NRG ONCOLOGY

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This amendment is being submitted in response to a Request for Rapid Amendment for XL184 (Cabozantinib s-malate, NSC 761968) from Dr. John Wright

SUMMARY OF CHANGES

For Protocol Amendment #3

NCI Protocol #: NRG-GY001

Local Protocol #: NRG-GY001

NCI Version Date: February 17, 2017
Protocol Date: February 17, 2017

#	Section	Page(s)	Comments
1.	Title Page	1	**NCI Version date has been updated.** **Document History has been updated.** **Revised has been added to the footer.**
3.	9.1.13	54-58	**CAEPR for Cabozantinib has been updated.**

NRG ONCOLOGY

NRG-GY001
(ClinicalTrials.gov NCT #02315430)

TITLE

A Phase II Trial of Cabozantinib (XL-184) (NSC #761968) in Women with Recurrent, Clear Cell Carcinoma of the Ovary, Fallopian Tube, or Peritoneum
NCI Version Date: February 17, 2017

Lead Organization: NRG / NRG Oncology

Participating Organizations
ALLIANCE / Alliance for Clinical Trials in Oncology
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
SWOG / SWOG

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Protocol Agent

Agent	Supply	NSC #	IND #	IND Sponsor
Cabozantinib	DCTD/CTEP	761968	116059	DCTD, NCI

Participating Sites
☒ U.S.
☐ Canada
☐ Approved International Member Sites

Document History

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Amendment 3	February 17, 2017	
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NRG ONCOLOGY

NRG-GY001

TITLE

A Phase II Trial of Cabozantinib (XL-184) (NSC #761968) in Women with Recurrent Clear Cell Carcinoma of the Ovary, Fallopian Tube, or Peritoneum

NCI Version Date: February 17, 2017

CONTACT INFORMATION		
To submit site registration documents:	**For patient enrollments:**	**Submit study data**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
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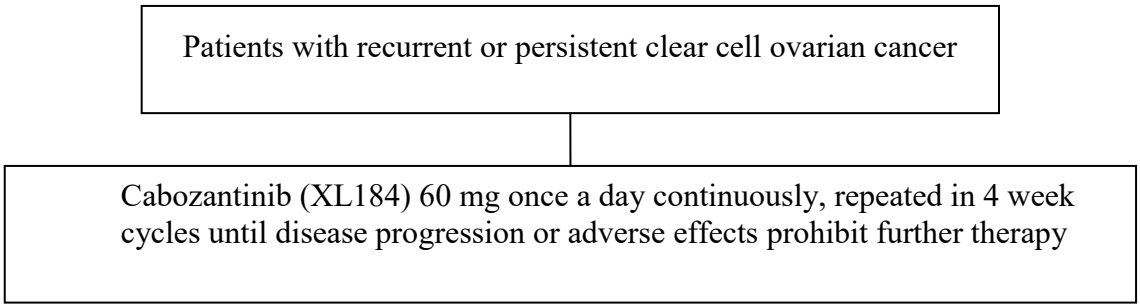
SCHEMA



1. OBJECTIVES

1.1 Primary Objective

To evaluate the anti-tumor activity of cabozantinib (XL184) in women with persistent or recurrent clear cell ovarian cancer, based on the proportion of patients who survive progression-free for at least 6 months and the proportion who have objective tumor response (complete or partial)**.**

1.2 Secondary Objectives

1.2.1 To determine the nature, frequency and maximum degree of toxicity as assessed by CTCAE v4 for cabozantinib (XL184)

1.2.2 To determine the PFS and OS for patients with persistent or recurrent clear cell ovarian cancer treated with cabozantinib (XL184)

1.3 Translational Science Objectives

1.3.1 To examine the expression of PTEN, pAKT, cyclin E, and MET in formalin-fixed, paraffin-embedded tumor.

1.3.2 To examine MET amplification (fluorescence *in situ* hybridization) in tumor specimens and the relationship to response.

2. BACKGROUND

2.1 Clinical Research Background

Ovarian cancer is the most lethal gynecologic malignancy (Siegel, 2012) In 2014 we could expect 21,980 cases of ovarian cancer and 14,270 deaths. Standard therapy for ovarian cancer includes surgical debulking of any primary tumor followed by adjuvant chemotherapy with carboplatin and paclitaxel when needed. Patients with advanced stage disease have a 5-year survival of only 29% (Siegel, 2012), (Christensen, 2005) Epithelial ovarian cancer is considered a chemoresponsive tumor with response rates of 80% to standard therapy of platinum and a taxane (Siegel, 2012), (Bhoola, 2006), (Cannistra, 2004), (Piccart, 2003), (Tummala, 2005) Unfortunately most patients develop recurrent disease, chemoresistant disease and the patients are essentially incurable. In the United States, ovarian clear cell carcinoma (OCCC) accounts for approximately 4-9.5% of ovarian tumors, whereas in Japan, the rate is upwards of 15-25%.

Age, performance status, tumor histology, and residual disease volume have been found to be statistically significant prognostic factors for advanced stage epithelial ovarian cancer in multivariate analyses (Winter, 2007) Clear-cell histology has been generally accepted as an unfavorable histology. Clear-cell epithelial ovarian carcinomas are associated with a worse PFS and OS when compared with serous histology. In a study of similarly treated advanced epithelial ovarian cancer patients clear cell tumors had a decreased median OS of 24 months compared to 45 and 56 months for serous and endometrioid histologies, respectively.

Expression profiling of epithelial ovarian cancer of varying histologies has afforded the elucidation of genes which contribute to the biological and clinical features seen in the four major histological types of ovarian carcinoma (Bonome, 2008), (Zorn, 2005) When clear cell ovarian cancer was compared with non–clear cell ovarian cancer (serous and endometrioid ovarian cancer grouped together), 171 differentially expressed genes were identified (Bonome, 2008) For clear cell tumors in general; there is a small set of differentially expressed genes common to tumors from all organs, ovary, endometrium and kidney. These genes include TFPI2 (tissue factor pathway inhibitor), ANXA4 (Annexin), UGT1A1 (UDP glycosyltransferase1family, polypeptideA1), FXYD2 (FXYD domain containing ion transport regulator 2), GLRX (Glutaredoxin), KIAA1922 (KIAA1922 protein), MAP3K5 (Mitogen-activated protein kinase kinase kinase 5), CXADR (Coxsackie virus and adenovirus receptor), and RFX5 (Regulatory factor X, 5). (Zorn, 2005) This over expression of certain types of genes in the clear cell histotype provides insights into their disproportionately poor prognosis relative to other types of ovarian cancer. Two of these genes have intriguing associations with chemotherapy response: ANXA4 has been associated with paclitaxel resistance, whereas UGT1A1 detoxifies the active metabolite of irinotecan (Pal, 2012), (Gibney, 2013) The sum total clinical and biological effect of these genes is to increase anti-apoptotic signals (ASK1/GLRX), inhibit cellular proliferation (TFP12), and increase resistance to chemotherapeutic agents (ANXA4 and UGT1A1), which is consistent with the slow

growth and relative chemoresistance of clear cell tumors.

MET. MET has a number of purported roles in the pathogenesis of RCC. Over a decade ago, germ line and somatic mutations were identified in the tyrosine kinase domain of MET in patients with papillary RCC [8]. MET plays a critical role in clear cell RCC. Inactivation of VHL may actually cause constitutive activation of the moiety, and VHL null RCC cell lines appear to be exquisitely sensitive to MET shRNA. (Zorn, 2005) c-Met protein expression was determined by automated quantitative analysis (AQUA) on a Tissue microarray (TMA) data incorporating 330 unique RCC specimens c-Met expression and selective inhibition with SU11274 and ARQ 197 were also studied in clear cell RCC cell lines. (Pal, 2012) Higher c-Met expression was detected in all RCC subtypes than in the adjacent normal renal tissue ($P < 0.0001$). Expression was highest in papillary and sarcomatoid subtypes, and high-grade and stage tumors. Higher c-Met expression correlated with worse disease-specific survival [risk ratio = 1.36; 95% confidence interval (CI) 1.08-1.74; $P = 0.0091$] and was an independent predictor of survival, maintained in clear cell subset analyses. c-Met protein was activated in all cell lines, and proliferation (and colony formation) was blocked by SU11274 and ARQ 197. They concluded that c-Met is associated with poor pathologic features and prognosis in RCC. Additionally, c-Met inhibition demonstrates in vitro activity against clear cell RCC.

Deregulation of the c-Met-HGF/SF (hepatocyte growth factor/scatter factor) signaling axis has been identified as a contributing factor to tumorigenesis and tumor progression in numerous cancers. (Zillhardt, 2011) This pathway has also been shown to show a critical role in the pathogenesis of ovarian cancer (Gibney, 2013), (Zillhardt, 2011). An examination of approximately 170 candidate genes/regions in a multistage analysis based initially on 312 Mayo Clinic ovarian cancer cases revealed the strongest initial mortality association was associated with HGF (hepatocyte growth factor). (Zillhardt, 2011) Analysis of TCGA data revealed consistent findings and suggested a potential genotype correlation with reduced HGF mRNA levels. In analysis of the Mayo Clinic TMAs, protein levels of phospho-MET were associated with reduced mortality. They concluded that although HGF signaling is critical to migration, invasion, and apoptosis, it is unlikely that HGF genetic variation plays a major role in ovarian cancer mortality.

Perturbation of the c-Met-HGF/SF pathway in ovarian cancer carcinogenesis has been demonstrated in the laboratory. Evaluation of a multikinase inhibitor of c-Met and vascular endothelial growth factor receptor-2 (foretinib, GSK1363089) was performed in a genetic mouse model. In the genetic mouse model, treatment with foretinib prevented the progression of primary ovarian tumors to invasive adenocarcinoma. (Gibney, 2013) Invasion through the basement membrane was completely blocked in treated mice, whereas in control mice, invasive tumors entirely replaced the normal ovary. In two xenograft mouse models using human ovarian cancer cell lines, the inhibitor reduced overall tumor burden. The mechanism of inhibition by foretinib involved (a) inhibition of c-Met activation and downstream signaling, (b) reduction of ovarian cancer cell adhesion, (c) a block in migration and invasion, (d) reduced proliferation mediated by a G2–M cell-cycle arrest, and (e) induction of anoikis. (Gibney, 2013) This study shows that a multikinase inhibitor of c-Met and VEGF-2 blocks tumorigenesis and reduces invasive tumor growth in different models of ovarian cancer by affecting several critical tumor

functions. These observations provide a rationale for the further clinical development of c-Met inhibitors for the treatment of ovarian cancer.

