumorigenicity in vitro.[18,19] MET is involved in numerous mitogenic pathways, including RAS, and PI3K.[20] Further studies have demonstrated that levels of c-Met expression correlate not only with angiogenesis, but also proliferation, and invasive behaviors in numerous varieties of STS. [21,22] Overexpression of MET has been demonstrated locally aggressive leiomyosarcoma, as well as other STS.[23] Subsequent in vitro studies have shown effectiveness of hepatocyte growth factor inhibitors in treating leiomyosarcoma.[24] Given the relationship between hepatocyte growth factor, and MET expression, and tumorigenicity of not only leiomyosarcoma, but also STS, further study of agents affecting this pathway is warranted.

1.2.3 Cabozantinib in Sarcoma

Cabozantinib, an inhibitor of multiple receptor tyrosine kinases, has been shown to affect hepatocyte growth factor receptor (MET), and vascular endothelial growth factor receptor 2 (VEGFR2). It also has activity against rearranged during transfection (RET), and growth arrest-specific 6 (GAS6) gene receptor (AXL), as well as c-KIT, TIE2, and FLT3 genes. [25]In vitro studies show its effectiveness in inhibition of the effects of HGF,

and VEGF on their respective receptors.[26] Historically, cabozantinib has also been demonstrated to have in vitro, and in vivo effectiveness in targeting MET in hepatocellular carcinoma.[27]

A phase 1 trial of cabozantinib in medullary thyroid cancer demonstrated a maximum tolerated dose of 175mg/d.[28] Subsequent studies in patients with RCC, and HCC have demonstrated efficacy with cabozantinib doses of 60mg/d. [29,30]

Prior phase II studies have demonstrated effectiveness of cabozantinib alone in the treatment of STS.[31] This study, performed with 27 patients, included alveolar soft part sarcoma (6), leiomyosarcoma (5), clear cell sarcoma (3), liposarcoma (2), synovial sarcoma (2), and one each of embryonal sarcoma, myxoid chondrosarcoma, myoepithelioma, myxoid cell sarcoma, and GIST. Cabozantinib was administered orally at 60mg po qd for 28d cycles, with antitumor response determined by RECIST 1.1 criteria. Four patients were shown to have confirmed partial response (PR), with response duration of 39 months. 12 patients had stable disease (SD) for six months. The most common adverse events included hypertension (21%), neutropenia (13%), abdominal pain (8%), lipase elevation (8%), thrombotic events (8%). 8 patients required dose reductions, including 2 reductions in 3 patients.

1.2.4 Temozolomide in Sarcoma

Temozolomide is an oral chemotherapeutic alkylating agent used in the treatment of a broad spectrum of malignancies, most notably including glioblastoma multiforme, and soft tissue sarcomas. [6,32,33] Triazene compounds, such as temozolomide, function through the methylation of DNA O^6-guanine, mediated by the methyldiazonium ion, a derivative of temozolomide. This process leads to base/base mismatches.[34] A phase II trial evaluated the efficacy of temozolomide in 25 patients with advanced STS, and showed improved PFS and OS, of 2, and 13.2 months, respectively.[35]

In 2003, Talbot et al studied 25 patients with TMZ dosing of 200mg/m^2 BID for days 1-5 followed by 90mg/m^2 every 4 week cycle. [35] This obtained an objective response rate of 8%, with median PFS and OS of 2.0, and 13.2 months, respectively. A subset analysis demonstrated an objective response rate of 18% in those patients with leiomyosarcoma of uterine, or nonuterine origin. There were no treatment related deaths in this study, with grade 3 toxicities including nausea, fatigue, elevated alkaline phosphatase, and neutropenic fever.

A 2005 follow-up phase 2 trial of temozolomide in advanced soft tissue sarcoma demonstrated a single agent optimal dose of 75mg/m^2 daily for a 6 week cycle.[33] In this study, performed on 45 eligible patients with advanced STS, a response was seen in 15.5% of patients. Reponses were seen in 5 of 11 gynecologic leiomyosarcoma patients. Median PFS was 2.2 months, and median OS was 8.1 months. Grade 3-4 adverse events included granulocytopenia, thrombocytopenia, and anemia.

1.2.5 Rationale for Combination Therapy

More recently, efforts have been made to potentiate the effect of chemotherapy without increasing toxicity. Simultaneous utilization of anti-angiogenic treatment with chemotherapy can have a synergistic effect and improve clinical outcomes.[36] Preclinical and clinical evidence shows that adding antiangiogenic agents to chemotherapy enhances anti-tumor and antiangiogenic effects. [37] We hypothesize that the dual targeting of VEGF and c-MET pathways with cabozantinib would result in clinical benefit for patients with soft tissue sarcoma when combined with temozolomide. Given the strong theoretical rationale for TKI treatment, we believe that the antitumor effect of temozolomide will be augmented in this instance. Retrospective case series have demonstrated efficacy of combination temozolomide with pazopanib in patients with advanced sarcomas. [38]

1.3 Rationale for the Current Study

There are several reasons to consider the combination of temozolomide and cabozantinib in STS. There is prior evidence that temozolomide, and cabozantinib individually have clinical benefit in patients with STS.[31,35] The targets of both agents are relevant in metastatic STS, with cabozantinib acting specifically on VEGFR2, and MET, and temozolomide mediating action through alkylation. The utilization of cabozantinib in combination with oral temozolomide is anticipated to produce a synergistic anti-tumor effect, and is worthwhile to explore in patients with STS. The desired effect of palliative chemotherapy is tumor shrinkage, and delay in progression in such a way that improves the wellbeing, and activity of patients.

A dose of 40 mg PO daily of cabozantinib combined with a dose of 150 mg/m^2 PO Days 1-5 of temozolomide (Cycle 1), the escalated to 200 mg/m^2 PO Days 1-5, based on absolute neutrophil and platelet counts, was chosen for this study. The dose outlined above for temozolomide during Cycle 1 was modified due to observed toxicity. For Cycles 2+, the dose is standard and has received FDA approval at the proposed dose and route of administration. The cabozantinib dose chosen for this study has previously been demonstrated to have a tolerable toxicity profile in a cabozantinib and temozolomide combination treatment in a phase I dose escalation study.[40] Results from this study reported that 40mg daily cabozantinib was found to be the MTD in combination treatment with temozolomide plus radiotherapy or after radiotherapy in patients with high-grade gliomas and was well tolerated in patients.[40]

1.4 Exploratory Analysis

There is data that anti-angiogenic therapy has benefit in advanced STS.[31,39,41] Sorafenib, a multitargeted oral tyrosine kinase inhibitor has been shown to be effective in treatment of advanced, heavily pretreated patients with STS. [42]

Its mechanism involves inhibition of VEGFRs, PDGFRs, and KIT—which are likewise affected by cabozantinib. In studies on advanced and metastatic sarcomas, sorafenib produced a median time to treatment failure of 92 days in

patients with leiomyosarcoma, and 45 days in patients with other histological subtypes.

While oral TKIs have had only modest responses, we anticipate that the addition of oral temozolomide will yield a higher response rate. There is data that temozolomide therapy has some benefit in advanced uterine leiomyosarcoma.[35] This provides background for further pursuing this variety of therapy in this disease subtype.

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

2.0 OBJECTIVES & ENDPOINTS

2.1 Primary Objective & Endpoint

The primary objective is to determine the progression-free survival (defined as CR+PR+SD) assessed at 12 weeks (~3-months) for subjects in Cohort 1 (Leiomyosarcoma Arm) treated with cabozantinib and temozolomide as defined by RECIST 1.1. The endpoint will be the time from the start of treatment to the time of progression, with progression defined as changes in RECIST 1.1 defined imaging, progression in non-target lesions as defined by RECIST 1.1, unequivocal clinical deterioration, or death from any cause. PFS, the primary endpoint, will be assessed after the first 12 weeks of therapy.

2.2 Secondary Objectives & Endpoints

2.2.1 The objective is to determine the overall response rate (defined as CR+PR) for subjects in Cohort 1 treated with a combination of cabozantinib and temozolomide. The endpoint is the presence of response (defined as CR+PR) assessed at week 6, 12 then every 2 cycles per RECIST v.1.1 in Cohort 1.

2.2.2 The objective is to determine the clinical benefit rate (CR+PR+SD) for subjects in Cohort 1 treated with a combination of cabozantinib and temozolomide. The end point is presence of clinical benefit (CR+PR+SD) assessed at week 6, 12 then every 2 cycles.

2.2.3 The objective is to evaluate the median progression free survival for subjects with combination of cabozantinib and temozolomide. The endpoint is the time from the first dose of study treatment until progression based upon changes in RECIST 1.1, unequivocal clinical deterioration, or death from any cause.

2.2.4 The objective is to evaluate overall survival for subjects in Cohort 1 treated with a combination of cabozantinib and temozolomide. The endpoint is the time from the first dose of the study treatment until death from any cause, up to a maximum follow-up of two years.

2.2.5 The objective is to assess safety and tolerability for subjects treated with a combination of cabozantinib and temozolomide. The endpoint is presence of all toxicities outlined in NCI CTCAE version 5.0 from time of first treatment.

2.2.6 The objective is to determine the overall response rate (defined as CR+PR) in Cohort 2 (other soft tissue sarcomas). The endpoint is to determine ORR in subjects with other soft tissue sarcomas assessed at week 6, 12 the every 2 cycles.

2.2.7 The objective is to assess Quality of Life (QoL) and subject-reported outcomes as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and the EuroQoL-Group Health Questionnaire (EQ-5D-3L).

2.3 Exploratory Objective & Endpoint

The objective is to estimate the correlation of PFR and OS to levels of sVEGFR2, PIGF, VEGF, HGF, sMET, VEGF-C, VEGF-D, and soluble AXL. To meet this endpoint, we will collect samples before starting the treatment at Cycle 1 Day 1, at 6 weeks, 12 weeks, and at end of treatment, to both verify the results of Tolaney et al, and to determine if there are additional correlations that can be

detected between levels of these cytokines, and PFR as well as OS, which may allow us to better predict treatment response early on in therapy.

3.0 SUBJECT ELIGIBILITY

The target population for this phase II study is subjects with unresectable or metastatic uterine and non-uterine leiomyosarcoma and other types of soft tissue sarcoma (non-leiomyosarcoma). This will be a multicenter trial conducted with City of Hope National Medical Center serving as the lead site and coordinating center for this study. Participating sites will include the University of Iowa, Washington University, University of Wisconsin and Northwestern University.

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

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

3.1 Inclusion Criteria

__1. Subjects must have a histologically confirmed diagnosis of unresectable or metastatic:

- Uterine and non-uterine leiomyosarcoma
- Other soft tissue sarcoma (non-leiomyosarcoma).

Note: Subjects with any one of the following soft tissue sarcoma histological subtypes will not be eligible for participation: alveolar soft-part sarcoma, dermatofibrosarcoma, GIST, Kaposi sarcoma, mixed mesodermal tumor/carcinosarcoma, rhabdomyosarcoma (embryonal and alveolar), and low grade (grade 1) sarcomas.

__2. Subjects must be age ≥ 18 years.

__3. Subjects must exhibit an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

__4. Subjects with 0 - 5 prior chemotherapy regimens for recurrent/metastatic disease are eligible. It will be up to the investigator to determine what constitutes a regimen in each case.

__5. Subjects must have measurable disease by RECIST 1.1.

__6. Subjects must have adequate organ and bone marrow function, based upon meeting all of the following laboratory:

- White blood cell count ≥ 2500/mm^3 (≥ 2.5 GI/L).
- Absolute neutrophil count (ANC) ≥ 1,500/mm^3 (≥1.5 GI/L) without granulocyte colony stimulating factor support.
- Hemoglobin ≥ 9 g/dL (≥90 g/L).
- Platelets ≥ 100,000/mm^3 (≥100 GI/L) without transfusion.
- Total bilirubin ≤ 1.5 x ULN (for subjects with Gilbert's disease ≤3x ULN).
- AST (SGOT)/ALT (SPGT) ≤ 3 X upper limit of normal (ULN).
- ALP ≤ 3 X ULN. ALP ≤ 5 x ULN with documented bone metastases.
- Serum albumin ≥ 2.8 g/dl.
- Serum creatinine ≤ 2.0x ULN or calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation:
  Males: (140-age) x weight (kg)/ (serum creatinine [mg/dL] x 72)
  Females: [(140-age) x weight (kg)/ (serum creatinine [mg/dL] x 72)] x 0.85
- Urine protein/ creatinine ratio (UPCR) ≤ 1 (≤ 113.2 mg/mmol).
- Prothrombin time (PT/INR) or partial thromboplastin time (PTT) test ≤ 1.3 x the laboratory ULN.