An additional study demonstrated that, among ovarian carcinomas, amplification of the MET gene and overexpression of MET specifically and commonly occur in clear-cell adenocarcinoma histology[12,1314]. Low-level (≥3 MET copies in ≥10% and ≥4 MET copies in 10-40% of tumor cells) gain of MET was detected in 4 (40%) of the 10 atypical endometrioses and 1 of the 2 borderline CCAFs. Moreover, high-level (≥4 MET copies in ≥40% of tumor cells) gain of MET were detected in five (50%) of the atypical endometrioses. In 4 (31%) of the 13 cases enrolled, intratumoral heterogeneity for MET gain was documented in invasive carcinoma components, wherein all the relatively differentiated carcinoma components showed low-level gain of MET and all the corresponding poorly differentiated carcinomas showed high-level gain. The overall incidence of MET overexpression gradually increased from the ovarian clear cell carcinoma precursors of non-atypical form (0%), through those of atypical form (67%) and the relatively differentiated carcinoma components (92%), to the poorly differentiated carcinoma components (100%). These results suggest that accumulative MET gene copy number alterations causing MET overexpression are associated with higher tumor grade ovarian clear cell carcinomas and might drive the development and progression of the MET amplification-positive ovarian clear-cell adenocarcinoma. (Goode, 2011), (Yamamoto, 2012) Also, in patients with early stage (stage I and 2) clear cell ovarian cancer, Met gene amplification is associated with worse survival (Yamashita et al. PLoS One. 2013; 8(3):e57724). Overexpression of the IL6-STAT3-HIF pathway commonly occurs in ovarian clear cell cancer and this pathway is known to activate MET promoter which contains hypoxia inducible factor-1 (HIF-1) binding sites and thus upregulate MET expression (Anglesio, 2011) (Anglesio et al. Clin Cancer Res. 2011 Apr 15; 17(8):2538-48). IL6 levels are also elevated in women with endometriosis. Therefore deregulation of IL6 expression seems to be an early event in the development of ovarian clear cell carcinoma. IL6 signals via STAT3 and activates expression of downstream genes including PTHLH and HIF1A. Strong expression of activated pSTAT3 in tumors and cell lines and nuclear HIF1A in TMA, were observed and consistent with autocrine activation of the pathway. Finally, in a phase II randomized discontinuation trial of cabozantinib in advanced ovarian cancer patients, there were 3 patients with clear cell ovarian cancer: one had a RECIST PR, one had a close to-PR response and the third had stable disease with decrease in her CA125 level (Buckanovich et al. ASCO 2011 meeting, J Clin Oncol 29: 2011 (suppl; abstr 5008). **Cabozantinib (NSC# 761968). Cabozantinib (NSC# 761968)**, is an orally bioavailable inhibitor of multiple receptor tyrosine kinases (RTKs) including c-Met and vascular endothelial growth factor receptor 2 (VEGFR2).

Mechanism of Action

Cabozantinib is a potent inhibitor of MET and VEGFR2. Cabozantinib strongly inhibited several kinases that have also been implicated in tumor pathobiology, including KIT, RET, AXL, TIE2, and FLT3. Cabozantinib did not potently inhibit kinases such as RON, EGFR, IGFR1, and EphA4/B4. In cellular assays, cabozantinib inhibited phosphorylation of MET and VEGFR2, as well as KIT, FLT3, and AXL. (Yakes, 2011)

The dual VEGFR2/MET targeting agent, cabozantinib, has recently shown unprecedented activity in the setting of metastatic castration resistant prostate cancer (mCRPC), causing regression of metastases visualized on bone scan in 56 of 65 evaluable patients (86%) enrolled in a randomized, phase II study. (Smith, 2013) Patients received 100 mg of cabozantinib daily. One hundred seventy-one men with CRPC were enrolled. Random assignment was halted early based on the observed activity of Cabozantinib. Seventy-two percent of patients had regression in soft tissue lesions, whereas 68% of evaluable patients had improvement on bone scan, including complete resolution in 12%. The objective response rate at 12 weeks was 5%, with stable disease in 75% of patients. Thirty-one patients with stable disease at week 12 were randomly assigned. Median PFS was 23.9 weeks (95% CI, 10.7 to 62.4 weeks) with Cabozantinib and 5.9 weeks (95% CI, 5.4 to 6.6 weeks) with placebo (hazard ratio, 0.12; P < .001). Cabozantinib had clinical activity in men with CRPC, including reduction of soft tissue lesions, improvement in PFS, resolution of bone scans, and reductions in bone turnover markers, pain, and narcotic use (Zorn, 2005), (Smith, 2013), (Vaishampayan, 2013) Early experiences with cabozantinib also indicate substantial activity in ovarian cancer and medullary thyroid carcinoma (Vaishampayan, 2013), (Kurzrock, 2011)_ENREF_29. Given these promising preliminary results, the further development plan for cabozantinib in OCCC is eagerly anticipated.

2.2 Cabozantinib (XL184)

Cabozantinib inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumor growth, metastasis, and angiogenesis (Investigator's Brochure, 2011). The primary targets of cabozantinib are MET (c-MET) and vascular endothelial growth factor receptor 2 (VEGFR2); additional targets include RET, AXL, KIT, and TIE-2. Both c-Met and VEGFR2 are important mediators of tumor growth and tumor angiogenesis, and *in vivo* pharmacodynamic activity of Cabozantinib against c-Met and VEGFR2 has been demonstrated in both preclinical and clinical studies.

RTKs regulate many processes including cell growth and survival, organ morphogenesis, neovascularization, and tissue repair (Christensen, 2005) Dysregulation of RTKs by mutation, gene rearrangement, gene amplification, and overexpression of both receptor and ligand have been implicated as causative factors in the development and progression of numerous human cancers.

The RTK c-Met, encodes the high-affinity receptor for hepatocyte growth factor (HGF) or scatter factor (SF) (Christensen, 2005) c-Met and HGF are each required for normal mammalian development and have been shown to be important in cell migration, morphogenic differentiation, and organization of three-dimensional tubular structures (*e.g.*, renal tubular cells, gland formation, *etc.*), as well as cell growth, angiogenesis, and tumor invasiveness and metastasis. Upregulation of MET is found in a wide range of malignancies including thyroid, prostate, ovarian, lung, and breast cancers, and is associated with more aggressive and invasive phenotypes of cancer cells *in vitro* and metastases *in vivo* (Investigator's Brochure, 2011). c-Met-driven metastasis may be exacerbated by a number of factors, including tumor hypoxia caused by selective

inhibition of the VEGF pathway.

Evidence linking c-Met and HGF as causative or progression factors in human cancers include: (1) the overexpression of both receptor and ligand in neoplasms relative to surrounding tissues; (2) the correlation of receptor and ligand overexpression with disease severity and outcome; (3) genetic alteration of c-Met by mutation of gene amplification in multiple cancer types; (4) introduction of c-Met and HGF (or mutant c-Met) into cell lines, conferred the properties of tumorgenicity and metastatic propensity on engineered cells; (5) introduction of c-Met or HGF as transgenes into the germline of mice resulted in primary and secondary neoplasms; and (6) the inhibition of c-Met or HGF function with dominant-negative receptors, antibody antagonists (both Met and HGF), and biologic antagonists (*e.g.*, NK4) have reversed cancer-associated phenotypes such as motility, invasion and proliferation of tumor cells, and tumor growth and dissemination *in vivo* (Christensen, 2005).

A wide variety of human cancers, including brain, colorectal, gastric, and lung, demonstrate dysregulated c-Met activity (Liu, 2010), either by means of c-Met kinase overexpression (Comoglio, 2008), activating c-Met gene mutations and/or amplification (Comoglio, 2008), (Jeffers, 1997), (Schmidt, 1997), or increased autocrine and/or paracrine secretion of the c-Met ligand, HGF/SF (Birchmeier, 2003), (Bocaccio, 2006). These alterations have been implicated in tumor progression and metastasis, and a high constitutive activation of c-Met has been correlated with poor clinical prognosis (Birchmeier, 2003).

VEGFR2 is the predominant mediator of VEGF-stimulated endothelial cell migration, proliferation, survival, and enhanced vascular permeability (Kurzrock, 2011). Increased expression of VEGFR2, often in combination with VEGFR3, has been observed in the tumor vascular endothelium in most common human solid tumor types, on tumor cells in melanoma and hematological malignancies, and in colitis-associated colon cancer (Tugues, 2011). High VEGFR2 expression is an unfavorable prognostic biomarker in hepatocellular carcinoma (HCC), and correlated with triple-negative (*i.e.*, therapy-resistant) breast cancer and poor survival.

Nonclinical Development of Cabozantinib

In Vivo Activity

Inhibition of VEGF signaling pathway was previously shown to result in more invasive tumors in the transgenic RIP-Tag2 mouse model of pancreatic neuroendocrine cancer that spontaneously develops aggressive tumors (Paez-Ribes, 2009). In RIP-Tag2 transgenic mice, tumors treated with cabozantinib were smaller (P <0.05) than in mice treated with vehicle or an anti-VEGF antibody, but were also less invasive (P <0.05) and had no liver metastases (Sennino, 2009). All mice treated with cabozantinib (n = 6) survived until 20 weeks, but none treated with vehicle (n = 14) or anti-VEGF antibody (n = 8) reached that endpoint. Tumor vascularity decreased after treatment, with reductions ranging from 67% at 3 mg/kg to 83% at 30 mg/kg for 7 days (You, 2011). Tumors were 35% smaller after cabozantinib treatment than corresponding values for vehicle control mice. c-Met

protein expression in tumors was slightly decreased, but phosphorylated c-Met was markedly reduced after treatment for 7 days.