__7. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (e.g., barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study treatment.

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

__8. Female subjects of childbearing potential must not be pregnant at screening. Females of childbearing potential are defined as premenopausal females capable of becoming pregnant (i.e., females who have had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons.

__9. Recovery to baseline or ≤ Grade 1 CTCAE v.5.0 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.

__10. Subjects with treated brain metastases or cranial epidural disease are eligible if adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks prior to first dose of study treatment after radiotherapy or at least 4 weeks prior to first dose of study treatment after major surgery (e.g., removal or biopsy of brain metastasis). Subjects must have complete wound healing from major surgery or minor surgery before first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of first dose of study treatment.

__11. Subjects must be capable of understanding and complying with the protocol requirements and must have signed the informed consent document.

3.2 Exclusion Criteria

__1. Inability to swallow tablets.

__2. Previously identified allergy or hypersensitivity to components of the study treatment formulation or dacarbazine.

__3. Subjects with a prior or concurrent malignancy whose natural history or treatment does have the potential to interfere with the safety or efficacy assessment of the investigational regiment are ineligible for this trial.

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

__4. Pregnant or lactating females. Pregnant women are excluded from this study because cabozantinib and temozolomide are antineoplastic agents with potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with cabozantinib and temozolomide, breastfeeding should be discontinued if the mother is treated with cabozantinib and temozolomide.

__5. Prior treatment with cabozantinib or temozolomide.

__6. Receipt of any of the following:

- Any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 14 days before first dose of study treatment.
- Any type of cytotoxic, biologic or other systemic anticancer therapy (including investigational) within 28 days before first dose of study treatment (excluding drugs in 3.2.4).
- Radiation therapy for bone metastasis within 14 days before first dose of study treatment,
- Any other radiation therapy within 28 days before first dose of study treatment.
- Systemic treatment with radionuclides within 42 days before the first dose of study treatment.

  Note: Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible.
- Major surgery (e.g., laparoscopic nephrectomy, GI surgery, removal or biopsy of brain metastasis) within 2 weeks before first dose of study treatment. Minor surgeries within 10 days before first dose of study treatment. Subjects must have complete wound healing from major surgery or minor surgery before first dose of study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

__7. Corrected QT interval calculated by the Bazetts formula (QTcF) >500 ms per electrocardiogram (ECG) within 28 days before first dose of study treatment.

- *Note: If a single ECG shows a QTcF with an absolute value >500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility.*

__8. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

a. Cardiovascular disorders:
   - Subjects with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, subjects should be class 2B or better.
   - Uncontrolled hypertension defined as sustained blood pressure (BP) > 140 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment.
   - Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic event within 6 months before the first dose.
     - Subjects with a diagnosis of incidental, subsegmental PE or DVT within 6 months are allowed if stable, asymptomatic, and treated with a stable dose of permitted anticoagulation (see exclusion criterion #9) for at least 1 week before first dose of study treatment.

b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
   - The subject has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (e.g., Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis -

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction.

- Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before the first dose.

Note: Complete healing of an intra-abdominal abscess must be confirmed before the first dose.

c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (e.g., pulmonary hemorrhage) within 84 days before the first dose.

d. Cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation.

e. Lesions invading or encasing any major blood vessels.

f. Other clinically significant disorders that would preclude safe study participation.

- Serious non-healing wound/ulcer/bone fracture.
- Uncompensated/symptomatic hypothyroidism.
- Moderate to severe hepatic impairment (Child-Pugh B or C).

__9. Concomitant anticoagulation with oral anticoagulants (e.g., warfarin, direct thrombin and factor Xa inhibitors) or platelet inhibitors (e.g., clopidogrel). Washout period is considered to be 5 half-lives of the drug. Allowed anticoagulants are the following :

a. Low-dose aspirin for cardio protection (per local applicable guidelines) is permitted.

b. Low-dose low molecular weight heparins (LMWH) are permitted.

c. Anticoagulation with therapeutic doses of LMWH or with direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban is allowed in subjects without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before first dose of study –

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

treatment without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

Eligibility Confirmed* by (Choose as applicable):	Print Name	Signature	Date
☐ Site PI			
☐ Authorized study MD			
☐ Study Nurse			
☐ Study CRA/ CRC			
☐ Other:_____			
*Eligibility should be confirmed per institutional policies.			

3.3 Inclusion of Women and Minorities

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

3.4 Population and Accrual Overview

The target population for this phase II study is subjects with unresectable or metastatic uterine and non-uterine leiomyosarcoma and other types of soft tissue sarcoma (non-leiomyosarcoma). This will be a multi-center study with City of Hope National Medical Center serving as the lead institution and coordinating center.

A total of 72 subjects will be enrolled including 42 of uterine and non-uterine leiomyosarcoma and up to 30 subjects in the exploratory cohort for other types of soft tissue sarcomas. Potential subjects may be referred to the Principal Investigator (PI) at City of Hope National Medical Center. Subjects at each of the participating sites may be referred to the respective local PI at each site.

4.0 TREATMENT PLAN

4.1 Overview

During the Pre Treatment Period, subjects are consented and qualified (screened) for the study. Informed consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before

informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the site's institutional review board (IRB)/ethics committee (EC) policies.

Study eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria at screening before registration and study treatment administration. The following assessments will be conducted before subjects receiving their first dose of cabozantinib/temozolomide on this protocol:

- Physical exam (Vital signs, height, weight, ECOG)
- Clinical laboratory tests (CBC with differential, CMP, amylase, lipase, GGT, LDH, Magnesium, Phosphorus, TSH, FT3, FT4, PT/INR, PTT, pregnancy test (urine or serum).
- Urinalysis/UPCR
- EKG
- Tumor assessment (all sites of known disease)

For each subject, the Pre-Treatment Period ends upon receipt of the first dose of study treatment or final determination that the subject is ineligible for the study.

4.2 Treatment Plan

Subjects will be registered to 2 cohorts based on disease. Subjects with unresectable or metastatic uterine and non-uterine leiomyosarcoma will be registered to cohort 1 and subjects with unresectable or metastatic other soft tissue sarcomas (non-leiomyosarcoma) will be registered to cohort 2. The first 14 subjects to be enrolled in the study in either cohort will serve as a safety lead in. After the first 14 subjects complete 1 cycle, investigators will review all grade 3 and 4 toxicities and confirm safety to proceed with additional subjects. These subjects will be observed for 2 weeks following completion of cycle 1. Refer to Section 4.4 for details. A simon stage II design will be employed in cohort 1 to determine favorable outcome. Cohort 2 is considered exploratory.

Subjects will take oral cabozantinib (40 mg starting dose) once daily for 28 days and temozolomide 150 mg/m^2 (Cycle 1) on Days 1-5 of each 28 day cycle. For

Cycles 2+, temozolomide should be escalated to 200 mg/m^2 on Days 1-5 of each 28 day cycle, if absolute ANC $\geq$ 1.5 × 10^9/L and platelet count $\geq$ 100 × 10^9/L. Treatment will continue until either disease progression, the occurrence of unacceptable drug-related toxicity or for other reason(s) for subject withdrawal as described in Section 4.8. Subjects who are removed from the study treatment for toxicity should be followed until toxicity resolves to Grade 1 or baseline. Subjects should be instructed to immediately inform the treating investigator of any AEs. Subjects experiencing dizziness, sleepiness, or other symptoms that could influence alertness or coordination should be advised not to drive or operate other heavy machinery.

4.3 Treatment Administration

Agent	Dose	Route	Schedule	Cycle Length
Cabozantinib	40 mg (starting dose)	PO	QD	4 Weeks (28 days)
Temozolomide	150 mg/m^2 (starting dose for Cycle 1), then 200 mg/m^2 (Cycles 2+)	PO	QD Days 1-5 of each cycle	

4.3.1 Temozolomide Administration

Subjects will take capsules of temozolomide by mouth QD, Days 1-5 during the first week of the cycle and none for the remainder of the cycle. Temozolomide should be taken on an empty stomach (1 hour before or 2 hours after meals or at bedtime) with full 8 ounces of water.

4.2.2 Cabozantinib Administration

Subjects will receive cabozantinib orally at a (starting) dose of 40 mg once daily. Cabozantinib should be swallowed whole with at least 8 ounces of water on an empty stomach at approximately the same time every day. Subjects must be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. If a subject misses a dose, the dose may be taken later only if it is within 12 hours of when the missed dose

should have been taken. The missed dose should not be made up if it is within 12 hours of the next scheduled dose. The tablets should not be crushed. Grapefruit, grapefruit juice, Seville oranges and their products should be avoided by subjects taking cabozantinib.

4.4 Toxicity Management & Dose Delays/Modifications/Discontinuation

Any subject who receives at least one dose of study therapy will be evaluable for toxicity endpoints. Each subject will be assessed for the development of toxicity according to the timeframe referenced in Section 5.0 Study Procedures Table). Toxicity will be assessed according to CTCAE v.5.0.

The following should be taken into consideration in decisions regarding dose modifications (reductions or interruption) (please refer to Appendix A for dose modification algorithms for potential combination treatment related adverse events).

As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity considered related to the study treatment. Should this be ineffective, dose interruptions and/or reductions should be considered to prevent worsening of toxicity.

The assigned starting dose for cabozantinib is 40mg/day. 20 mg dose reduction level of cabozantinib is permitted (see Table 0-1).

Dose modification criteria for cabozantinib are shown in Table 0-2. Dose interruptions and/or reductions should be implemented for unacceptable toxicity. Doses may be modified at any time while a subject is on treatment.

Dose reductions or interruptions may also occur in the setting of lower grade toxicity than defined in Table 0-2, if the investigator feels it is in the interest of a subject's safety and will optimize drug tolerability.

Interruption of cabozantinib treatment for cabozantinib-related AEs may occur at any time per investigator discretion. If treatment is interrupted due to related AEs for more than 6 weeks, cabozantinib should be discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity per the discretion of the investigator.

Dose interruptions for reason(s) other than related AEs (e.g., surgical procedures) can be longer than 6 weeks per the discretion of the investigator.

Drug interaction and increased toxicity is not anticipated; however, there is limited clinical experience with the combination of cabozantinib and temozolomide. To exclude prohibitive toxicity, up to 14 subjects will be treated with combined therapy as outlined above. If a subject goes off treatment before completing a 4 week observation period of safety run-in for reasons other than toxicity, then that subject should be replaced. Accrual will be interupted after the initial 14 subjects have been enrolled. All subjects in the run-in cohort will be observed for at least 2 weeks after completion of Cycle 1 for toxicities.

Table 0-1: Dose Reductions of Cabozantinib

Assigned Dose	First Dose Level Reduction	Second Dose Level Reduction
40-mg cabozantinib oral qd	20-mg cabozantinib oral qd	No dose reduction permitted
qd, once daily Cabozantinib will be discontinued if a qd dose of 20-mg cabozantinib (minimum dose) is not tolerated		

Table 0-2: Dose Modifications of Cabozantinib for Treatment-Related Averse Events

CTCAE v.5.0 Grade	Recommended Guidelines for Management[a]
Grade 1 AEs	• Add supportive care as indicated. • Continue cabozantinib treatment at the current dose level if AE is manageable and tolerable.

Grade 2 AEs which are tolerable and are easily managed	• Continue cabozantinib treatment at the current dose level with supportive care.
Grade 2 AEs which are **intolerable** and **cannot be adequately managed**	• At the discretion of the investigator, cabozantinib may be dose reduced or interrupted. *Note: It is recommended that dose holds be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	• Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care. *Note: It is recommended that dose holds be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	• Subjects should have cabozantinib interrupted immediately. • Discontinue cabozantinib unless the following criteria are met: o Subject is deriving clear clinical benefit as determined by the investigator o Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care
[a] Study treatment dose adjustment is only needed if the toxicity was deemed related to cabozantinib treatment or had an unclear relationship to cabozantinib treatment. See Section 4.4.3 for additional instructions for management of cabozantinib related adverse events	

4.4.1 Cabozantinib Dose Reinstitution and Reescalation

See Section 4.4 for permitted timeframes for dosing delays and interruptions.

If the subject recovers from his or her toxicities to CTCAE v.5.0 Grade ≤ 1 or to the baseline value (or lower) and the toxicity was unrelated to study treatment, then study treatment may be restarted with no change in dose.

If the subject recovers from his or her toxicities to Grade ≤ 1 or to the baseline value (or lower) the toxicity was deemed possibly related to study

treatment, then study treatment may be restarted at a reduced dose (see Table 0-1 for the schedule of dose reductions).

Subjects receiving a daily dose of 20 mg may be restarted at the same dose if deemed safe at the discretion of the investigator. Subjects unable to tolerate a daily dose of 20 mg should discontinue study treatment.

Re-escalation to the previous dose, (but not higher than 40 mg/day) may be allowed at the discretion of the investigator for AEs which have resolved or recovered to Grade 1 (or baseline value) and deemed tolerable and easily managed by optimized supportive treatment. Dose re-escalation is not allowed for a drug-related dose reduction triggered by Grade 4 hematologic toxicities or by Grade 4 AEs affecting major organs (e.g., central nervous system, cardiac, hepatic, and renal).

4.4.2 Guidelines for Management of Potential Adverse Events

Subjects will be monitored for AEs from the time of signing informed consent through their last follow-up visit (30 days after the date of the last dose of cabozantinib treatment). Subjects will be instructed to notify their physician immediately at the onset of any AE. Seriousness, severity grade, and relationship to study treatment of AEs will be determined by the investigator. AE severity will be graded by the investigator in accordance with CTCAE v.5.0.

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption for cabozantinib.

4.4.3 Management of Cabozantinib Related Adverse Events

The most frequent AEs experienced by ≥ 20% of subjects treated with cabozantinib in descending order of frequency were diarrhea, fatigue, decreased appetite, nausea, PPES, weight decreased, vomiting, hypertension, constipation, asthenia, dysphonia, and AST increased. For a full description of the safety profile of cabozantinib, refer to the current Cabozantinib Investigator's Brochure.

Other medically important but less frequent AEs including arterial thrombotic AEs (e.g., transient ischemic attack [TIA], and myocardial

infarction [MI]) and venous thrombotic AEs (e.g., deep vein thrombosis [DVT] and pulmonary embolism), severe hemorrhagic events, proteinuria, wound healing complications, gastrointestinal (GI) perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS).

Adverse events associated with laboratory abnormalities experienced by ≥ 5% of subjects treated with cabozantinib in descending order of frequency were AST increased, ALT increased, anemia, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, proteinuria, hypophosphatemia, ALP increased,lactate dehydrogenase (LDH) increased, neutropenia, lipase increased, hyponatremia, platelet count decreased, GGT increased, hypoalbuminemia, leukopenia, andblood TSH increased.

Adverse events may occur within the first few weeks in the course of treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting. Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable.

Cabozantinib should be discontinued for the following AEs: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, and RPLS.

4.4.3.1 Gastrointestinal Disorders

Gastrointestinal perforation, GI fistula, and intra-abdominal and pelvic abscess:

Prior to initiation of treatment with cabozantinib, subjects should be carefully evaluated for potential risk factors including (but not limited to) the following:

- Tumors invading GI or respiratory tracts.

- Active peptic ulcer disease, inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease), diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis.

- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess.

- Ongoing visceral complications from prior radiation therapy.

- Prior GI surgery (particularly when associated with delayed or incomplete healing).

Complete healing following abdominal surgery and radiation therapy and/or resolution of intra abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

After starting cabozantinib, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula (Turnage et al. 2008) are present.[43]

Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

Diarrhea: Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Guidelines for the evaluation and management of diarrhea are shown Table 0-3 below.

Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, cabozantinib should be temporarily interrupted or dose reduced. When the diarrhea is controlled, retreatment with cabozantinib may be acceptable per Investigator decision.

In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

Recurrent or prolonged diarrhea can be associated with anal or perianal skin erosions which increase the risk for anal abscesses, fistulas, or proctitis. Good personal hygiene should be emphasized. Regular examinations of the perianal region should be performed whenever diarrhea has occurred during treatment with cabozantinib. Infections of the perianal region should be treated per local guidelines.

Table 0-3: Management of Diarrhea Associated with Cabozantinib

Event	Management
Tolerable Grade 1-2 (duration < 48 h)	• Continue with study treatment and consider dose reduction. • Initiate treatment with an antidiarrheal agent (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]). • Dietary modifications (e.g., small lactose-free meals, bananas and rice). • Intake of isotonic fluids (1-1.5 L/day). • Re-assess after 24 hours: o Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval. o Diarrhea not resolving: Continue/resume antidiarrheal treatment .
Intolerable Grade 2, Grade 2 > 48 h, or ≥ Grade 3	• Interrupt study treatment. • Ask subject to attend clinic. • Rule out infection (e.g., stool sample for culture). o Administer antibiotics as needed (e.g., if fever or Grade 3-4 neutropenia persists > 24 h). • Administer fluids (1-1.5 L/day orally or IV, as appropriate) for hydration or to correct electrolyte abnormalities. • For Grade 3-4 or complicated lower grade diarrhea consider hospitalization and IV hydration. • Re-assess after 24 h. o Diarrhea resolving to baseline bowel habits or Grade ≤ 1: consider restarting study treatment at reduced dose. o Diarrhea not resolving: Start and or continue antidiarrheal treatment (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]). Consider starting second line antidiarrheal or referral to gastroenterologist.

4.4.3.2 Nausea and Vomiting

Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented.

Antiemetic medications should be assessed for potential drug interactions (refer to Section 4.5.3 for further details).

4.4.3.3 Non-Gastrointestinal Fistula

Radiation therapy (in certain areas of the body) has been identified as a possible predisposing risk factor for fistula formation in subjects undergoing treatment with cabozantinib.

Subjects with any clinically relevant ongoing complications from prior radiation therapy (e.g., radiation esophagitis or other inflammation of the viscera) should not be treated with cabozantinib until these complications have resolved.

Radiation therapy to the thoracic cavity (including mediastinum) should be avoided within 4 weeks of starting treatment with cabozantinib (excluding local radiation for bone metastases). Fistula should be ruled out as appropriate in cases of onset of severe mucositis or difficulty swallowing after start of therapy. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with a non GI fistula.

4.4.3.4 Hemorrhage

Hemorrhagic events, including serious and sometimes fatal events, have been reported with cabozantinib. Subjects should be evaluated for potential bleeding risk factors prior to initiating cabozantinib treatment and should be monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

- Tumor of the lung with cavitary lesions or tumor lesions which invade or encase major blood vessels. NSCLC with squamous cell differentiation is known for significant lung cavitations and centrally located tumors that may invade major blood vessels. Thus, the anatomic location and characteristics of

tumor as well as the medical history should be carefully reviewed in the selection of subjects for treatment with cabozantinib.

- Recent or concurrent radiation to the thoracic cavity.
- Active peptic ulcer disease, inflammatory GI diseases including Crohn's disease and ulcerative colitis.
- Underlying medical conditions which affect normal hemostasis (eg, deficiencies in clotting factors and/or platelet function, or thrombocytopenia).
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis.
- History of clinically significant hemoptysis, hematemesis, or hematuria.

The risk of hemorrhage in cabozantinib-treated subjects with brain metastases has not been thoroughly analyzed. Though the incidence of CNS hemorrhage events in a study of subjects with glioblastoma was higher than observed in general population of subjects with cancer treated with cabozantinib, it is not clear how the risk of hemorrhage in glioblastoma translates to a risk of hemorrhage for subjects with brain metastases. Currently, brain metastases of carcinomas are not contraindications to the use of cabozantinib, but subjects with brain metastases should be monitored with a high index of suspicion if symptoms that could be due to a CNS hemorrhage occur.

Complete healing from radiation-induced side effects should have occurred before initiating cabozantinib treatment, and cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood).

4.4.3.5 Thromboembolic Events

Thromboembolic events are frequent in cancer subjects due to procoagulant changes induced by the malignancy or anticancer therapy. DVT and pulmonary embolism have been observed in clinical studies with cabozantinib, including fatal events. Subjects

who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the investigator and according to individual protocols. Low molecular weight heparins are the preferred management for thrombotic events; oral anticoagulants (e.g., warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines) are not allowed.

Arterial thrombotic events (e.g., TIA, MI) have been observed in studies with cabozantinib. Further treatment with cabozantinib should be discontinued in subjects who develop an acute MI, cerebral infarction, or any other clinically significant arterial thromboembolic complication.

4.4.3.6 Hypertension

Table 0-4 provides treatment guidelines for hypertension deemed related to cabozantinib.

Blood pressure should be monitored in a constant position visit to visit, either sitting or supine in a relaxed setting.

Decisions to reduce or interrupt the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement.

Cabozantinib should be discontinued in subjects with hypertensive emergency.

Table 0-4: Management of Hypertension Associated with Cabozantinib

Event	Management
Subjects NOT receiving optimized anti-hypertensive therapy	
> 140 mm Hg (systolic)[a] and < 160 mm Hg OR > 90 mm Hg (diastolic) and < 110 mm Hg	• Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP <140 mm Hg systolic or <90 mm Hg diastolic • If subject is symptomatic interrupt cabozantinib treatment
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce cabozantinib by one dose level[b] or interrupt cabozantinib treatment per Investigator discretion. • Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 140 mm Hg systolic or < 90 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted. • Cabozantinib treatment should be dose interrupted if upper limits of systolic BP (≥ 160 mm Hg) are sustained and not adequately manageable or if systolic BP is > 180 mm Hg or diastolic BP > 110 mm Hg, or if subject is symptomatic. • Re-start cabozantinib treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 140 mm Hg systolic and < 90 mm Hg diastolic.
Hypertensive emergency[c]	• Discontinue cabozantinib treatment.

[a] Permitted dose levels are defined by individual protocols.
[b] Hypertensive emergency is defined as uncontrolled elevated BP with clinical evidence of progressive or impending end-organ damage (e.g., myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage).

4.4.3.7 Stomatitis and Mucositis

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with cabozantinib, good oral hygiene and standard local treatments such as non-traumatic and non-irritating cleansing, and oral rinses (e.g., with a weak solution of salt and baking soda) should be maintained. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss, and Vaseline should be avoided.

Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as clinically indicated.

4.4.3.8 Skin and Subcutaneous Tissue Disorders

Wound healing and surgery: Cabozantinib has the potential to cause wound healing complications and wound dehiscence which may even occur long after a wound has been considered healed. Therefore, surgical and traumatic wounds must not only be completely healed prior to starting cabozantinib treatment but must also be monitored for wound dehiscence, wound infection and other signs of impaired wound healing while the subject is being treated with cabozantinib. If dehiscence occurs, cabozantinib treatment should not be restarted until complete healing has taken place.

Treatment with cabozantinib should be stopped at least 3 weeks prior to elective surgery. Do not administer cabozantinib for at least 2 weeks after major surgery and until complete wound healing.

4.4.3.9 Palmar-plantar Erythrodysesthesia Syndrome

PPES; also known as hand-foot syndrome, skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and pappular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported with cabozantinib. All subjects on study should be advised on prophylactic measures including the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water leading to vasodilatation, protection of pressure-sensitive areas of hands and feet, and use of cotton gloves and socks to prevent injury and keep the palms and soles dry. Early manifestations include tingling, numbness, mild hyperkeratosis, and symmetrical red and swollen areas on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas. Analgesics may be required for pain control. Aggressive management of symptoms is recommended, including early dermatology referral. Treatment recommendations in response to PPES are summarized in Table 0-5.

Table 0-5: Management of Hand-Foot Syndrome (PPES) Associated with Cabozantinib

CTCAE v.5.0 Grade	Action To Be Taken
Grade 1	• Cabozantinib treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. • Otherwise, cabozantinib should be reduced to the next lower dose level. • [a] Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. • Reassess at least weekly; if PPES worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	• Cabozantinib treatment may be continued if PPES is tolerated. • Cabozantinib should be dose reduced or interrupted if PPES is intolerable. • Continue urea 20% cream twice daily AND high potency steroid cream (e.g., clobetasol 0.05%) once daily and add analgesics (e.g., NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. • Reassess at least weekly; if PPES worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	• Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. • Continue treatment of skin reaction with high potency steroid cream (e.g., clobetasol 0.05%) twice daily AND analgesics. • Resume study drug at a reduced dose if PPES recovers to Grade ≤ 1. • Discontinue subject from study treatment if PPES does not improve within 6 weeks.

CTCAE, Common Terminology Criteria for Adverse Events; NSAID, non-steroidal anti-inflammatory drug; PPES, palmar plantar erythrodysesthesia syndrome.

[a] Permitted dose levels are defined by individual protocols.