Mice bearing MDA-MB-231 cells (expressing MET and VEGF) were administered four oral doses of 100 mg/kg (Yakes, 2011). Cabozantinib increased tumor hypoxia (13-fold) and apoptosis (TUNEL; 2.5-fold) at 8 and 4 hours after the first and second doses, respectively, when compared to vehicle-treated tumors. In addition, Cabozantinib disrupted tumor vasculature by inducing endothelial cell death that negatively affected tumor viability. Cabozantinib treatment resulted in significant tumor growth inhibition of MDA-MB-231 tumors (P <0.001) at all doses (1, 3, 10, 30, or 60 mg/kg) when compared to vehicle-treated tumors. Dose-dependent inhibition was observed for the 3 and 10 mg/kg doses (P <0.01), and complete inhibition was observed at the 30 and 60 mg/kg doses. A single 100 mg/kg dose resulted in sustained MDA-MB-231 tumor growth inhibition for ~8 days after which tumors began growing at a rate similar to vehicle-treated control tumors. In addition, cabozantinib inhibited tumor growth (P <0.001) in the MET-expressing rat C6 glioma cell line for all doses (1, 3, 10, 30, or 60 mg/kg) when compared with vehicle-treated tumors. The 3 mg/kg and 10 mg/kg doses resulted in significant tumor regression (62% and 85%, P <0.0001) when compared with predose tumor weights. Subchronic administration of cabozantinib was well tolerated in mice and rats with no signs of toxicity, as determined by stable and/or increasing body weights during the treatment period.

ARCaP-M is a human prostate cancer model which expresses both c-Met and VEGF co-receptor NP-1 used in a human prostate tumor xenograft study in mouse bone (Zhang, 2010). ARCaP-M cells were injected into the tibia of nude mice on Day 1, and on Day 31 animals with established bone lesions were randomized to receive Cabozantinib or vehicle daily (qd) for 7 weeks of treatment(Investigator's Brochure, 2011). Tibiae from vehicle-treated animals exhibited both osteoblastic and osteolytic lesions, whereas tibiae from Cabozantinib treated animals appeared mostly normal. Thus, Cabozantinib treatment blocked both osteoblastic and osteolytic progression of ARCaP-M xenograft tumors in bone.

<u>Nonclinical Pharmacodynamics</u>
In mice, the effective dose resulting in 50% inhibition (ED_{50}) of targets was achieved at well tolerated doses of Cabozantinib and at plasma exposures comparable to exposure observed in clinical trials (Investigator's Brochure, 2010). Cabozantinib produced prolonged inhibition of receptor phosphorylation, such as sustained inhibition of c-Met and VEGFR2 for 10 hours after administration of a single dose of cabozantinib. This extended inhibition occurred in a manner that was generally predicted by plasma exposure, *i.e.*, inhibition was diminished when plasma levels fell below approximately 20 μM for c-Met, 5 μM for VEGFR2, and 23 μM for TIE-2.

Once daily administration of cabozantinib resulted in significant inhibition of c-Met phosphorylation in TT tumors, relative to tumors from vehicle control-treated mice, with maximal inhibition of 70% seen at 60 mg/kg (Investigator's Brochure, 2010). Dose-dependent inhibition of phosphorylation of c-Met and RET was observed among the 3,

10, and 30 mg/kg dose groups as well.

c-Met phosphorylation was inhibited by a single 100 mg/kg oral dose of Cabozantinib, 2–8 hours post dose in H441 tumors (human lung papillary adenocarcinoma) that harbor constitutively phosphorylated c-Met (Yakes, 2011). This effect was reversible, as c-Met phosphorylation returned to basal levels by 48 hours after treatment.

Nonclinical Pharmacokinetics

In the various xenograft models, plasma exposures were similar and plasma concentrations in the range of 3 to 27 μM were associated with efficacy (Investigator's Brochure, 2010). In rats, plasma concentrations in the range of 5 to 15 μM were associated with maximal anti-tumor activity. Despite the apparent requirement for high peak concentrations, trough concentrations as low as 0.1 μM were observed at highly efficacious doses in mice. These results were consistent with *in vivo* target modulation studies in mice which demonstrated long (4- to 10-hour) durations of action, and indicated that continuous high exposure was not required to maintain efficacy.

Dose proportional increases in exposure occurred at oral doses of 3–100 mg/kg in mice and at 3–30 mg/kg in rats (Investigator's Brochure, 2010). In rats, the oral bioavailability of cabozantinib dosed as a solid was approximately 100% of cabozantinib dosed as a liquid. In comparison, oral bioavailability was much lower in dogs (20%) and monkeys (18%) for the solid versus liquid dosage forms.

Systemic drug exposure parameters (maximum plasma concentration [C_{max}] and area under the time-concentration curve from 0 to t hours post-dose [AUC_{0-t}] values) associated with single cabozantinib oral doses in rats increased less than dose-proportionally with increasing dose (100–900 mg/kg) (Investigator's Brochure, 2010). With repeat daily oral dosing in rats, systemic exposure (AUC_{0-t} values) increased generally dose-proportionally following 14 and 178 dosing days (dose ranges 1–15 mg/kg/day and 0.1–1 mg/kg/day, respectively). The C_{max} and AUC_{0-t} values in rats administered 100 mg/kg were approximately 2-fold and 3-fold higher, respectively, than for dogs given 2000 mg/kg; therefore, the higher systemic exposure to cabozantinib in rats correlated with the greater toxicity observed in this species at lower administered doses.

Systemic drug exposure parameters (C_{max} and AUC_{0-t} values) associated with single cabozantinib oral doses in dogs increased less than dose-proportionally with increasing Cabozantinib dose (400–2000 mg/kg), suggesting possible saturation of systemic absorption (Investigator's Brochure, 2011). With repeat daily dosing, exposure (C_{max} and AUC_{0-24} values) both increased greater than dose-proportionally from 10 to 100 mg/kg and less than dose proportionally from 100 to 1000 mg/kg following 14 dosing days.

Toxicology

In rodents and non-rodents, histopathological changes associated with cabozantinib administration were observed in gastrointestinal (GI) tract, bone marrow, lymphoid tissues, kidney, and adrenal and reproductive tract tissues (Investigator's Brochure,

2011). Histopathological changes present in the bone and pancreas were considered secondary to cabozantinib administration. Adverse effects following oral exposure to cabozantinib were generally dose-related, clinically monitorable, and self-resolving upon discontinuation of dosing. In 6-month chronic toxicity studies, treatment-related changes were present only in kidney (rats) and reproductive tissues (dog). In reproductive/developmental toxicity studies, Cabozantinib administration resulted in decreased fertility in male and female rats, in embryotoxicity when given to pregnant rats, and in a visceral tissue malformation (small spleen) when given to pregnant rabbits. The no-observable-adverse-effect-levels (NOAELs) for the chronic toxicity and reproductive/developmental toxicity studies occurred at plasma exposures (AUC) below steady-state values measured in subjects with solid tumors administered 175 mg Cabozantinib capsule form daily (Study XL184-001).

In definitive genotoxicity bioassays, Cabozantinib was negative in an *S. typhimurium/E.coli* bacterial mutagenicity study, an *in vitro* chromosome aberration study using human peripheral blood lymphocytes, and an *in vivo* mouse bone marrow micronucleus study (Investigator's Brochure, 2010). In safety pharmacology studies, no adverse effects occurred on neurobehavioral or respiratory functions in Cabozantinib-treated rats or on cardiovascular function in Cabozantinib-treated dogs.

Clinical Experience

As of May 4, 2011, 1003 patients have been studied in 12 ongoing Exelixis-sponsored clinical trials with Cabozantinib treatment 1) as a single agent at does ranging from 0.08 to 11.52 mg/kg on an intermittent dosing schedule, 2) from 25 to 265 mg (19.7-209 mg freebase equivalent weight) on a fixed daily dosing schedule and 3) in combination with temozolomide (TMZ) and radiation therapy (RT), or with erlotinib (Exelixis Communication, 2011). The maximum tolerated dose (MTD) on once daily (qd) by mouth (PO) dosing schedule was determined to be 175 mg L-malate salt (or approximately 138 mg freebase equivalent weight).

Detailed information for each of these studies, including pharmacokinetic data, can be found in the Investigator's Brochure (2011). Safety and efficacy information, from the 2011 Investigator's Brochure, is summarized below.

Phase 2 Studies

In a phase 2 study, **XL184-201**, subjects with progressive or recurrent GB in first or second relapse were enrolled to receive cabozantinib qd as a single agent. Group A received an initial dose of 175 mg (Group A), subsequent cohorts (Groups B and C) received an initial dose of 125 mg. Forty-six subjects were enrolled in Group A, and a total of 176 subjects were enrolled in Groups B/C. Fifty-seven subjects experienced one or more serious adverse events (SAEs) that were assessed to be related to treatment, including five fatal related.

Study **XL184-203** is a phase 2 randomized discontinuation trial. Subjects are enrolled

into one of nine tumor-specific cohorts: breast cancer, gastric/gastroesophageal (GEJ) cancer, hepatocellular carcinoma (HCC), melanoma, NSCLC, ovarian cancer, pancreatic cancer, prostate cancer, and small cell lung cancer (SCLC). Eligible subjects with advanced solid tumors receive open-label cabozantinib at starting dose of 100 mg qd for 12 weeks. Of the 531 subjects enrolled in this study as of May 2011, 92 experienced one or more SAEs that were assessed to be related to treatment with cabozantinib, including seven fatal related SAEs.

Study **XL184-205** is a randomized phase 2 trial for subjects with grade IV astrocytic tumors in first or second relapse. Subjects received one of four regimens: 25 mg qd (Arm 1) continuously, 75 mg qd (Arm 2) continuously, 125 mg qd for 2 weeks followed by 50 mg qd continuously (Arm 3), and 125 mg qd on an intermittent 3 week on/1 week off schedule (Arm 4). A total of 19 subjects were accrued before the study was terminated. Three subjects were rolled over to maintenance Study XL184-900. One subject experienced an SAE assessed to be related to treatment with cabozantinib.

Study **XL184-301** is a blind trial for subjects with unresectable, locally advanced or metastatic MTC, randomized 2:1 to cabozantinib or placebo. SAEs reported in Study XL184-301 are: one grade 4 reversible posterior leukoencephalopathy syndrome (RPLS), one grade 5 cardiac arrest following asystolic vagal reaction after aspiration on study medication, and three SAEs of acquired trachea-esophageal fistula (two grade 3, one grade 5).