4.4.3.10 Osteonecrosis

Osteonecrosis has been reported in subjects treated with cabozantinib. Additional risk factors include use of bisphosphonates and denosumab, chemotherapy and anti-angiogenic drugs, use of corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.

Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of osteonecrosis.

Perform an oral examination prior to initiation of cabozantinib and periodically during cabozantinib treatment. Advise subjects regarding oral hygiene practice and to quickly report symptoms to Investigator. Caution should be used in subjects receiving bisphosphonates.

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment with cabozantinib should be interrupted for at least 3 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

Withhold CABOZANTINIB for development of ONJ until complete resolution.

4.4.3.11 Proteinuria

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. Table 0-6 provides treatment guidelines for proteinuria deemed related to cabozantinib.

Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria > 3.5 grams per day in combination with low blood protein levels, high cholesterol levels, high triglyceride levels, and edema).

Table 0-6: Management of Proteinuria Associated with Cabozantinib

Severity of Proteinuria (UPCR)	Management of Proteinuria
≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in cabozantinib treatment or monitoring
> 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol)	• Consider confirming with a 24-h protein assessment within 7 days • No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 h on 24-h urine collection. • Dose reduce or interrupt cabozantinib treatment if UPCR > 2 mg/mg on repeat UPCR testing or urine protein > 2 g/24 h on 24-h urine collection. • Continue cabozantinib on a reduced dose if UPCR decreases to < 2 mg/mg. • Consider interrupting cabozantinib treatment if UPCR remains > 2 mg/mg despite a dose reduction until UPCR decreases to < 2 mg/mg. • Restart cabozantinib treatment at a reduced dose after a dose interruption. • Repeat UPCR within 7 days and once per week. • If UPCR < 1 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading.) • If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• Interrupt cabozantinib treatment pending repeat UPCR within 7 days and/or 24-h urine protein. • If ≥ 3.5 mg/mg on repeat UPCR, continue to interrupt cabozantinib treatment and check UPCR every 7 days. • If UPCR decreases to < 2 mg/mg, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1 mg/mg. • If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
Nephrotic syndrome	• Discontinue cabozantinib treatment

4.4.3.12 Nervous System Disorders

Cabozantinib appears to represent minimal risk of adverse neurological effects based on nonclinical Good Laboratory Practice (GLP)-compliant toxicology studies. Dysphonia, dysgeusia, headache, dizziness, confusional state, convulsion, depression, memory impairment, hypoesthesia, peripheral neuropathy, insomnia, ataxia, and encephalopathy have been observed in clinical studies with cabozantinib. The development of any new or progressive, unexplained neurological symptoms should be assessed for underlying causes.

RPLS has been reported. RPLS should be considered in any subject presenting with seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in subjects with RPLS.

4.4.3.13 Hepatocellular Toxicity

Investigators should monitor for DILI diligently and report any potential events. Elevation of aminotransferases (ALT and AST) and bilirubin have been observed during treatment with cabozantinib. It is recommended that subjects with elevations of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications should be discontinued in subjects who develop increased values of ALT, AST, or bilirubin, and other potential causes for these increases (e.g., cancer-related, infection) should be evaluated. See Table 0-7 for management of hepatocellular toxicity.

Table 0-7 Management of Hepatocellular Toxicity Associated with Cabozantinib

Event – Elevation of ALT, AST, or Total Bilirubin (CTCAE v4)	Management
Grade 1 ALT or AST > ULN – 3.0 x ULN Bilirubin > ULN – 1.5 x ULN	• Dose adjustment is usually not required. • Consider discontinuing concomitant hepatotoxic medications and add supportive care as indicated.
Grade 2[a,b] ALT or AST > 3.0 – 5.0 x ULN Bilirubin > 1.5 – 3.0 x ULN	• Interrupt cabozantinib if lasting longer than 1 week and consider more frequent monitoring of ALT, AST, and bilirubin. • Restart cabozantinib after lab abnormalities have resolved to at least CTCAE Grade ≤ 1 or baseline.
Grade 3[a,b] ALT or AST > 5.0 – 20.0 x ULN Bilirubin > 3.0 – 10.0 x ULN	• Interrupt cabozantinib and consider more frequent monitoring of ALT, AST, and bilirubin. • Restart cabozantinib at a reduced dose after lab abnormalities have resolved to at least CTCAE Grade ≤ 1 or baseline. • Discontinue if lab abnormalities cannot be reversed despite interruption of study treatment.
Grade 4[b] ALT or AST > 20.0 x ULN Bilirubin > 10 x ULN	Subjects should have cabozantinib interrupted immediately. Discontinue cabozantinib unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the Investigator, and approved by the Principal Investigator. • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care.
[a]Elevations of aminotransferases when hepatic metastases are present may not require dose modifications if there is less than a doubling in the aminotransferases from baseline and if there are no progressive elevations in serum bilirubin concentration or coagulation factors. [b]The following condition requires discontinuation of cabozantinib: Drug-related ALT or AST >3 × ULN in combination with total bilirubin >2 x ULN without other reasonable explanation, consistent with drug-induced liver injury (DILI).	

4.4.3.14 Infections and Infestations

Infections are commonly observed in cancer subjects. Predisposing risk factor include a decreased immune status (e.g., after myelosuppressive anticancer therapies, splenectomy), destructive growth of the underlying malignancy including bone marrow infiltration with suppression of normal hematopoiesis, as well as the presence of IV devices.

Infections and abscesses should be treated with appropriate local care and systemic therapy. Cabozantinib should be interrupted until complete healing has taken place.

4.4.3.15 Blood and Lymphatic System Disorders

Hematological toxicities (i.e., neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions and/or dose reductions. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

Dose reductions or dose interruptions for hematological toxicities are not mandated but can be applied as clinically indicated. Supportive care for thrombocytopenia or anemia, such as transfusions, may be managed according to institutional guidelines. The use of colony-stimulating growth factors should be considered. Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

4.4.3.16 Fatigue

Common causes of fatigue, such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, dehydration, sleep disturbance, and hypothyroidism should be ruled out and treated according to standard of care. Pharmacological management should be considered after disease specific morbidities have been excluded when not prohibited.

4.4.3.17 Weight Loss

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy should be considered for appetite enhancement when not prohibited by a particular protocol.

4.4.3.18 Corrected QT Prolongation

The effect of orally administered cabozantinib 140 mg qd on QTc interval was evaluated in a placebo-controlled study in subjects with MTC. A mean increase in QTcF of 10-15 ms was observed after 4 weeks after initiating cabozantinib treatment. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib-treated subjects in this study had a QTcF > 500 ms. Review of the larger safety database (~5000 subjects exposed to cabozantinib in clinical trials and in post-marketing experience) confirmed the absence of safety concerns associated with QT prolongation. There were no events of torsades de pointes reported. Concomitant treatment with strong cytochrome P450 (CYP) 3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided. If at any time on study there is an increase in QTcF to an absolute value > 500 ms, two additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

If the average QTcF from the three ECGs is > 500 ms, the following actions must be taken:

- Interrupt cabozantinib treatment
- Hospitalize symptomatic subjects (e.g., with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated

- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org)
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 msec, or otherwise determined by consultation with a cardiologist or appropriate expert.
- Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. Cabozantinib treatment may be restarted at a reduced dose level if all of the following conditions are met:
- Symptoms are determined to be unrelated to the QT interval prolongation
- The QTcF value > 500 ms is not confirmed
- Cabozantinib treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms.
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved
- Following reinitiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points.
- Cabozantinib treatment must be permanently discontinued if either of the following applies:
- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation after reinitiation of study treatment at a reduced dose

4.4.3.19 Electrolyte Disorders

Serum electrolyte disorders including hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia have been reported during treatment with cabozantinib, and serum electrolyte levels should be monitored frequently while receiving cabozantinib. Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines as outlined in Section 4.4 or as clinically indicated. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or intravenous replacement.

4.4.3.20 Endocrine Disorders

Thyroid dysfunction, primarily hypothyroidism, has been observed with cabozantinib treatment. The underlying potential mechanism of thyroid dysfunction observed wit cabozantinib treatment remains unclear. Management of thyroid dysfunction (e.g., symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

4.4.3.21 Angioedema

Angioedema should be managed according to standard practice. The subject should be observed until symptoms resolve, with particular attention to maintaining an open airway.

4.4.3.22 Musculoskeletal and Connective Tissue Disorders

Cabozantinib appears to represent minimal risk of adverse musculoskeletal effects based on nonclinical GLP-compliant toxicology studies. The development of new or progressive, unexplained musculoskeletal symptoms such as pain or weakness should be assessed for underlying causes. Rhabdomyolysis has been reported. Cabozantinib should be discontinued in subjects with serious and life-threatening rhabdomyolysis and interrupted if less severe forms occur when there are no other clear causes. Reinitiation of cabozantinib treatment must be discussed with and

approved by the sponsor. Therapy of rhabdomyolysis should include supportive care and standard medical intervention.

4.4.3.23 Respiratory, Thoracic and Mediastinal Disorders

Dyspnea has been reported in clinical studies with cabozantinib. Symptoms should be managed according to locally accepted clinical practice including an assessment for underlying causes. Pulmonary embolism should be considered as possible causes for new onset dyspnea given the risk of thrombosis associated with inhibition of VEGF signaling. Furthermore, fistula formation (Section 6.2.2) and pneumonia have been reported in subjects treated with cabozantinib and should be considered as clinically indicated in subjects presenting with pulmonary symptoms.

4.4.3.24 COVID-19

If a diagnosis of COVID-19 is confirmed on study, the disease should be managed as per local or institutional guidelines. The overall risk-benefit ratio for the subject should be evaluated to determine whether holding study treatment(s) is in the best interest of the subject. More specific guidance regarding COVID-19 is included in the study protocols.

4.4.4 Management of Temozolomide Related Adverse Events

The most common adverse reactions (≥ 10% incidence) are: alopecia, fatigue, nausea, vomiting, headache, constipation, anorexia, convulsions, rash, hemiparesis, diarrhea, asthenia, fever, dizziness, coordination abnormal, viral infection, amnesia, and insomnia.

The most common Grade 3 to 4 hematologic laboratory abnormalities (≥ 10% incidence) that have developed during treatment with temozolomide are: lymphopenia, thrombocytopenia, neutropenia, and leukopenia.

Allergic reactions have also been reported.

Please refer to Appendix A for dose modification algorithms for potential combination treatment related adverse events.

Table 0-8: Temozolomide Dosing Interruption or Discontinuation during Treatment Period

Toxicity	Temozolomide Interruption	Temozolomide Discontinuation	Reduce Temozolomide by 1 Dose Level
Absolute Neutrophil Count (ANC)	≥ 0.5 and $< 1.5 \times 10^9$/L	$< 0.5 \times 10^9$/L	≥ 0.5 and $< 1.0 \times 10^9$/L
Platelet Count	≥ 10 and $< 100 \times 10^9$/L	$< 10 \times 10^9$/L	≥ 10 and $< 50 \times 10^9$/L
NCI-CTCAE non-hematological toxicity (except for alopecia, nausea and vomiting)	Grade 2	Grade 3 or 4	Grade 3

Treatment with temozolomide may be continued when all of the following conditions are met:

- ANC $\geq 1.5 \times 10^9$/L
- Platelet count $\geq 100 \times 10^9$/L
- NCI-CTCAE non-hematological toxicity $\leq$ Grade 1 (except for alopecia, nausea and vomiting)

Table 0-9: Temozolomide Dose Levels

Dose 0 (Assigned Starting Dose)	Dose Level 1	Dose Level 0	Dose Level -1
150 mg/m²/day	200 mg/m²/day	150 mg/m²/day	100 mg/m^2 /day

Please see Appendix B for Daily Dose Calculations by Body Surface Area (BSA).

4.5 Concomitant Medications/Treatments

4.5.1 Allowed Therapy

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.

- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (e.g., ASCO or ESMO guidelines).
- Bisphosphonates or RANK-L inhibitors can be used to control bone loss or hypocalcemia if the benefit outweighs the risk per the Investigator's discretion.

  Note: osteonecrosis of the jaw has been reported in subjects using bisphosphonates (Section 4.4.3.10). Oral examinations are recommended at screening to determine eligibility and periodically during the study. In addition, subjects should be advised regarding oral hygiene practice and to quickly report symptoms to the Investigator. Frequent monitoring for potentially overlapping toxicities with study treatment is recommended. Withhold cabozantinib for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. **Withhold cabozantinib for development of ONJ until complete resolution**.
- Transfusions and hormone replacement should be utilized as indicated by standard clinical practice.
- Individualizedanticoagulation therapy with heparin or direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban is allowed if it can be provided safely and effectively under the following circumstances:
    - At the time of first dose of study treatment:
        - Low dose low molecular weight heparins (LMWH) for prophylactic use are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion.
        - Therapeutic doses of LMWH or the direct factor Xa inhibitors rivaroxaban, edoxaban, or apixaban are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of the

anticoagulant for at least 1 week, and has had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor. See Section 4.5.2 for prohibited anticoagulants.

- After first dose of study treatment:
  - Low dose low molecular weight heparins (LMWH) for prophylactic use are allowed if clinically indicated and the benefit outweighs the risk per the Investigator's discretion.
  - Therapeutic doses of LMWH or the direct factor Xa oral inhibitors rivaroxaban, edoxaban, or apixaban are allowed if clinically indicated (e.g., for the treatment of DVT), and the benefit outweighs the risk per the Investigator's discretion. See Section 4.4.3.5 for management of thromboembolic complications while on study. See Section 4.5.2 for prohibited anticoagulants.

- Accepted clinical guidelines regarding appropriate management while receiving any kind of anticoagulation therapy must be followed. This includes, but is not limited to, subject education regarding the potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (e.g., due to kidney dysfunction). Caution is warranted in settings associated with an increased risk for bleeding such as gastrointestinal cancers, urothelial cancers, gastrointestinal mucosal abnormality (e.g., mucositis), renal or hepatic impairment, thrombocytopenia, arterial hypertension, or prior history of gastrointestinal bleed. For direct factor Xa inhibitors, the potential for drug-drug interaction with other concomitant medications, as well as gastrointestinal absorption, should be considered. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) should not be used concomitantly with heparin or factor Xa inhibitors due to the

increased risk for bleeding complications. The risks and benefits of the use of anticoagulants should be reassessed on a regular basis. For more information regarding the use of anticoagulants, refer to the prescribing information of the anticoagulant and accepted clinical practice guidelines.

Potential drug interactions with cabozantinib are summarized in Section 4.5.3.

4.5.2 Prohibited or Restricted Therapy

The following therapies are prohibited until study treatment has been permanently discontinued:

- Any investigational agent or investigational medical device.
- Oral anticoagulation with coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct factor Xa inhibitor betrixaban, platelet inhibitors (e.g., clopidogrel), and chronic use of aspirin above low dose levels for cardio-protection per local applicable guidelines), until 4 weeks after cabozantinib has been permanently discontinued.
- Any non-protocol systemic anticancer treatment (e.g., chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of the cancer under investigation).

The following therapies should be avoided until study treatment has been permanently discontinued or until otherwise specified:

- Local anticancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions should not be performed until radiographic progression per RECIST 1.1 has been established.
- Erythropoietic stimulating agents (e.g., epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor

recurrence/progression associated with erythropoietin (Wright et al 2007).

- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc interval).

- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

- Caution must be used when discontinuing treatment with a strong CYP3A4 inhibitor in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations and should be avoided. Grapefruit, star fruit, and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.

Additional information on potential drug interactions with cabozantinib is provided in Section 4.5.3.

4.5.3 Potential Drug Interactions

Potential Drug Interactions with Cabozantinib

Cytochrome P450: Data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the area under the plasma concentration-vs-time curve (AUC) of

co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared to CYP2C8 (i.e., CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations. Grapefruit, star fruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Strong

CYP3A4 inhibitors should be avoided and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Please refer to Appendix C for the drug interaction table lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways.

Other Interactions: A case of a drug-drug interaction between cabozantinib and warfarin has been reported in the literature (Foxx-Lupo et al. 2016). However, a causal relationship to drug exposure for the drug-drug interaction case described abov cannot be established. As a precaution, administration of warfarin at therapeutic doses is not allowed in subjects receivieng cabozantinib.

In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but has the potential to inhibit the P-glycoprotein transport activity (IC_{50}=7.0 μM) at high concentrations. Additional details related to these overall conclusions can be found in the investigator brochure.

Administration of the proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (i.e., PPIs, H_2 receptor antagonists, and antacids) is allowed in subjects administered cabozantinib.

Additional details regarding potential drug interactions with cabozantinib can be found in the investigator brochure.

Cabozantinib was shown to be a substrate of drug transporter MRP2 in an in vitro assay. Administration of MRP2 inhibitors to subjects may result in increases in cabozantinib plasma concentrations.

Food Effects: As food increases exposure levels of cabozantinib, subjects should fast (with the exception of water) for at least 2 h before taking their dose of cabozantinib. After the 2-hour fast, subjects are to take

cabozantinib with a full glass of water (minimum of 8 oz or 240 mL) with no more food intake for one hour post-dose.

5.4.4 Palliative Care

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

- Palliative Radiation: protocol treatment should be held 3 weeks before, during, and at least 2 weeks after palliative radiation and complete wound healing, if a wound is present. If treatment is not resumed within 3 weeks, the case will be reviewed by PI and DSMC to determine whether or not subject can restart treatment.
- Palliative Surgery: Protocol treatment should be held 3 weeks before and until complete wound healing. Complete healing following abdominal surgery and radiation therapy and/or resolution of intra abdominal abscess must be confirmed prior to initiating treatment with cabozantinib. If the treatment is not resumed within 3 weeks, the case will be reviewed by PI and DSMC to determine whether or not subject can restart treatment.

4.6 Duration of Therapy

Subjects will continue on study treatment until progressive disease, unacceptable toxicity or subject withdrawal.

4.7 Duration of Follow-up

Subjects with PD at the end of treatment will be followed every 6 months for 2 years (or until death) for survival. Subjects without PD at the end of treatment will be followed every 6 months for 5 years (or until death) for survival and progression. Patients will be followed by either clinic visits or phone call. Subjects who are removed from the study treatment for toxicity should be followed until toxicity resolved to grade 1 or baseline.

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

Subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. The investigator may withdraw a subject from study treatment or from the study if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol. The COH DCC and the Study PI should be promptly notified of the change in participant status.

In addition, any of the following conditions require discontinuation of the subject from study treatment:

- An AE or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment;
- The investigator believes it is not in the best interest of the subject to continue on study;
- Specific conditions described in the Management of Adverse Events Section 4.4;
- Necessity for treatment with other anticancer treatment prohibited by protocol;
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g., male condom, female condom) during the course of the study and for 4 months after discontinuation of study treatment;
- Women who become pregnant or are breastfeeding;
- If the subject does not recover from his or her toxicities to tolerable Grade ≤ 2 within 6 weeks, the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity and with agreement of the principal investigator /Sponsor;
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol;

- Significant noncompliance with the protocol schedule in the opinion of the investigator;
- Subjects who cannot tolerate the minimum protocol-specified dose of study treatment will have study treatment discontinued;
- Progressive disease (PD) or the subject no longer experiences clinical benefit as determined by the investigator;

4.9 Subject Replacement

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

5.0 STUDY PROCEDURES TABLE

1. Screening assessments should be done within 28 days of first dose of study treatment (unless otherwise specified).
2. Cycle 1 Day 1 assessments should be done within 7 days of starting treatment. Pre-study procedures completed within 7 days of C1D1 do not need to be repeated. If a pre-study procedure was done more than 7 days prior to C1D1, then procedure needs to be repeated, but may be done within 5 days of starting therapy.

	Study Treatment Period			**Post-Treatment Period**
	Screening	**Cycle 1 Day 1**	**C1D15, C2D1, C2D15, C3D1 and Day 1 of every following cycle (± 5 days)**	**30 Days after Last Dose/ Survival Follow-up**
Informed Consent	X			
Demographics	X			
Medical and Cancer History/Demographics	X			
Physical Examination	X	X	X	X
Height	X			
Weight	X	X	X	X
Vital Signs	X	X	X	X
ECOG Performance Status	X	X	X	X
CBC with differential[a]	X[a]	X	X	X
Chemistry Panel[a]	X[a]	X	X	X
Urinalysis	X			X
Urine Protein/Urine Creatinine Ratio-UPCR[f]	X[f]	X[f]	X[f] every 8 weeks	X
PT/INR, PTT[k]	X[k]			
TFTs (TSH, FT3, FT4)[d]	X		X[d] every other cycle	
12-lead ECG[c]	X[c]		X[c]	
Cabozantinib Administration [j]		X	X (daily)	
Temozolomide Administration [j]		X	X (Days 1-5)	
Pregnancy Test[e]	X	X	X[e]	X
QOL[h]	X[h]	X[h]	X[h]	X
Correlative Blood Sample[i]		X[i]	X[i]	X[i]
Tumor Assessment[b]	X		X[b]	
Concomitant Medications	X	X	X	X

NGS[m] Report, if available	X			
Adverse Events	Continuous			X
Follow-up/Survival FU[g]				X[g]

a. Laboratory tests should include a standard hematology panel (CBC, differential, platelets) and chemistry panel (albumin, alkaline phosphatase, ALT, amylase, AST, bicarbonate, bilirubin, blood urea nitrogen, calcium, chloride, creatinine, γ-glutamyltransferase [GGT], glucose, lactate dehydrogenase, lipase, magnesium, phosphorus, potassium, sodium, total protein). Screening labs need to be done within 14 days of registration.

b. All sites of known disease must be assessed. Radiology assessment by CT or MRI will be done atC2D15, C4D1, Cycle 6 and every 8 weeks (± 7 days) thereafter. After 1 year of protocol treatment, the scans can be obtained every 12 weeks (±7 days) at the discretion of the subject and the treating physician.

c. ECG: Performed during screening (within 28 days of first dose of treatment) and then **every 3 cycles** until end of treatment (± 5 days).

d. Thyroid function tests (TSH, FT3, FT4) are performed during the screening period and then every 8 weeks (±5 days). TSH is mandatory, FT3/FT4 are only required to be performed if TSH level is abnormal. Screening test should be done within 28 days of Cycle 1, Day 1.

e. Pregnancy test: urine or serum at screening and on Day 1 of each cycle (-5 days) for women of child-bearing potential.

f. Urine protein/urine creatinine will be assessed during screening and **every 2 cycles** (-5 days of D1 of the cycle) until the end of treatment. Screening UPCR should be done within 14 days of Cycle 1, Day 1 in which case Cycle 1, Day 1 assesment may be skipped.

g. End of treatment visit will be completed within 30 days of the last dose of study drugs. Subjects with PD at end of treatment will be followed every 6 months for 2 years (or until death) for survival (from the last day of treatment). Subjects without PD at the end of treatment will be followed every 6 months for 5 year (or until death) for survival and progression (from the last day of treatment).

h. The QOL questionnaires (EORTC QLQ-C30 and EuroQoL EQ-5D-3L) should be completed during screening, on Day 1 of every cycle prior to the study treatment administration, and at the end of treatment.

i. Blood samples for mandatory correlative study will be collected at Cycle 1 Day1 prior to starting the treatment, and at C2D15, C4D1, and at the end of treatment (EOT) visit (±5 days).

j. Day 1 of each cycle should be every 28 days. In the event that this day falls on a holiday or other such event, study team should use ± 5 days window to complete pre-treatment procedures, and dispense protocol agents to subjects with drug diaries and instructions to commence treatment on Day 1. Any missed doses will not be made up and should be skipped to maintain a 28-day cycle. Collection of drug diaries and drug accountability will be completed for the previous cycle on Day 1 of the following cycle.

k. Screening PT/INR and PTT should be within 14 days of registration.

l. Subjects with prior Next Generation Sequencing (NGS) reports completed on their tumor specimen will have this data collected.

*Once on treatment, if the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (e.g., clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule.

The Treatment Period ends when a subject receives his or her last dose of study treatment; the subject then enters the Post-Treatment Period.

5.1 Laboratory Assessments

Please see Appendix D for composition of laboratory panels.

Abnormalities in clinical laboratory tests that lead to a change in subject management (e.g., dose delayed [withheld] or reduced, requirement for additional medication, treatment or monitoring) are considered clinically significant for the purposes of this study, and will be recorded on the Adverse Events Case Report Form (CRF). If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE. Please see Section 7 of the study for further instructions on the reporting and recording of adverse events.

5.2 Post-Treatment Period

Subjects will return to the study site approximately 30 days after their last dose of cabozantinib to complete end-of-study assessments.

Laboratory and physical examinations will be performed. Remaining study treatment will be returned by the subject, and treatment compliance will be documented. Additional follow-up will occur for subjects with AEs related to study treatment that are ongoing at the time of this visit, and for subjects with SAEs related to study treatment that occur after the time of this visit.