Study **GOG-0186K** is a phase II trial for subjects with persistent or recurrent ovarian, fallopian tube, or primary peritoneal cancer. The study demonstrated a low rate of Grade 3 and 4 toxicities with only 1 bowel perforation among 52 patients who received Cabozantinib.

Adverse Events

The clinical studies with cabozantinib are ongoing and thus the AE data from the clinical database as of March 1, 2011 and May 4, 2011 do not yet include all SAEs (Exelixis Communication, 2011). As of March 2011, AE data are available for 913 subjects who have been dosed with Cabozantinib (806 in single-agent studies and 107 in combination studies of cabozantinib with erlotinib, rosiglitazone, or TMZ ± radiation) (Investigator's Brochure, 2011). Data from the 806 subjects who received single-agent cabozantinib show that the most frequently (>20%) observed AEs regardless of causality were fatigue, diarrhea, nausea, decreased appetite, constipation, palmar-plantar erythrodysesthesia (PPE) syndrome, vomiting, dysphonia, and hypertension. Effects that may be related to the inhibition of VEGF, including hypertension, thromboembolic events, GI perforation, fistula formation, hemorrhage, wound dehiscence, and proteinuria, have been observed in the single-agent and combination cabozantinib studies. The most commonly reported SAEs that were assessed as related to study treatment with cabozantinib (as a single-agent or combination) were pulmonary embolism (PE), diarrhea, dehydration, deep vein thrombosis (DVT), vomiting, nausea, thrombocytopenia, fatigue, wound dehiscence, and PPE syndrome.

There have been 15 grade 5 AEs related to study treatment: GI hemorrhage (two subjects), PE (two subjects), respiratory failure (two subjects), respiratory disorder (one subject), hemoptysis (one subject), death due to unknown cause (two subjects), intracranial hemorrhage (one subject), intestinal perforation (one subject), enterocutaneous fistula (one subject), hemorrhage (presumed to be hemoptysis; one subject), and diverticular perforation, peritonitis (one subject) (Investigator's Brochure, 2011).

Pharmacokinetics

Pharmacokinetic analysis of 74 patients in trial **XL184-001** showed dose proportional increases in maximum plasma concentration (C_{max}) and AUC both for PIB (dose range 0.08-11.52 mg/kg) and the capsule formulation (dose range: 125 to 175 mg) (Kurzrock, 2011). Terminal-phase half-life ($t_{1/2,z}$) values were 59.1 to 136 hours (Investigator's Brochure, 2011). After repeat dosing, $t_{1/2,z}$ values (mean ± standard deviation) for cabozantinib were 91.3 ± 33.3 hours (n = 23), and apparent steady-state plasma levels were reached by Day 15 [18]. Steady-state clearance for the 175 mg capsule dose derived from repeat dose data was 4.2 ± 1.5 L/h. Patients who received 175 mg capsules had four- to five-fold higher steady-state exposure (AUC) compared with Day 1 (7.68 ± 2.85 mcg·h/mL; n = 23 vs. 41.6 ± 15.3 mcg·h/mL; n = 23), indicating that cabozantinib accumulated with repeat daily dosing. There was no significant difference in exposure between patients with MTC and those without MTC.

Based on the preliminary PK data from 23 subjects in **XL184-005** who completed both treatments, after a single oral dose of cabozantinib at 100 mg, the terminal $t_{1/2,\,z}$ of cabozantinib appeared to be similar for both tablet and capsule formulations, with approximately mean values of 110 hours (Exelixis Communication, 2012). The median time to the maximum plasma concentration (t_{max}) was 4 hours for the tablet formulation and 5 hours for the capsule formulation. High inter-subject variability for C_{max} and the area under the plasma drug concentration time curve (AUC) values were observed for both formulations (coefficient of variation [CV]% C_{max}: 51% for the tablet formulation, 61% for the capsule formulation; CV% for the AUC from time zero to the last quantifiable timepoint or to infinity [$AUC_{0\text{-last}}$ or $AUC_{0\text{-inf}}$]: 40-43% for the tablet formulation, 43% for the capsule formulation). The geometric mean C_{max} of the tablet formulation was approximately 39% higher than the value observed for the capsule formulation. The geometric mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values for the tablet formulation were also higher (15% and 19%, respectively) than those observed for the capsule formulation. However, due to the high within-formulation variability observed, no statistical difference in exposure between the two formulations was apparent.

Based on the preliminary PK data from 46 subjects who completed both treatments on trial **XL184-004**, a high-fat meal did not appear to alter the terminal $t_{1/2,\,z}$ of cabozantinib [mean $t_{1/2,\,z}$: 131 hours (fed) vs 128 hours (fasted)]. The high-fat meal significantly increased the median t_{max} to 6 hours from 4 hours (fasted). The high-fat meal also significantly increased both the cabozantinib C_{max} and AUC values by 39% and 56%, respectively. The geometric mean ratio of C_{max} fed/fasted was 1.39 (90% CI: 1.16-1.67), and the geometric mean ratio of $AUC_{0\text{-last}}$ fed/fasted was 1.56 (90% CI: 1.34-1.80).

Based on this result, cabozantinib must be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each cabozantinib dose).

2.3 Inclusion of Women and Minorities

The NRG Oncology Group and NRG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire serous ovarian and peritoneal population treated by participating institutions.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the NRG Statistics and Data Management Center – Buffalo Office (via the contact list on the NRG web site).

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Women of childbearing potential should be willing and able to use medically acceptable forms of contraception during the trial.

3.2 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.2.1 A retrospective review of all patients entered will be performed to confirm clear cell histology. Patients must have recurrent or, progressive clear cell ovarian cancer not solely based on CA-125. Primary tumors must be at least 50% clear cell histomorphology in order to be eligible or have a histologically documented recurrence with at least 50% clear cell histomorphology. Recurrence should be biopsy proven unless the tumor is located in an area deemed unsafe to biopsy by the surgeon. If a biopsy can be obtained without significant risk, then biopsy should be obtained

3.2.1.1 If the primary tumor had at least 50% clear cell histomorphology, a biopsy of the recurrent or persistent tumor is not required. The percentage of clear cell histomorphology must be documented in the pathology report or in an addendum to the original report. If slides of the primary tumor are not available for review due to disposal of slides by the histology laboratory (typically 10 years after diagnosis), biopsy of recurrent or persistent disease is required.

3.2.1.2 If slides of the primary tumor are not available for review, a biopsy of the recurrent or persistent tumor is required to confirm at least 50% clear cell histomorphology. The percentage of involvement must be documented in the pathology report or in an addendum to the original report.

3.2.2 All patients must have measurable disease as defined by RECIST 1.1.

3.2.3 All patients must submit unstained slides of primary or recurrent tumor for translational analysis

3.2.4 Patients must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST 1.1

3.2.5 Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease. Platinum sensitive and resistant patients are eligible.

3.2.6 Patients are allowed to receive, but are not required to receive, one additional cytotoxic regimen for management of recurrent or persistent disease

3.2.7 Concomitant use of additional anti-neoplastic agents will not be allowed in this study

3.2.8 Patients may not have received previous therapy with a MET inhibitor.

3.2.9 Patients must not be eligible for a higher priority (e.g.; Phase II/III), NRG protocol for the same population if one exists.

3.2.10 Patients must be recovered from effects of recent surgery (28 days must elapse between surgery and the start of treatment with cabozantinib).

3.2.11 Patients must have ≥ 4 weeks since prior chemotherapy or radiation (≥ 6 weeks for nitrosoureas or mitomycin C).

3.2.12 Appropriate stage for study entry based on the following diagnostic workup:

- History/physical examination within 28 days prior to registration

3.2.13 Age ≥ 18

3.2.14 The trial is open only to women with recurrent, progressive clear cell carcinoma of the ovary.

3.2.15 Patients must have an ECOG Performance Status of 0, 1, or 2 (Karnofsky ≥ 60% (See Appendix VI) within 28 days prior to registration (09/08/15)

3.2.16 Adequate hematologic function within 14 days prior to registration defined as follows:

- Absolute neutrophil count (ANC) ≥1,500/mcl
- Platelets greater than or equal 100,000/mcl.
- Leukocytes ≥3,000/mcL
- Hemoglobin ≥9 g/dL
- serum albumin ≥2.8g/dL

3.2.17 Adequate blood coagulation parameters within 14 days prior to registration defined as follows:

- PT such that international normalized ratio (INR) is less than or equal to 1.3 x ULN
- PTT less than or equal to 1.3 x ULN

3.2.18 Adequate renal function within 14 days prior to registration defined as follows:

- Creatinine less than or equal to 1.5 times the ULN

OR

- Creatinine clearance ≥50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
- The UPCR is derived as follows: protein concentration (mg/dL)/creatinine

(mg/dL). Patients must have a UPCR < 1.0 to allow participation in the study

3.2.19 Adequate hepatic function within 14 days prior to registration defined as follows:

- Bilirubin less than or equal to 1.5 ULN.
- AST and ALT less than or equal to 2.5 times the ULN, unless subjects have liver metastasis, in which case both AST and ALT must be less than or equal to 5 times the ULN.

3.2.20 Adequate pancreatic function within 14 days prior to registration defined as follows:

- Lipase less than or equal to 2 x ULN
- No clinical evidence of pancreatitis

3.2.21 Adequate thyroid function within 28 days prior to registration defined as follows: Patients must have a normal baseline TSH. A history of hypothyroidism and/or hyperthyroidism is allowed.

3.2.22 Women of childbearing potential must have a negative pregnancy test at screening. Women of childbearing potential include women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are not postmenopausal. Post-menopause is defined as amenorrhea ≥12 consecutive months. Note: 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, anti-estrogens, ovarian suppression or any other reversible reason. Women should stop breastfeeding while participating in this trial. Male partners of women participants should also use medically-acceptable forms of contraception during the study

3.2.23 The patient must provide study-specific informed consent prior to study entry.

3.3 Ineligibility Criteria

Patients with one or more of the following conditions are NOT eligible for this study.

3.3.1 HIV positive patients.

3.3.2 Patients with serious non-healing wound, ulcer, or bone fracture.

3.3.3 Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels.

3.3.4 The subject requires concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (*e.g.*, clopidogrel). Low dose aspirin (≤81 mg/day), low-dose warfarin (≤1 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted.

3.3.5 Patients with history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage within 6 months of the first date of treatment on this study.

3.3.6 Patients with clinically significant cardiovascular disease. This includes:

3.3.6.1 Poorly controlled hypertension (>140 mm Hg and > 90 mm Hg for systolic and diastolic BP) are ineligible.

3.3.6.2 Myocardial infarction or unstable angina within 6 months prior to registration; New York Heart Association (NYHA) Grade II or greater congestive heart failure (see Appendix III)

3.3.6.3 Cardiac arrhythmia requiring medication

3.3.7 Grade II or greater peripheral vascular disease based on NCI CTC; e.g. ischemic rest pain, minor tissue loss, and ulceration or gangrene

3.3.8 Patients with a pre-existing thyroid abnormality who are unable to maintain thyroid function in the normal range with medication are ineligible. Patients with a history of hypothyroidism are eligible provided they are currently euthyroid.

3.3.9 Patients who have a major surgical procedure, or significant traumatic injury within 28 days prior to the first date of treatment on this study, or anticipation of need for major surgical procedure during the course of the study; patients with placement of vascular access device or core biopsy within 7 days prior to the first date of treatment on this study.

3.3.10 Patients with other invasive malignancies, with the exception of non-melanoma skin cancer, who had (or have) any evidence of other cancer present within the last 5 years or whose previous cancer treatment contraindicates this protocol therapy.

3.3.11 Patients must not be eligible for a higher priority NRG clear cell protocol (GOG-0283). Rare patients ineligible for GOG-0283 may be eligible for this trial without prior treatment on dasatinib therapy (e.g. they have been deemed allergic to dasatinib).

3.3.12 Patients who cannot swallow pills

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

PRE-TREATMENT ASSESSMENTS (07/05/16)

Assessments	Prior to Registration (within specified number of calendar days prior to study therapy)
History & Physical	28
Performance Status	28
Height	28
Weight	28
Vital Signs (blood pressure, heart rate and temperature)	28
Toxicity Assessment	28
CBC, differential,	14

hemoglobin, platelets, Electrolytes, BUN, Creatinine, UPC, Ca, Mg, PO4, Bilirubin, AST/SGOT, ALT/SGPT, Alkaline Phosphatase, Amylase, Lipase, Urine protein/creatinine ratio	
PT, INR, PTT	14
Pregnancy test	3
TSH	28
CA125	14
Chest Imaging (CT of Chest)	28
Radiographic disease assessment	28
Electrocardiogram	28
Review of medications	28

ASSESSMENTS DURING TREATMENT

Assessments	**During Adjuvant Chemotherapy**
History & Physical	Prior to each treatment cycle
Performance Status	Prior to each treatment cycle
Height	
Weight	Prior to each treatment cycle
Vital Signs (blood pressure, heart rate and temperature)	Prior to each treatment cycle
Toxicity Assessment	Prior to each treatment cycle
CBC, differential, hemoglobin, platelets, Electrolytes, BUN, Creatinine, UPC, Ca, Mg, PO4, Bilirubin, AST/SGOT, ALT/SGPT, Alkaline Phosphatase, Amylase, Lipase, Urine protein/creatinine ratio	Prior to each treatment cycle Within 4 days prior to retreatment
PT, INR, PTT	Prior to each treatment cycle Within 4 days prior to retreatment
CA125	Prior to each treatment cycle
Chest Imaging (CT of Chest)	After second cycle then every 8 weeks
Radiographic disease	After second cycle then every

assessment	8 weeks
Patient diary documenting cabozantinib dosing	Prior to each treatment cycle Within 4 days prior to retreatment

ASSESSMENTS IN FOLLOW UP

Assessments	**Example: From end of Chemotherapy: q3 mos. x 2 yrs.; q6 mos. x 3 years; then annually, unless otherwise indicated**
History & Physical	X
Performance Status	X
Height	X
Weight	X
Vital Signs (blood pressure, heart rate and temperature)	X
Routine blood tests	X
CT scan or MRI of Abdomen and pelvis to measure detectable tumor	X

5. TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 Chemotherapy

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the NRG Oncology Procedures Manual.

See the General Chemotherapy Guidelines (Appendix I).

5.1.1 Cabozantinib (XL184) 60 mg once a day continuously , repeated in 4 week cycles until disease progression or adverse effects prohibit further therapy

5.1.1.1 One cycle equals 28 days.

5.1.2 Patients will be given a Patient Medication Calendar to complete daily (Appendix IV). The Patient Medication Calendar should be reviewed prior to the start of each cycle.

5.1.3 Cabozantinib must be taken on an empty stomach. Patients must fast for 2 hours before and 1 hour following each dose of Cabozantinib.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Because there is a potential for interaction of cabozantinib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

5.2.2 Concomitant Medications and Therapies

5.2.2.1 Anticancer Therapy

If a subject requires additional systemic anticancer treatment, study treatment must be discontinued. Local intervention is discouraged unless medically unavoidable.

5.2.2.2 Other Medications

Subjects must be instructed to inform the investigators of the current or planned use or all other medications during the study (including prescription medications, over-the-counter medications, vitamins and herbal and nutritional supplements). It is the responsibility of the investigator to ensure that details regarding all medications are documented.

Bisphosphonates started prior to screening activities or initiated during the course of the study to control bone pain may be used with caution.

Colony stimulating factors (*e.g.*, erythropoietin and granulocyte colony-stimulating factors) and pain medications administered as dictated by standard practice are acceptable while the subject is enrolled in the study. However, colony stimulating factors should not be administered prophylactically prior to the first dose of study treatment.

No concurrent investigational agents are permitted.

5.2.2.3 Potential Drug Interactions

CYP450 isozymes:
In vitro, XL184 is a substrate of CYP3A4 and a weak substrate of CYP2C9. Co-administration of ketoconazole, a strong inhibitor of CYP3A4, increases XL184 AUC (37%) and rifampin, a strong inducer of CYP3A4, reduces XL184 AUC (77%) . Therefore, avoid chronic use of strong CYP3A4 inducers such as rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifampentin, phenobarbital, and St. John's Wort while taking XL184. Avoid chronic use of strong CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir. Use alternative medications.

[**Note:** Use caution when discontinuing medication that is a strong inducer of CYP3A4 in patients who has been on a stable dose of XL184, as this could significantly increase the exposure to XL184.]

XL184 is a noncompetitive inhibitor of CYP2C8 (K_{iapp} = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (K_{iapp} = 10.4 μM) and CYP2C19 (K_{iapp} = 28.8 μM), and a weak competitive inhibitor of CYP3A4 (estimated K_{iapp} = 282 μM) in human liver microsomal (HLM). IC_{50} values >20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes. XL184 is an inducer of CYP1A1 mRNA in human hepatocyte incubations,

Avoid grapefruit/ grapefruit juice and Seville oranges while participating in this trial.

P-glycoprotein/ MRP2:
In vitro data indicate that XL184 is unlikely to be a substrate but may be an inhibitor of P-glycoprotein transport activity (IC_{50} = 7.0 μM). Co-administration of XL184 with a P-gp substrate may result in an increase in P-gp substrate plasma concentration. Therefore, use caution when administering XL-184 with drugs known to be P-gp substrates (e.g., fexofenadine, aliskiren, ambrisentan, digoxin, colchicine, maraviroc, posaconazole, tolvaptan, etc.). In an in vitro assay, XL184 has shown to be a substrate of drug transporter MRP2, which may result in an increase plasma concentration of XL184 when administered with an inhibitor of MRP2. Use caution and monitor adverse events when administering XL184 with MRP2 inhibitors such as cyclosporine, delavirine, efavirenz, emtricitabine.

Please refer to the Flockhart drug interaction tables for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways. Table available at (Flockhart 2007; http://medicine.iupui.edu/clinpharm/ddis/table.aspx).

Protein bound:
XL184 is highly protein bound (≥ 99.9%). Use caution when coadministering XL184 with medications that are highly protein-bound (e.g., diazepam, furosemide, dicloxacillin, and propranolol). Avoid administration of warfarin with XL184 as warfarin is highly protein-bound and has a very narrow therapeutic index.

Antacids, H2-blockers, PPIs:
Co-administration of gastric pH modifying drugs such as PPI, H_2-blockers or antacids has no clinically-relevant effect on XL184 plasma PK in healthy volunteers; thus, concomitant use of these drugs with XL184 is allowed.

QTc prolongation:
Use caution when administering XL184 in patients with QT prolongation risk, a history of QT interval prolongation, or who are receiving antiarrhythmic drugs. Concomitant use of strong CYP3A4 inhibitors should be avoided as itmay increase XL184 plasma concentrations. Refer to the protocol for QTcF criteria.

5.2.3 Participation in Other Trials

- Patients must not be eligible for a higher priority NRG clear cell protocol (GOG-0283). Rare patients ineligible for GOG-0283 may be eligible for this trial without prior treatment on dasatinib therapy (e.g. they have been deemed allergic to dasatinib).

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT

6.1 Cabozantinib (XL184)-Related Adverse Event Management

Subjects will be monitored continuously for AEs throughout the study. **Subjects must be instructed to notify their physician immediately for any and all toxicities**.

General guidelines for the management of non-hematologic and hematologic toxicities are provided in Table 6-1 and Table 6-2, respectively. As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. Calcium, magnesium, potassium and phosphorus should be kept above the lower limits of the laboratory normal values. For more specific guidelines on gastrointestinal AEs (diarrhea, nausea/vomiting, stomatitis/mucositis), hepatobiliary disorders, pancreatic disorders including lipase and amylase elevations, skin disorders (PPE), embolism and thrombus, hypertension, proteinurea, hemorrhage, rectal and perirectal abscess, gastrointestinal (GI) perforation and GI fistula, non-GI fistula, wound healing and surgery, osteonecrosis of the jaw (ONJ), endocrine disorders and management of treatment-emergent prolongation of the QTc interval, refer to the appropriate below. Guidance for the management of fatigue, anorexia, weight loss, eye disorders, musculoskeletal and connective tissue disorders, nervous system disorders, respiratory/thoracic/mediastinal disorders and congenital, familial and genetic disorders can be found in the Cabozantinib Investigator's Brochure.