Subjects with PD at end of treatment will be followed every 6 months for 2 years (or until death) for survival (from the last day of treatment). Subjects without PD at the end of treatment will be followed every 6 months for 5 year (or until death) for survival and progression (from the last day of treatment).

6.0 ENDPOINT ASSESSMENTS

6.1 Definitions

6.1.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques (CT, MRI, x-ray) or as >10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Lymph nodes are considered measurable in

RECIST 1.1 if their short diameter exceeds 15 mm. Lymph nodes are considered normal if they have a short axis of less than 10 mm; this applies to determination of response as well. Lesions that are previously irradiated must show clear evidence of progression over a minimum of 3 months to include as measurable. This period of time is used to discount tumor edema in an irradiated field as a false sign of disease progression.

6.1.2 Non Measurable Disease

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

6.1.3 Target Lesions

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

6.1.3.1 Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesion

Partial Response (PR)

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

Progressive Disease (PD)

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

Stable Disease (SD)

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

6.1.4 Non-Target Lesions

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

6.1.4.1 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions

Incomplete Response/Stable Disease (SD)

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

Progressive Disease (PD)

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

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in

such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

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

Table 0-10: Response Criteria

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
CR	CR	No	CR	≥ 4 week Confirmation
CR	Non-CR/ Non-PD	No	PR	≥ 4 week Confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥ 4 week from baseline
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.				

Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration*".

6.2 Antitumor Effect

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

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

6.3 Evaluable for Objective Response

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

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

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

6.4 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

6.4.1 Chest X-ray

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

6.4.2 Conventional CT and MRI

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

6.4.3 Cytology, Histology

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

6.5 Primary Endpoint

Rate of progression-free survival at 3 months. Time from enrollment to progression, with progression defined as changes in RECIST 1.1 defined imaging, progression in non-target lesions as defined by RECIST 1.1, unequivocal clinical deterioration, or death from any cause. Cohort 1 and 2 analyzed separately.

6.6 Secondary Endpoints (cohorts 1 and 2 analyzed separately).

- The presence of response (ORR-CR+PR) per RECIST version 1.1
- The presence of clinical benefit (CR+PR+SD) per RECIST version 1.1
- The endpoint is to determine OS and PFS for subjects in Cohort 1 and 2 (separately) treated with combination cabozantinib and temozolomide.
- The presence of all toxicities outlined in NCI CTCAE 5.0 from time of first treatment.

7.0 REPORTING OF ADVERSE EVENTS UNANTICIPATED PROBLEMS & OTHER EVENTS OF INTEREST

The research team is responsible for classifying AEs and UPs as defined in the relevant regulations and reporting to all applicable parties, including but not limited to the COH IRB, DSMC, Food and Drug Administration (FDA), National Institutes of Health (NIH) and other collaborators, e.g., pharmaceutical companies. The research team is responsible for the continued monitoring and tracking of all AEs in order to ensure non-reportable events are reviewed and monitored and do not rise to a reporting level.

7.1 Assessment of Adverse events

The site Investigator will be responsible for determining the event name, and assessing the severity (i.e., grade), expectedness, and attribution of all adverse events as applicable per the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy (available from the DCC). Adverse events will be characterized using the descriptions and grading scales found in NCI CTCAE v5.0.

A copy of the scale can be found at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

Per the CTCAE 5.0 an Adverse Event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly NOT related to study treatment, and is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely –** The event is unlikely related to the study treatment, and is most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event may be related to study treatment, as it follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event is most likely related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is unlikely related to the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Definite –** The event is clearly related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is not reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs.

7.2 Adverse Events of Special Interest (AESI)

There are no Adverse Events of Special Interest for this study.

7.3 Routine AE Collection and Reporting Guidelines

AEs will be collected from the signing of informed consent until ending study participation. Routine AE reporting will occur via data entry into the study eCRF. AEs will be monitored by the Protocol Management Team (PMT). AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

AEs recorded in the eCRF include:

- Any Grade 1-5 AE during Cycle 1
- Highest grade AE in subsequent cycles
- All SAEs

7.4 Expedited Reporting

Table 0-11 indicates what events must be reported expeditiously.Adverse events that meet the criteria of serious OR are unanticipated problems will be reported according to the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. Reporting of SAEs will begin on or after Cycle 1 Day 1 and must be followed until the event is resolved, stabilized, or determined to be irreversible by the investigator. Follow-up SAE reports must be submitted for all events that require expedited reporting when the status of the event changes and until the resolution or stabilization of the event.

Table 0-11: Criteria for Expedited Reporting

Time point	What to report
From signing of the consent to study completion	• All UPs
For the time period beginning at treatment through 30 days following cessation of treatment	• All SAEs regardless of relationship to protocol therapy • All UPs and AEs that meet the definition of a UP • AESIs (Section 7.2)

From Day 1 of protocol therapy up to 120 days post-last dose of study therapy	• Pregnancies and lactation
Post Safety Follow-Up to removal from study	• All SAEs that are considered possibly, probably or definitely related to cabozantinib or temozolomide.
NOTE: All events reported expeditiously require follow-up reporting until the event is resolved, stabilized, or determined to be irreversible by the investigator. **The DCC should be consulted prior to ending the follow-up of events that have stabilized.**	

Expedited reporting guidelines (COH only):

Serious Adverse Events that require expedited reporting and unanticipated problems will be reported according to the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. This includes all SAEs and UPs that meet COH DSMC/IRB expedited reporting criteria that

ccurred at COH and non-COH sites. For non-COH sites, the DCC will be responsible for reporting.

Expedited reporting guidelines (Non-COH Sites):

All events that meet the criteria specified in Table 0-11will be reported to the Data Coordinating Center (DCC) and PI within 24 hours of notification that the eventmet the expedited reporting criteria.

Procedure for reporting SAEs/UPs to the COH DCC:

1. Sites are to report to their local IRB per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH DCC copies of the IRB submission and corresponding IRB response.
2. Document/describe the SAE/UP on each of the following:
    a. MedWatch 3500A or local IRB submission document*

    MedWatch 3500A: Downloadable form at http://www.fda.gov/medwatch/getforms.htm

    *The local IRB submission document may be used if the document template is approved by the DCC.

    b. Expedited Reporting Coversheet: A modifiable Microsoft Word document is available from the DCC. An electronic signature on the document will be accepted.
3. Scan and email above documents to the Study PI (magulnik@coh.org) and DCC@coh.org with the subject title as "COH IRB 20664 SAE". If available, sites may include the local IRB submission for this event in the submission.
4. If an email receipt from DCC personnel is not received within one working day, please email DCC@COH.org.

7.5 Reporting to the FDA

The study PI (or designee) will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting

of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy.

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the MedWatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA **no later than 7 calendar days** after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted **no later than 15 calendar days** after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported **as soon as** the relevant information becomes available. [21 CFR 312.32(d)(3)]

In addition, on behalf of the study PI, OIDRA will submit annually within 60 days of the anniversary of the date the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report of adverse drug experiences, and history of actions taken since the last report because of adverse drug experiences.

7.6 Reporting to Exelixis

7.6.1 SAE Reporting to Exelixis

All SAEs, regardless of attribution, and all pregnancy/lactation reports regardless of outcome must be sent to Exelixis within one (1) business day of the PI's knowledge of the event. The reports must be sent to

drugsafety@exelixis.com or fax 650-837-7392. Please ensure to include the Exelixis study number for the protocol - IST87 clearly on the Medwatch 3500A or local IRB reporting form.

The PI will perform adequate due diligence with regard to obtaining follow-up information on incomplete reports. All follow-up information must be sent to Exelixis within one (1) business day of the PI's receipt of the new information. Upon Exelixis request, the PI will query for follow-up information.

The Investigator will assess the expectedness of each related SAE. The current cabozantinib Reference Safety Information will be used as the reference document for assessing the expectedness of the event with regard to cabozantinib. All serious unexpected adverse drug reactions (unexpected related SAEs) must be reported to all appropriate regulatory authorities and Ethics Committees by the investigator as required by 21 CFR 312.32 or by Directive 2011/20/EC:

- These reports are to be filed utilizing a Medwatch 3500A or local IRB reporting Form;
- Exelixis reserves the right to upgrade the Investigator assessment of an SAE based on Exelixis assessment.
- Institutions and PIs shall promptly provide all information requested by Exelixis regarding all adverse events occurring during the conduct of the study.

7.6.2 Regulatory Reporting to Exelixis

- The PI is responsible for complying with all regulatory authority reporting requirements for the study that are applicable to the sponsor of a clinical trial. The PI shall provide a copy of all responses to regulatory agency requests, periodic reports, and final study reports to Exelixis within one (1) business day of the submission.
- Exelixis will provide relevant product safety updates and notifications, as necessary. In the case of multi-center studies, it is

the responsibility of the sponsoring PI/Institution to disseminate these updates to participating PIs.

7.7 Reporting to Participating Investigators

The study PI (or designee) will report all reportable serious adverse events to participating investigators on a MedWatch 3500A form within 30 calendar days of notification of the event. A cover letter will indicate the protocol title, the IND# and whether the FDA was informed (if applicable), whether or not a protocol and/or consent form change is required, and for non-COH sites, a statement that the report should be submitted to their local IRB for review if applicable per local IRB policy.

The study PI will also forward to participating sites all IND safety reports received from Exelixis within 30 days of notification, indicating whether a consent form or protocol change is required.

8.0 DRUG INFORMATION

8.1 Cabozantinib

8.1.1 Composition, Formulation, and Storage

At study sites, all study medication will be stored as described in the appropriate prescribing information for that country (if applicable) or the pharmacy manual and inventoried in accordance with applicable state and federal regulations.

8.1.2 Investigational Treatment: Cabozantinib

Cabozantinib tablets are supplied as film coated tablets containing cabozantinib malate equivalent to 20 mg of cabozantinib and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. Doses of 40 mg will comprise two 20-mg tablets. The components of the tablets are listed in Table 0-12.

Table 0-12: Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w[a]
Cabozantinib Drug Substance (25% drug load as free base)	Active Ingredient	31.7
Microcrystalline Cellulose	Filler	38.9
Lactose Anhydrous	Filler	19.4
Hydroxypropyl Cellulose	Binder	3.00
Croscarmellose Sodium	Disintegrant	6.00
Colloidal Silicon Dioxide	Glidant	0.30
Magnesium Stearate	Lubricant	0.75
Opadry® yellow film coating which includes: - HPMC 2910/hypromellose 6 cp - Titanium dioxide - Triacetin - Iron oxide yellow	Film Coating	4.00
[a] weight fraction, expressed in percentage; HPMC, hydroxypropyl methylcellulose		

*Refer to the Pharmacy Manual for details on storage and handling of cabozantinib

8.1.3 Availability & Supply

Cabozantinib will be provided in 60 cc HDPE white bottles containing 30 tablets each. Each bottle will be printed with a unique 7-digit bottle number and a lot number for tracking purposes. Please complete the drug order form located in the pharmacy manual. This form includes directions for ordering.

All sites will use Cabozantinib that is provided by Exelixis. Cabozantinib will be shipped directly to lead site (City of Hope) and affiliate sites by Exelixis.

8.1.4 Preparation/Dispensation/Administration

All cabozantinib should be dispensed in the original container supplied by Exelixis and should not be repackaged at any time.

8.1.5 Storage and Stability

Store at controlled room temperature (20-25 degrees Centigrade, or 68-77 degrees Fahrenheit); allowing for excursions between 15 and 30 degrees

Centigrade (59 and 86 Fahrenheit). Please contact Exelixis Clinical Supplies at Clinicalsupplies@exelixis.com immediately in case of any temperature excursions outside the accepted range. All affected IP will need to be quarantined until further notification.

8.1.6 Side Effects

Very common side effects (occurring in ≥ 10 % of subjects) of Cabozantinib are: abdominal pain, hypothyroidism, increased liver enzymes, change in voice, diarrhea, constipation, fatigue, mouth sores, hand-foot syndrome, weight loss, decreased appetite, nausea, vomiting, fatigue, oral pain, neutropenia, thrombocytopenia, taste changes, hair color changes, high blood pressure.

Common side effects (occurring in ≥ 1% but <10% of subjects) are: abnormal thickening of the skin, change in the feeling of touch (paresthesia),cough, bleeding (stomach or intestines, within the brain), blood clots in lungs or legs, confusion and disorientation, anemia, electrolyte imbalance, thrombocytopenia, dehydration, difficulty swallowing, dizziness, dry mouth, dry skin, fever, fungal infections, headache, hemorrhoids, increase in lipase and amylase, muscle spasm, pain and swelling in extremities, protein in urine, shortness of breath, upset stomach or indigestion, stomach acid, ulcer.

Uncommon (occurring in ≥0.1% but <1% of subjects: ventricular arrhythmia, QT prolongation, fistulas, abscesses, blood clot, chest discomfort, cataract, damage to the skeletal muscle tissue, encephalopathy, pancytopenia, destruction of bone tissue, anxiety, gallstones, heart attack, infections, inflammation of the intestine, appendix, gall bladder or thin tissue lining the inner wall of the abdomen, reduced kidney function, liver failure, syncope, pneumonia, rapid heart rhythm, respiratory failure, seizure, stroke, ataxia, throat swelling, temporary paralysis of the intestines.

Please refer to the current Investigator's Brochure (IB) for a complete listing of all toxicities.

8.1.7 Return and Retention of Cabozantinib

The investigator or designee will maintain accurate records of receipt of all study treatment including dates of receipt. In addition, accurate records will be kept regarding the date, lot number, and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused study treatment will be reconciled and destroyed according to applicable state, federal, and local regulations (any unused study drug will not be returned to lead site, but destroyed per local pharmacy SOPs).

8.2 Temodar/Temozolomide

Temodar contains temozolomide, an imidazotetrazine derivative. The chemical name of temozolomide is 3, 4-dihydro-3-methyl-4-oxoimidazo (5, 1-d) - as-tetrazine-8-carboxamide.

Each capsule for oral use contains either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of temozolomide.

Only during Cycle 1, temozolomide should be taken orally at 150 mg/ m^2 Days 1-5 of a 28-day cycle. Thereafter, if absolute ANC $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L, the dose should be escalated to 200 mg/m^2 Days 1-5 of a 28-day cycle.

Temozolomide is contraindicated in subjects who have a history of hypersensitivity reaction (such as urticarial, allergic reaction including anaphylaxix, toxic epidermal necrolysis, and Stevens-Johns syndrome) and subjects who have a history of hypersensitivity to dacarbazine.

8.2.1 Drug Interactions

Administration of valproic acid decreases oral clearance of temozolomide by about 5%.

8.2.2 Warnings and Precautions

- Myelosuppression (subjects treated with temozolomide may experience myelosuppression, including prolonged pancytopenia, which may result in aplastic anemia, which in some cases has resulted in a fatal outcome).
- Myelodysplastic syndrome (cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have been observed)
- Pneumocystis pneumonia (there may be a higher occurrence of PCP when temozolomide is administered during a longer dosing regimen).
- Hepatotoxicity (fatal and severe hepatotoxicity have been reported in subjects receiving temozolomide).

8.2.3 Mechanism of Action/Absorption

Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Temozolomide is rapidly and completely absorbed after oral administration with a peak plasma concentration (C_{max}) achieved in a median T_{max} of 1 hour. Food reduces the rate and extent of temozolomide absorption. About 38% of the administered temozolomide total radioactive dose is recovered over 7 days: 37.7% in urine and 0.8% in feces.

8.2.4 Side Effects

The most common adverse reactions of Temozolomide (≥ 10% incidence) are: alopecia, fatigue, nausea, vomiting, headache, constipation, anorexia, convulsions, rash, hemiparesis, diarrhea, asthenia, fever, dizziness, coordination abnormal, viral infection, amnesia, insomnia, lymphopenia, thrombocytopenia, neutropenia, and leukopenia.

Please refer to the current Package Insert for a complete listing of all toxicities.

8.2.5 Availability & Supply

Temozolomide is commercially supplied and will not be provided by the study.

9.0 CORRELATIVES/SPECIAL STUDIES

Tolaney et al. published a translational study in which they evaluated whether cytokine levels in subjects enrolled in a phase II trial of cabozantinib for metastatic triple negative breast cancer. They measured levels of several cytokines at baseline, and every 3 weeks after starting cabozantinib therapy demonstrating that high levels of baseline sMET were associated with longer PFS. Furthermore, they showed that cabozantinib treatment was associated with changes in biomarker concentrations consistent with antivascular effects. Based on their preliminary data, we propose to measure sVEGFR2, PIGF, VEGF, HGF, sMET, VEGF-C, VEGF-D and soluble AXL in blood to verify the results collected by Tolaney et al.

In particular, we will determine if there is an earlier correlation that can be detected between levels of these cytokines, and PFR, as well as OS which may allow us to better predict treatment response early on in therapy.

9.1 Sample Collection Guidelines

Mandatory whole blood samples will be collected at Cycle 1 Day 1 before starting the treatment, at C2D15 (6 weeks), C4D1 (12 weeks), and at EOT. Approximately 20 ml of anticoagulated whole blood will be collected in 2 EDTA purple top tubes at each time point. Samples should be labeled with the corresponding subject's study ID number, initials, and date of collection. See the lab manual for more details, including shipping instructions.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

For Cohort 1, this is a single arm two-stage Simon design comparing 20% vs 39% 3-months PFS rate. If 3 or fewer out of first 14 subjects Cohort 1 are progression free at 3-months the trial will stop early. Otherwise, additional 28 more subjects will be enrolled to Cohort 1 in stage 2 (total sample size 42). At the end of the study a favorable outcome will be concluded if 13 or more subjects have documented PFS at 3 months . This is based on Simon two-stage optimal design, with alpha=0.05, and beta=0.20.

Exploratory group (Cohort 2): Up to 30 subjects with unresectable or metastatic soft tissue sarcoma (non-leiomyosarcoma) will be enrolled to obtain exploratory information for subjects with these histologies. If 3 or fewer out of first 14 subjects are progression-free at 3-months the final 16 subjects will not be enrolled. Cohort 2, will have the same first stage stopping rule (3 or fewer progression-free at 3 months), but due to the heterogeneity of disease, no formal hypothesis testing is planned if accrual is continued to a total of 30 patients.

The first 14 subjects to be enrolled in the study in either cohort will serve as a safety lead in. After the first 14 subjects complete 1 cycle, investigators will review all grade 3 and 4 toxicities and confirm safety to proceed with additional subjects.

10.2 Sample Size and Accrual

Cohort 1: Minimum 14, Maximum 42.

Cohort 2: Minimum 14, Maximum 30.

Accrual is expected to take 2 years (~ 3 per month across multiple centers).

10.3 Data Analyses Plans

PFS and OS will be estimated using Kaplan-Meier methods for Cohort I and II. The percent progression-free at 3 months will be summarized in terms of these point estimates, along with a 95% confidence interval. Toxicities will be tabulated and summarized by the number of subjects experiencing each toxicity.

No formal hypothesis test is planned for Cohort 2.

The first 14 subjects will serve as a safety lead in and will be compromised of subjects that enroll in both Cohort 1 and Cohort 2. During the safety lead-in, any grade 5 possibly related event in this first 3 months will hold accrual pending review by the DSMC/IRB. In addition, if 2 of the first 6, or subsequently more than 30% have to stop therapy in the first cycle, the study will be put on hold pending review by the DSMC/IRB. The DSMC will also receive a report after the 14th subject is enrolled and treated for at least one cycle, to review drug-related AEs and ensure the safety to continue enrollment.

11.0 PARTICIPANT ENROLLMENT

NOTE: Sites must meet activation requirements prior to enrolling participants.

11.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained.

The informed consent process is to be fully documented (see Section 15.4), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in Section 5.0 (Study Calendar).

11.2 COH DCC Availability and Contact Information

Eligible participants will be registered on the study centrally by the Data Coordinating Center (DCC) at City of Hope.

DCC staff are available **between the hours of 8.00 am and 5.00 pm PST, Monday through Friday (except holidays)**.

- E-mail: DCC@coh.org

11.3 Slot verification and reservation

A designated study team member should email the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject (provide DCC

with subject initials), including a tentative treatment date. Slots can only be held for a limited time, at the discretion of the study PI.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

11.4 Registration Process

Allow up to 24 hours for the DCC to review eligibility. To register a participant the subsequent procedure is to be followed:

1. The study team should contact the DCC via email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The study team will email a **Complete Registration Packet** to the DCC, which consists of a copy of the following documents:
    - Registration Cover Sheet (Appendix F)
    - Completed eligibility checklist (printed from Section 3.0 of the protocol) with required signature(s)
    - Signed Informed Consent
    - Signed HIPAA authorization form (if separate from informed consent)
    - Signed subject's bill of Rights (California only)
3. In some cases, the DCC may request additional documentation prior to registration. Please refere to the Work Instructon – Reviewing Registration Packets and Registering Subjects for more information. A copy of this work instruction can be provided by the DCC, upon request.
4. When all source documents are received, the DCC will review and work with the study team to resolve any missing elements. Any missing documents may delay registration. A participant failing to meet all requirements will not be registered and the study team will be immediately notified.

5. The DCC will send a Confirmation of Registration Form,including the Subject Study Number and cohort assignment to:
    - The study team: Site Lead Investigator, treating physician/ sub-investigator, protocol nurse, CRC and pharmacy (as needed).
    - The COH Study PI and COH study team designees (including but not limited to study monitor(s) and statistician(s)).
6. Upon receipt of the Confirmation of Registration Form, COH study team will register the patient in OnCore. The DCC will register non-COH patients in OnCore.

11.5 Screen Failures and Registered Participants Who Do Not begin Study Treatment

Notify the DCC immediately if the participant screen fails after registration or if the participant does not start treatment.

For non-COH sites, the reason for screen failure will be documented in the registration coversheet (Appendix F) and submitted to the DCC.

Issues that would cause treatment delays should be discussed with the Study Principal Investigator.

12.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

12.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

12.2 Data Capture Methods and Management

Data for this trial will be collected using City of Hope's electronic capture system (EDC) that is compliant with 21 CFR Part 11.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

12.3 Case Report Forms/Data Submission Schedule

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated in Section 12.2, and will be submitted according to the timelines indicated in Table 0-14.

Table 0-14 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 10 calendar days of treatment administration
Adverse Event Report Forms	Within 10 calendar days of AE assessment/notification
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms	Within 10 calendar days of the assessment

	Form	Submission Timeline
	(concomitant medications)	
	Off Treatment/Off Study Forms	Within 10 calendar days of end of treatment/study
	Follow up/Survival Forms	Within 14 calendar days of the follow up activity

12.4 Regulatory Records

The Investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

13.0 ADHERENCE TO THE PROTOCOL & REPORTING OF PROTOCOL DEVIATIONS

Deviations from the protocol should be avoided, except when necessary to eliminate immediate hazard(s) for the protection, safety, and well-being of a research participant. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. All protocol deviations and planned protocol deviations will be reported in accordance with the Clinical Research Protocol Deviation policy.

Reporting by non-COH Sites:

Deviations meeting the criteria specified in the City of Hope Clinical Research Protocol Deviation policy (available from the DCC) will be reported to the Data Coordinating Center (DCC) and PI within **24 hours** of notification that the event occurred.

Procedure for reporting deviations to the COH DCC:

1. Document the deviation on the Deviation Reporting Coversheet or submit your site-specific protocol deviation log if the log format has been approved for use by the DCC. This modifiable Microsoft Word document is available from the DCC. An electronic signature on this document will be accepted.
2. Scan and email the Deviation Reporting Coversheet or deviation log to the Study PI (magulnik@coh.org) and DCC@coh.org **within 24 hours** of notification of the

deviation with the email subject title of "COH IRB 20664 Deviation". If an email receipt from the DCC is not received within one working day, please email DCC@coh.org.

3. Sites are to report to their local IRB and DSMC per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH DCC copies of the IRB and/or DSMC submission and corresponding response(s).

14.0 STUDY OVERSIGHT, QUALITY ASSURANCE, & DATA AND SAFETY MONITORING

14.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

14.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities are executed in accordance with federal regulations.

14.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, collaborating investigators, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) to review study status. The meeting is a forum to discuss study related issues including accrual, SAE/AE/UPs experienced, study response, deviations/violations, and study management issues. The appropriateness of further subject enrollment and the

specific intervention for subsequent subject enrollment are addressed. Monitoring/ Auditing

14.4 Quality Assurance

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the City of Hope Office of Clinical Trials Monitoring (OCTM), within City of Hope's Office for Safety and Data Quality.

Details of clinical site monitoring are documented in the OCTM SOP and the Risk Based Monitoring (RBM) plan. These documents specifiy the frequency of monitoring, monitoring procedures, the amount of subject data to be reviewed, and the distribution of monitoring reports to the study team and the COH DSMC.