Dose adjustments for Cabozantinib

	Cabozantinib Dose mg/day
Initial	60
-1	40
-2	20

Table 6-1. General Approach to the Management of Cabozantinib-Related Non-Hematologic Adverse Events

CTCAE Version 4 Grade	Guidelines/Intervention
Grade 1:	Add supportive care as indicated. Continue cabozantinib at the current dose level.
Grade 2:	
Grade 2 AEs considered related to cabozantinib that are subjectively tolerable or easily managed	Add supportive care as indicated. Continue cabozantinib at the current dose level.
Grade 2 AEs considered related to cabozantinib that are intolerable to the subject or deemed unacceptable in the investigator's judgment; or are not easily managed or corrected	Dose reduce • If the AE dose not resolve to Grade ≤1 or baseline in 7 to 10 days or worsens at any time, cabozantinib dosing should then be interrupted. Then upon resolution to baseline or Grade ≤ 1, the reduced dose should be restarted. • If the AE does resolves to resolves to Grade ≤1 or baseline without a dose interruption, continue the reduced dose.
Grade 3:	
Grade 3 AEs considered related to cabozantinib which occurred without optimal prophylaxis or which is easily managed by medical intervention or resolved quickly	• Interrupt cabozantinib and add supportive care as indicated • For AEs that are easily managed (e.g., correction of electrolytes) with resolution to baseline or Grade ≤1 within 24 hours, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced • For AEs that require supportive care, the dose should be held while supportive care is initiated and optimized. Then upon resolution of the AE to baseline or Grade ≤1, cabozantinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced
Grade 3 AEs considered related to study treatment that occurred despite optimal prophylaxis or is not easily managed by medical intervention	Interrupt study treatment until recovery to ≤ Grade 1 or baseline, and resume treatment with a dose reduction
Grade 4:	
Grade 4 AEs considered related to study treatment	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor but only with sponsor approval.
Dose reductions or delays may occur in the setting of lower grade toxicity than defined above if the investigator believes that it is in the interest of the subject's safety.	

Table 6-2. General Approach to the Management of Cabozantinib-Related Hematologic Adverse Events

CTCAE Version 4 Grade	Intervention
Neutropenia	
Grade 3 neutropenia with documented infection Grade 3 neutropenia ≥ 5 days Grade 4 neutropenia	Interrupt cabozantinib treatment until resolution to Grade ≤1, and resume cabozantinib treatment at a reduced dose.
Thrombocytopenia	
Grade 3 thrombocytopenia with clinically significant bleeding or Grade 4 thrombocytopenia	Interrupt cabozantinib treatment until platelet count is ≥100,000/mm^3, and resume cabozantinib treatment at a reduced dose
Febrile Neutropenia	
Grade 3 febrile neutropenia	Interrupt cabozantinib treatment until recovery of ANC to Grade ≤1 and temperature to ≤38.0°C and resume cabozantinib treatment at a reduced dose.
Grade 4 febrile neutropenia	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor but only with sponsor approval.
Other Grade 4 Hematologic Toxicities	
Grade 4 hematologic toxicities other than anemia	Permanently discontinue study treatment unless determined that the subject is clearly deriving clinical benefit. In this case, upon recovery to Grade ≤1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor and only with approval by the sponsor.
Grade 4 anemia	Permanent discontinuation for Grade 4 anemia is not mandated. Dose reductions or dose delays for anemia should be applied as clinically indicated. Supportive care such as red blood cell transfusions should be managed according to institutional guidelines.

ANC, absolute neutrophil count; LLN, lower limit of normal

Neutropenia: Grade 1 (LLN ≤ ANC < 1.5 × 10^9/L; Grade 2 (1 × 10^9/L ≤ ANC <1.5 x 10^9/L), Grade 3 (0.5 × 10^9/L ≤ ANC < 1 × 10^9/L), Grade 4 (ANC < 0.5 × 10^9/L).

Febrile Neutropenia: Grade 3 (present); Grade 4 (Life-threatening consequences; urgent intervention indicated).

Thrombocytopenia: Grade 1 (Platelet count <LLN – 75 x 10^9/L); Grade 2 (Platelet count <75.0 – 50.0 x 10^9/L); Grade 3 (Platelet count ≤ 50 - 25 × 10^9/L); Grade 4 (Platelet count < 25 × 10^9/L).

6.2 Diarrhea, Nausea, Vomiting, Stomatitis, and Mucositis

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. Administration of antidiarrheal agents is recommended at the first sign of diarrhea as initial management. Loperamide is recommended as standard first line therapy. Alternatively, diphenoxylate/atropine can be used. Additional agents to consider in subjects with diarrhea that is refractory to the above include deodorized tincture of opium and octreotide (Benson *et al.,* 2004). Some subjects may require concomitant therapy with loperamide, diphenoxylate/atropine, and deodorized tincture of opium to control diarrhea. The dose modification guidance in Table 6-1 should be followed. In addition, general supportive measures should be implemented including continuous oral hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals and alcohol.

Nausea and Vomiting

Anti-emetic agents along with supportive care are recommended as clinically appropriate at the first sign of nausea and vomiting. The dose modification guidance in Table 6-1 should be followed.

The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure. Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4. Caution is also recommended with ondansetron, as ondansetron may result in QTc prolongation when administered with cabozantinib. Ondansetron is a 5-HT3 antagonist.

Stomatitis and Mucositis

Preventive measures may include a comprehensive dental examination to identify any potential 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 cleansing, and oral rinses (*e.g.*, with a weak solution of salt and baking soda) should be maintained. The oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered.

6.3 Hepatobiliary Disorders

Elevations of transaminases have also been observed during treatment with cabozantinib. In general, it is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more

frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications and alcohol should be discontinued in subjects who develop elevated transaminases. Since subjects may enter the study with elevations of AST/ALT at baseline, the following guideline should be used for dose modifications:

Transaminase elevation CTCAE v4.0	**Intervention**
Subjects with AST and ALT less than or equal to the ULN at baseline	
Grade 1	Continue cabozantinib with weekly monitoring of liver function tests (LFTs) for at least 4 weeks. Then resume the standard protocol-defined monitoring of LFTs.
Grade 2	Continue cabozantinib with at least twice weekly monitoring of LFTs for 2 weeks. Then weekly for 4 weeks. If LFTs continue to rise within Grade 2, interrupt cabozantinib treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib
Grade 3	Interrupt cabozantinib treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Cabozantinib may then be resumed at a one-dose-level reduction.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose of cabozantinib as determined by the investigator and sponsor but only with sponsor approval.
Subjects with AST or ALT above the ULN but ≤ 3.0 x ULN (i.e., Grade 1) at baseline	
≥ 1.5 fold increase of AST or ALT AND both AST and ALT are ≤ 5.0 x ULN	Continue cabozantinib treatment with at least twice weekly monitoring of LFTs for 4 weeks and weekly for 4 weeks. If LFTs continue to rise, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib
≥ 1.5 fold increase of AST or ALT and at least one of AST or ALT is Grade 3 (i.e. AST or ALT > 5.0 but ≤ 20.0 x ULN)	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator and sponsor but only with sponsor approval.

Cabozantinib treatment should also be interrupted when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (*e.g.*, International Normalized Ratio [INR]). Monitoring of transaminases should be intensified (2–3 times per week) and cabozantinib should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels (INR < 1.5 × ULN, total bilirubin < 1.5 × ULN, aminotransferases ≤ baseline grade).

Subjects must have cabozantinib permanently discontinued if transaminase elevations are accompanied by evidence of impaired hepatic function (bilirubin elevation >2 ×ULN), in the absence of evidence of biliary obstruction (*i.e.*, significant elevation of alkaline phosphatase) or some other explanation of the injury (*e.g.*, viral hepatitis, alcohol hepatitis), as the combined finding (*i.e.*, Hy's Law cases) represents a signal of a potential for the drug to cause severe liver injury.

All subjects who develop isolated bilirubin elevations of Grade 3 should have study treatment held until recovered to Grade ≤1 or baseline (or lower). If this occurs within 6 weeks of the dosing delay, study treatment may continue at a reduced dose. In subjects without biliary obstruction and Grade 4 bilirubin elevation, or with recurrence of Grade 3 bilirubin elevation after a dose reduction, study treatment must be discontinued.

6.4 Pancreatic Conditions

Amylase and lipase elevations have been observed in clinical studies with cabozantinib. The clinical significance of asymptomatic elevations of enzymes is not known but in general have not been associated with clinically apparent sequelae. It is recommended that subjects with lipase elevation and/or symptoms of pancreatitis have more frequent laboratory monitoring of lipase and/or amylase (2-3 times per week). Subjects with symptomatic pancreatitis should be treated with standard supportive measures.

Asymptomatic Lipase or Amylase Elevations

Asymptomatic Lipase or Amylase Elevations	
Grade 1 or Grade 2	Continue at current dose level. More frequent monitoring is recommended
Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤1 or baseline, cabozantinib may be restarted at the same dose or at a reduced dose provided that this occurs within 6 weeks. • If retreatment following Grade 3 lipase or amylase elevation is at the same dose and Grade 3 or Grade 4 elevations recur, then treatment must be interrupted again until lipase and amylase levels have resolved to Grade ≤1 or baseline and retreatment must be at a reduced dose.
Grade 4	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤1 or baseline and if resolution occurred within 4 days, cabozantinib may be restarted at the same dose or a reduced dose. If resolution took more than 4 days, the dose must be reduced upon retreatment provided that resolution occurred within 6 weeks. • If retreatment following Grade 4 lipase or amylase elevation is at the same dose and Grade 3 or 4 elevations recur, then treatment must be interrupted again until lipase and amylase have resolved to Grade ≤1 or baseline and retreatment must be at a reduced dose.

Pancreatitis

Pancreatitis	
Grade 2 and asymptomatic	• Continue at current dose level. More frequent monitoring of lipase and amylase and radiographic evaluation is recommended.
Grade 2 symptomatic and Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤1 or baseline , cabozantinib may be restarted at a reduced dose if resolution occurred within 6 weeks
Grade 4	Permanently discontinue treatment. However, if the subject was unequivocally deriving benefit from cabozantinib therapy, treatment may resume at a reduced dose agreed to by the investigator and sponsor but only with sponsor approval.

6.5 Skin Disorders

Palmar-plantar erythrodysesthesia syndrome (PPE; also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform,

and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported in cabozantinib-treated subjects. All subjects on study should be advised to use prophylactic measures for skin care. These measures includes the use of hypoallergenic moisturizing creams, ointment for dry skin, sunscreen with SPF ≥30; avoidance of exposure of hands and feet to hot water; protection of pressure-sensitive areas of hands and feet; and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry. Subjects with skin disorders should be carefully monitored for signs of infection (*e.g.*, abscess, cellulitis, or impetigo).

Early signs of hand-foot syndrome can include tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, 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. Aggressive management of symptoms is recommended, including early dermatology referral.

Treatment guidelines for PPE related to study treatment are presented in the table below.

In the case of study treatment-related skin changes (*e.g.*, rash, hand-foot syndrome), the investigator may request that additional assessments be conducted with the subject's consent. These assessments may include digital photographs of the skin changes and/or a biopsy of the affected skin and may be repeated until the skin changes resolve.

Hand-Foot Skin Reaction and Hand Foot Syndrome (PPE)	
Grade 1	Continue cabozantinib at current dose if tolerable or reduce to the next lower dose if intolerable. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time or if there is no improvement after 2 weeks, proceed to the management guidelines for Grade 2 PPE
Grade 2	Reduce cabozantinib dose to next lower level and/or interrupt dosing. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Add analgesics for pain control with NSAIDs/GABA agonists/narcotics if needed.. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time, or affects self-care, or if there is no improvement after 2 weeks, proceed to the management guidelines for Grade 3 PPE. If the dose was only reduced but not interrupted, treatment may continue at the reduced dose. If the dose was only interrupted but not reduced, then treatment may be restarted upon resolution to Grade 0 or Grade 1 at one dose level lower.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Pain control with NSAIDs/GABA agonists/narcotics. Treatment may restart at one dose level lower when reaction decreases to Grade 1 or 0. Permanently discontinue subject from study if reactions worsen or do not improve within 6 weeks.

GABA, γ-aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drugs; PPE, palmar-plantar erythrodysesthesia

6.6 Embolism and Thrombosis

Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the IB). Subjects who develop a PE or DVT should have study treatment held until therapeutic anticoagulation with heparins is established. Study treatment may be resumed with a one dose-level reduction in subjects who have uncomplicated PE or DVT and are deriving clinical benefit from study treatment. During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. Subjects with life-threatening PE or DVT should have study treatment discontinued unless toxicity can be managed and subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor. Venous filters (*e.g.* vena cava filters) are not recommended due to the high incidence of complications associated with their use. Once a subject is fully anticoagulated, treatment can be restarted per investigator judgment at one dose lower. Subjects should permanently discontinue after a second thrombotic event. Although routine prophylactic anticoagulation is not necessary for all subjects, prophylactic anticoagulation is allowed for individual subjects at the discretion of the investigator.

Arterial thrombotic events (*e.g.*, transient ischemic attack, myocardial infarction) have been observed rarely in studies with cabozantinib. Cabozantinib should be discontinued in subjects who develop an acute MI or any other clinically significant arterial thromboembolic complication.

6.7 Hypertension

Hypertension is a relatively common complication of other VEGF-pathway inhibitors and has been observed in cabozantinib clinical studies.

Decisions to decrease or hold 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. Subjects with known hypertension should be optimally managed prior to study entry. Clinical judgment should be used in deciding whether new or worsened hypertension emerging during treatment with cabozantinib requires immediate therapy, or whether therapeutic intervention can be delayed in order to confirm the finding of new or worsened hypertension at a second visit before taking new therapeutic action. It is recommended that this second visit occur within 1 week. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine. Cabozantinib dosing should be interrupted in subjects with severe hypertension (180 mm Hg systolic or 120 mm Hg diastolic; or sustained ≥160 mm Hg systolic or ≥110 diastolic) who cannot be controlled with medical interventions and discontinued in subjects with hypertensive crises or hypertensive encephalopathy (see next Table below).

Management of Hypertension Related to Cabozantinib

Criteria for Dose Modifications	Treatment/cabozantinib Dose Modification
Subjects not receiving optimized anti-hypertensive therapy	
> 140 mm Hg (systolic) and < 160 mm Hg OR > 90 mm Hg (diastolic) and < 110 mm Hg	• Increase antihypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications) • Maintain dose of cabozantinib • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, or if the subject is symptomatic, the dose of cabozantinib should be reduced.
≥ 160 mm Hg (systolic) and < 180 mm Hg OR ≥ 110 mm Hg (diastolic) and < 120 mm Hg	• Reduce cabozantinib by one dose level. • Increase antihypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications) • Monitor subject closely for hypotension. • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced further.
≥ 180 mm Hg (systolic) OR ≥ 120 mm Hg (diastolic)	• Interrupt treatment with cabozantinib Add new or additional anti-hypertensive medications and/or increase dose of existing medications. • Monitor subject closely for hypotension. • When SBP < 140 and DBP < 90, restart cabozantinib treatment at one dose level lower • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced further.
Hypertensive crisis or hypertensive encephalopathy	Discontinue all study treatment
BP, blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure NOTE: If SBP and DBP meet different criteria in table, manage per higher dose-modification criteria	

6.8 Proteinuria

Proteinuria has been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Any level of proteinuria diagnosed by dipstick should be quantified by a UPCR (mg/dL protein / mg/dL creatinine). When a UPCR exceeds 1, a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm the result. Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria >3.5 g/day in combination with hypoalbuminemia, edema and hyperlipidemia) or any other relevant renal disease. Also, given the nephrotoxic potential of bisphosphonates, these agents should be used

with caution in patients receiving treatment with cabozantinib. Details of management are described in the next Table below.

Management of Treatment Emergent Proteinuria

Urine Protein/Creatinine Ratio	Action To Be Taken
≤ 1	• No change in treatment or monitoring
> 1 and < 3.5	• No change in study treatment required • Consider confirming with a 24-hour protein excretion within 7 days • Repeat UPCR within 7 days and once every week. If UPCR is < 1 on two consecutive readings, then UPCR monitoring can revert to protocol specific time points. (The second reading is a confirmatory reading and can be done within 1 week of the first reading.).
≥ 3.5	• Hold cabozantinib immediately and confirm with 24 hour urine protein excretion. • Evaluate for nephrotic syndrome. If present, discontinue cabozantinib treatment permanently, and monitor subject for resolution of nephrotic syndrome. • If proteinuria of ≥ 3.5 g/24 hours is confirmed without diagnosis of nephrotic syndrome, continue to hold cabozantinib and monitor UPCR weekly. If UPCR decreases to < 1.5, restart cabozantinib at a reduced dose. Continue monitoring UPCR once every week until two consecutive readings are < 1, then revert to UPCR monitoring frequency specified in the protocol.

UPCR, urine protein/urine creatinine ratio

6.9 Guidelines for the Prevention of Hemorrhagic Events

Hemorrhagic events have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. As preventive measures, subjects should be evaluated for potential bleeding risk factors prior to initiating cabozantinib treatment and 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 lesions with cavitations or tumor lesions which invade, encase, or abut major blood vessels. The anatomic location and characteristics of primary tumors or metastases 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, ulcerative colitis, and other inflammatory GI diseases.
- Underlying medical conditions which affect normal hemostasis (*e.g.*, 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.

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥0.5 teaspoon (2.5mL) of red blood). Treatment with cabozantinib should be interrupted if less severe forms of clinically significant hemorrhage occur and may be restarted after the cause of hemorrhage has been identified and the risk of bleeding has subsided at a dose agreed to by the sponsor and the investigator. Therapy of bleeding events should include supportive care and standard medical interventions.

Furthermore, subjects who develop tumors abutting, encasing, or invading a major blood vessel or who develop cavitation of their pulmonary tumors while on study treatment must be discontinued from cabozantinib treatment.

6.10 Rectal and Perirectal Abscess

Rectal and perirectal abscesses have been reported, sometimes in subjects with concurrent diarrhea. These should be treated with appropriate local care and antibiotic therapy. Cabozantinib should be held until adequate healing has taken place.

6.11 Guidelines for Prevention of GI Perforation/Fistula and Non-GI Fistula Formation

GI perforation/fistula and Non-GI fistula formation have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Carefully monitor for episodes of abdominal pain, especially in subjects with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis. Such risk factors include (but may not be limited to) the following:

GI-perforation/fistula:

- Intra-abdominal tumor/metastases invading GI mucosa.
- Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis .
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess
- Prior GI surgery (particularly when associated with delayed or incomplete healing). Complete healing following abdominal surgery or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

Additional risk factors include concurrent chronic use of steroid treatment or non-steroidal anti-inflammatory drugs. Constipation indicative of bowel obstruction should be monitored and effectively managed.

Non-GI fistula:

- Radiation therapy has been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with drugs that inhibit VEGF pathways. In addition, subjects who have undergone extensive surgery may be at increased risk of developing a fistula of the involved organs Non-GI fistula should be ruled out as appropriate in cases of onset of mucositis after start of therapy.

Discontinue all study treatment in subjects who have been diagnosed with GI or non-GI perforation/fistula.

6.12 Wound Healing and Surgery

VEGF inhibitors can cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. Therefore, surgical and traumatic wounds must have completely healed prior to starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with cabozantinib.

Treatment with cabozantinib must be interrupted for any wound healing complication which needs medical intervention. Treatment with cabozantinib can be resumed once wound healing has occurred unless otherwise prohibited in specific protocols. Cabozantinib should be discontinued in subjects with serious or chronic wound healing complications.

The appropriate dose hold interval prior to elective surgery to reduce the risk for wound healing complications has not been determined. In general, cabozantinib should be stopped at least 3 weeks (5 half-lives) prior to elective surgery.

6.13 Endocrine Disorders

Prospective studies of markers of thyroid functions are currently ongoing in two single-agent studies to characterize the effects of cabozantinib on thyroid function. Preliminary data indicate that cabozantinib affects thyroid function tests (TFTs) in a high number of subjects (see Cabozantinib Investigator's Brochure). Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended for subjects treated with cabozantinib. Management of thyroid dysfunction (*e.g.*, symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

Other endocrine disorders such as hypocalcemia and hyperglycemia, and associated laboratory changes, have been observed in less than 10% of subjects. Monitoring with standard laboratory tests for endocrine disorders and clinical examination prior to initiation and during treatment with cabozantinib is required. Cabozantinib should be discontinued in subjects with severe or life-threatening endocrine dysfunction.

6.14 Guidelines for Prevention of Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported with use of antiangiogenic drugs and bisphosphonates and denosumab in cancer patients. Additional risk factors for ONJ have been identified such as use of corticosteroids, chemotherapy, local radiotherapy, poor oral hygiene,

smoking, dental or orofacial surgery procedures, and cancer disease itself. Cases of osteonecrosis have been reported in subjects treated with cabozantinib, the details of which are provided in the current version of Investigator's Brochure. As a preventive measure, invasive dental procedures should be avoided if possible in subjects who have previously been treated with or concomitantly receive bisphosphonates or denosumab. In cases where dental procedures are unavoidable, the risks and benefits of a dental procedure and the extent of the procedure as well as the risk of developing osteonecrosis of the jaw need to be considered when deciding on the duration of a temporary treatment interruption of cabozantinib. If clinically possible, treatment with cabozantinib should be held for at least 2 weeks prior to a dental procedure and resumed after complete wound healing occurred.

Subjects with any documented case of osteonecrosis should have study treatment interrupted, and appropriate clinical management should be initiated. Re-initiation of study treatment must be discussed with and approved by the Sponsor on a case by case basis.

6.15 Guidelines for Management of Treatment-Emergent Corrected QT (QTc) Prolongation

Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Other factors which may contribute to QTc prolongation include

- Treatment with other drugs associated with QTc prolongation (see http://www.qtdrugs.org).
- Treatment with CyP 3A4 inhibitors (which may increase cabozantinib drug levels)
- Electrolyte changes (hypokalemia, hypocalcemia, hypomagnesemia).
- Medical conditions which can alter electrolyte status *e.g.*, severe or prolonged diarrhea.

Subjects having any of these additional risk factors while on cabozantinib must have ECGs performed approximately one week after the onset of these factors.

If at any time on study there is an increase in QTc interval to an absolute value >500 msec, two additional ECGs should be performed within 30 minutes after the initial ECG with intervals not less than 3 minutes apart. If the average QTcF from the three ECGs is >500 msec, study treatment must be withheld and the following actions should be taken:

- Check electrolytes, especially potassium, magnesium and calcium. Correct abnormalities as clinically indicated.
- If possible, discontinue any QTc-prolonging concomitant medications.
- Repeat ECG triplets hourly until the average QTcF is ≤500 msec or otherwise determined by consultation with a cardiologist.

The Sponsor should be notified immediately of any QTc prolongation event.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation has resolved. Cardiology consultation is recommended for evaluation and subject management. Symptomatic subjects must be treated according to standard clinical practice. No additional study treatment is to be given to the subject until after the event has resolved, the

subject has been thoroughly evaluated, and further treatment has been agreed to by the Sponsor. If any additional study treatment is given (*e.g.*, after correction of electrolyte abnormalities and normalization of QTcF), it will be at a reduced dose as agreed to by the investigator and the Sponsor.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 ADVERSE EVENT REPORTING FOR AN INVESTIGATIONAL AGENT

7.1.1 Definition of Adverse Events (AE)

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs in a patient administered a medical treatment, whether the event is considered related or unrelated to the medical treatment.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTCAE version 4.0 is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

The CTCAE Manual is also available on the NRG member web site (http://www.gog.org under MANUALS).

7.1.2 Reporting Expedited Adverse Events

Depending on the phase of the study, use of investigational agents, and role of the pharmaceutical sponsor, an expedited AE report may need to reach multiple destinations. For patients participating on a NRG trial, all expedited AE reports should be submitted by using the CTEP automated system for expedited reporting (CTEP-AERS). All CTEP-AERS submissions are reviewed by NRG before final submission to CTEP. Submitting a report through CTEP-AERS serves as notification to NRG, and satisfies the NRG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of AEs to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In signing the FDA-1572, the investigator assumes the responsibility for reporting AEs

to the NCI. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

7.1.3 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 3 calendar days of the initial 24-hour report.
  - "7 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND:

- Grades 2-4 myelosuppression (including neutropenia, anemia, and thrombocytopenia) that do not require hospitalization are exempt from expedited reporting

7.1.4 Procedures for Expedited Adverse Event Reporting

7.1.4.1 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy.

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

For the purposes of expedited reporting of adverse events to CTEP,

unexpected events are those not listed in the Specific Protocol Exceptions to Expedited Reporting (SPEER). The SPEER is a subset of AEs within the Comprehensive Adverse Event and Potential Risks List (CAEPR). This list of events is based on CTEP's clinical experience with this agent and defines "expected" Grade 2 and 3 AEs not requiring hospitalization as exempt from expedited reporting. The CAEPR is a complete list of reported and/or potential AEs associated with an agent under a CTEP IND. For questions or comments regarding the SPEER or CAEPR, please contact the CTEP-AERS MD Help Desk at CTEP-AERSmd@tech-res.com.

Secondary Malignancy:

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via AdEERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified. "

7.1.5 Routine Adverse Event Reporting

For studies using investigational agents, the NRG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The AEs reported through CTEP-AERS will also be included with the quarterly CDUS data submissions.

8. REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

Access requirements for OPEN, Medidata Rave: Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members' web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

8.1 Investigator Registration Requirements

8.1.1 This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Lead Protocol Organization. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch (PMB), CTEP, DCTD, NCI. These forms are available on the CTSU Member web site or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

All site staff (Lead Group and CTSU Sites as applicable) will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

8.2 Site Registration Requirements

Requirements for NRG-GY001 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

In addition to the requirements noted above, ALL institutions must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206); study-related regulatory documentation also may be e-mailed to the CTSU at CTSURegulatory@ctsu.coccg.org. This must be done prior to registration of the institution's first patient:

- IRB/REB approval letter
- IRB/REB approved consent (English and native language versions*)

***Note**: Institutions must provide certification/verification of IRB/REB consent translation to NRG Headquarters (described below IRB/REB registration number renewal information as appropriate.

8.2.1 Non-English Speaking Canadian and International Institutions:
Not Applicable

8.2.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS
Not Applicable

8.2.3 Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS
Not Applicable

8.3 Pre-registration Requirements

8.3.1 Surgeon Credentialing
Not Applicable.

8.3.2 Neurocognitive Function Testing Certification (09/08/15)
Not Applicable

8.4 RT-Specific Pre-Registration Requirements
Not Applicable

8.5 Patient Enrollment
Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.5.1 Oncology Patient Enrollment Network (OPEN)
Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. All site staff (NRG and CTSU Sites) will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- See beginning of Section 8 for information on obtaining a CTEP-IAM account.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the NRG, you must have an equivalent 'Registrar' role on the NRG roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records. *[Add if applicable: Additionally, a transmittal form to be used when faxing the signed consent form to the NRG Biostatistical Center will be provided. If it is necessary to reprint the randomization confirmation or the transmittal form, they can be reprinted through Coordinator Online via the* ***View a Patient Entry Report*** *under Patient Entry.]*

Further instructional information is provided on the OPEN tab located on the CTSU members' web site at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact NRG web support for assistance with web registration: [email to come] or call the NRG Registration Desk at [phone number to come], Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

9. DRUG INFORMATION

9.1 Cabozantinib (XL184) (NSC 761968)

9.1.1 Chemical Name: *N*-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate

Other Names: Cabozantinib, EXEL-7184, EXEL-02977184

Classification: Receptor Tyrosine Kinases Inhibitor (RTK)

CAS Registry Number: 1140909-48-3

Molecular Formula: $C_{28}H_{24}FN_3O_5.C_4H_6O_5$ **M.W.:** 635.6

9.1.2 Mode of Action: Cabozantinib (XL184) inhibits multiple RTKs implicated in tumor growth, metastasis, and angiogenesis, and targets primarily MET and VEGFR2. Other targets are RET, AXL, KIT, TIE-2, and FLT-3.

9.1.3 How Supplied: Cabozantinib (XL184) is supplied by Exelixis and distributed by the DCTD. Cabozantinib (XL184) is available in 20 mg and 60 mg tablet. The tablets are yellow film coated containing cabozantinib malate equivalent to 20 mg and 60 mg of cabozantinib. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape, and they are packaged as 30 tablets per bottle.

Cabozantinib (XL184) should be dispensed in its original container. Cabozantinib tablets are stable for up to 24 hours when dispensed in an open container, such as in a pill cup, and are stable for up to 7 days when dispensed in a closed container, such as a pharmacy dispensing bottle.

Cabozantinib (XL184) Tablet Components and Composition

Ingredient	Function	% w/w
Cabozantinib malate (25% drug load as cabozantinib)	Active Ingredient	31.7
Microcrystalline Cellulose (Avicel PH-102)	Filler	38.9
Lactose Anhydrous (60M)	Filler	19.4
Hydroxypropyl Cellulose (EXF)	Binder	3.0
Croscarmellose Sodium (Ac-Di-Sol)	Disenegrant	6.0
Colloidal Silicon Dioxide,	Glidant	0.3
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

9.1.4 Storage: Store intact bottles at controlled room temperature, 20^0 to 25^0C.

9.1.5 Stability: Stability testing of the intact bottles is on-going. cabozantinib is stable up to 24 hours when dispensed in an open container such as a pill cup, and up to 7 days when dispensed in a closed container such as a pharmacy bottle other than the original container.

9.1.6 Route of Administration: Oral.

9.1.7 Method of Administration: Take cabozantinib on an empty stomach; i.e., do not eat 2 hours before or 1 hour after each dose of cabozantinib. Do not crush or chew. Do not take missed dose within 12 hours of the next dose.

9.1.8 Potential Drug Interactions:

CYP450 isozymes:

In vitro, XL184 is a substrate of CYP3A4 and a weak substrate of CYP2C9. Co-administration of ketoconazole, a strong inhibitor of CYP3A4, increases XL184 AUC (37%) and rifampin, a strong inducer of CYP3A4, reduces XL184 AUC (77%). Therefore, avoid chronic use of strong CYP3A4 inducers such as rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifampentin, phenobarbital, and St. John's Wort while taking XL184. Avoid chronic use of strong CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir. Use alternative medications.

[**Note:** Use caution when discontinuing medication that is a strong inducer of CYP3A4 in patients who has been on a stable dose of XL184, as this could significantly increase the exposure to XL184.]