14.5 Risk Determination

This is a high risk study, as defined in the City of Hope Institutional DSMP. This determination was made because the study involves a COH IND.

14.6 City of Hope Data and Safety Monitoring Committee

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor study progress, compliance, toxicity, safety, and accrual data from this trial via the PMT Progress Report (submitted by the Study Principal Investigator according to the frequency outlined in the City of Hope Institutional DSMP). The DSMC is composed of clinical specialists who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Protocol Management Team.

15.0 ETHICAL AND REGULATORY

15.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

15.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable institutional research policies and procedures

15.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any

additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

Each participating non-COH institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate IRB holding a current US Federal wide Assurance issued by and registered with the Office for Human Research Protections (OHRP). The protocol and consent will be reviewed and approved by the COH IRB before submission to a participating site IRB.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator, and, for external sites, the possession of the DCC, before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

15.4 Informed Consent

Each participating non-COH institution will be provided with a model informed consent form. Each institution may revise or add information to comply with local and/or institutional requirements, but may not remove procedural or risk content from the model consent form. Furthermore, prior to submission to the site's IRB (initial submission and amendments), the consent and accompanying HIPAA form, if separate to the consent, must be reviewed and approved by the DCC.

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights if applicable, and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or participating institution or any relationship they have with City of Hope. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

15.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies. The COH DCC should be promptly notified of the change in participant status.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and survival follow-up.

- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

15.6 Special and Vulnerable Populations

15.6.1 Women and Minorities

The study is open to anyone regardless of gender, race or ethnicity. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded because it is not known what effects the study drugs have on human pregnancy or development of the embryo or fetus.

15.6.2 Pediatric Population

Pediatric participants (< 18 years of age) are excluded from this study because safety and effectiveness of protocol therapy has not yet been defined for the study population. Additional studies may be performed in the pediatric population once safety and effectiveness of protocol therapy is defined in the adult study population.

15.6.3 HIV Positive Individuals

Participants with HIV are excluded due to concerns about inadvertent augmentation of infectious and/or inflammatory activity.

15.6.4 Vulnerable Populations

Per 45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, and economically or educationally disadvantaged persons as vulnerable populations.

Adults lacking capacity to consent are not excluded from participation. This study does not pose additional risks for adults lacking capacity than for the general population. In such instances, informed consent will be sought and documented from the prospective participant's legally authorized representative in agreement with institutional policies and local IRB approval.

Economically/educationally disadvantaged persons are not actively targeted for participation, nor are they excluded from participation. This study does not pose additional risks for economically/educationally disadvantaged persons than for the general population.

15.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, and the rights of a research participant to revoke their authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR

164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

Source documents provided to the DCC for the purpose of auditing or monitoring will be de-identified and labeled with the study number, subject ID, and if applicable patient initials.

The Investigator/Institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant specimens will be de-identified (coded) prior to submission to research laboratories. The specimens will be labeled with the study number, subject (accession) ID, date and time point of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

15.8 Use of Unused (Leftover) Specimens Collected for this Trial

Unused samples in existence at study completion (i.e. completion of all research activities under this study) will be discarded.

15.9 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

15.10 Financial Obligations, Compensation, and Reimbursement of Participants

Cabozantenib will be provided free of charge to participants.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

Standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the participant were not in a research study.

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope or at the non-COH site to the injured participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

15.11 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of

performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement between City of Hope and Exelixis, and participating non-COH institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov. Results will be reported on ClinicalTrials.gov generally within 12 months after the completion date unless criteria to delay submission are met per the final rule.

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APPENDIX A - DOSE MODIFICATION ALGORITHMS FOR POTENTIAL COMBINATION TREATMENT RELATED ADVERSE EVENTS

AE Terms & Descriptions	Dose Modification Algorithms
Diarrhea	
a. Grade 1-2 (duration < 48 hr)	a. Continue Cabozantinib at the current dose. If it does not improve with supportive measures consider a dose reduction. Continue temozolomide at the current dose.
b. Intolerable Grade 2 or Grade 3	b. Interrupt Cabozantinib and temozolomide until Grade ≤1 then consider restarting Cabozantinib at reduced dose. Dose reduce temozolomide by one dose level for Grade 3 only. Discontinue temozolomide for grade 4. c. Refer to the Table 0-3 for the management of diarrhea.
Neutropenia	
a. Neutrophil count <1.5 b. Neutrophil count <1.0 c. Neutrophil count <0.5	a. Interrupt temozolomide and cabozantinib until neutrophil count $\geq 1.5 \times 10^9$/L. b. Interrupt temozolomide and cabozanitinib until $\geq 1.5 \times 10^9$/L. Reduce temozolomide by 1 dose level. Continue cabozantinib at the same. c. Discontinue temozolomide, interrupt cabozantinib until neutrophil count is $\geq 1.5 \times 10^9$/L then resume at same dose.
Febrile Neutropenia	
Grade 3 or 4	Interrupt temozolomide and cabozantinib until resolved. Upon resumption, reduce temozolomide by 1 dose level. Continue cabozantinib at the same dose.
Thrombocytopenia	
Grade 1 or 2	Interrupt temozolomide until $\geq 100 \times 10^9$/L. Continue cabozantinib.
Grade 3 or 4	Interrupt temozolomide and cabozantinib until $\geq 100 \times 10^9$/L. Dose reduce temozolomide by 1 dose level. Continue cabozantinib at the same dose or reduce dose by one level-at the investigator's discretion. At platelet count of $< 10 \times 10^9$/L discontinue temozolomide.

Hypertension	
> 140 mm Hg (systolic)[a] and < 160 mm Hg OR > 90 mm Hg (diastolic) and < 110 mm Hg	• Optimize antihypertensive therapy. Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP <140 mm Hg systolic or <90 mm Hg diastolic. • Continue temozolomide at the current dose
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce cabozantinib by one dose level or interrupt cabozantinib treatment per investigator discretion. • Re-start cabozantinib treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 140 mm Hg systolic and < 90 mm Hg diastolic. Interrupt/continue temozolomide at the investigator's discretion.
Hypertensive emergency[a]	• Discontinue cabozantinib treatment
[a] Hypertensive emergency is defined as uncontrolled elevated BP with clinical evidence of progressive or impending end-organ damage (e.g. myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage).	
Hand-foot Syndrome (PPES)	
Grade 1	• Cabozantinib treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. • Otherwise, cabozantinib should be reduced to the next lower dose level. • [a] Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPES worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2. • Continue temozolomide at the current dose.

Grade 2	• Cabozantinib treatment may be continued if PPES is tolerated. • Cabozantinib should be dose reduced or interrupted if PPES is intolerable. • Continue urea 20% cream twice daily AND high potency steroid cream (e.g., clobetasol 0.05%) once daily and add analgesics (e.g., NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPES worsens or affects self-care, proceed to the intervention guidelines for Grade 3. • Continue temozolomide at the investigator's discretion
Grade 3	• Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. • Continue treatment of skin reaction with high potency steroid cream (e.g., clobetasol 0.05%) twice daily AND analgesics. • Resume study drug at a reduced dose if PPES recovers to Grade ≤ 1. • Discontinue subject from study treatment if PPES does not improve within 6 weeks • Interrupt/continue temozolomide at the investigator's discretion
Proteinuria (UPCR)	
≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in cabozantinib or temozolomide treatment
> 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol)	• Refer to Table 0-6 for the management of cabozantinib treatment. No change in temozolomide treatment
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• Refer to Table 0-6 for the management of cabozantinib treatment. No change in temozolomide treatment.
Nephrotic syndrome	• Discontinue cabozantinib
Hepatocellular Toxicity	
Grade 2 AST or ALT or Total Bili lasting longer than a week	• Interrupt cabozantinib and temozolomide until Grade 1. • Refer to the Section 4.4.3.13 for the management of DILI
Other Treatment Related Adverse Events (such as fatigue, nausea, vomiting, anorexia, weight loss, etc)	

Grade 1 or Grade 2 (tolerable)	• Add supportive care as indicated. • Continue cabozantinib and temozolomide treatment at the current dose; monitor as clinically indicated
Intolerable Grade 2 or Grade 3	• Interrupt cabozantinib and temozolomide treatment until it is a Grade 1 or tolerable grade 2. Restart both cabozantinib and temozolomide at the current dose or dose reduced by one level.[b] For Grade 3 AEs related to Temozolomide dose reduce by one level. • *Note: It is recommended that dose holds be as brief as possible
Grade 4-related to temozolomide Grade 4-related to cabozantinib (except clinically non-relevant laboratory abnormalities)	• Discontinue temozolomide. • Subjects should have cabozantinib interrupted immediately. • Discontinue cabozantinib unless the following criteria are met: Subject is deriving clear clinical benefit as determined by the investigator Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care
Study treatment dose adjustment is only needed if the toxicity was deemed related to cabozantinib treatment or had an unclear relationship to cabozantinib treatment. [b] except nausea, vomiting, and alopecia- no dose interruption required for temozolomide	

APPENDIX B- DAILY DOSE CALCULATIONS BY BODY SURFACE AREA BSA

Total BSA (m^2)	200 mg/m^2 (mg daily)	150 mg/m^2 (mg daily)
1.0	200	150
1.1	220	165
1.2	240	180
1.3	260	195
1.4	280	210
1.5	300	225
1.6	320	240
1.7	340	255
1.8	360	270
1.9	380	285
2.0	400	300
2.1	420	315
2.2	440	330
2.3	460	345
2.4	480	360
2.5	500	375

APPENDIX C – DRUG INTERACTION TABLES

Please refer to the drug interaction tables at the following websites for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

Http://medicine.iupui.edu/clinpharm/ddis/table.aspx

3.0 HTTPS://WWW.FDA.GOV/DRUGS/DRUG-INTERACTIONS-LABELING/DRUG-DEVELOPMENT-AND-DRUG-INTERACTIONS-TABLE-SUBSTRATES-INHIBITORS-AND-INDUCERS

APPENDIX D – LABORATORY PANELS

Laboratory panels are composed of the following:

Hematology		
• WBC count with differential (including at minimum: neutrophils, basophils, eosinophils, lymphocytes, monocytes)	• hematocrit • platelet count • RBC count • hemoglobin	
Serum chemistry		
• albumin • ALP • amylase • ALT • AST • bicarbonate • BUN • chloride	• creatinine • GGT • Glucose • calcium • lactate dehydrogenase • lipase	• magnesium • phosphorus • potassium • sodium • total bilirubin • total protein
Urinalysis		
• appearance • color • pH • specific gravity • ketones • protein • UPCR	• glucose • bilirubin • nitrite • creatinine • urobilinogen	• occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)
Other		
• TSH (FT3, FT4) • Pregnancy text (urine or serum) for women of child-bearing potential		• PT/INR or PTT • 24 hour urine collection for protein

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate ; GGT, γ-glutamyltransferase; INR, International Normalized Ratio; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; TSH, thyroid stimulating hormone; UPCR, urine protein/creatinine ratio; WBC, white blood cell.

APPENDIX E - ECOG PERFORMANCE STATUS

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

APPENDIX F – REGISTRATION COVERSHEET

COH IRB# 20664 A Phase II Study of Cabozantinib and Temozolomide in Patients with Unresectable or Metastatic Leiomyosarcoma and Other Soft Tissue Sarcomas

Data Coordinating Center:
City of Hope
1500 Duarte Road
Duarte, CA 91010
Tel: (626)-218-7904
Email: DCC@coh.org (use #secure# in subject line)

Site Principal Investigator
Name:

CRA/Study Coordinator:	Contact Number:
Patient's Initials: (F M L):	Institution: PI/ Sub-Investigator:
Patient's DOB:	IRB approval valid until (date):
Sex: _____Male _____Female	Date Informed Consent Signed: Projected start date of treatment:

Race		Ethnicity	
☐	Black	☐	Hispanic
☐	Caucasian	☐	Non-Hispanic
☐	Asian	☐	Other_____
☐	American Indian		
☐	Native Hawaiian/Pacific Islander		
☐	Other_____		

Method of Payment:_____

Codes:

01 Private	**06** Military or Veterans Adm. sponsored
02 Medicare	**07** Self-pay (no insurance)
03 Medicare & private ins.	**08** No means of payment (no insurance)
04 Medicaid	**09** Unknown
05 Medicaid & Medicare	

Reason for Screen Failure:

Reason for Failing to Initiate Protocol Therapy: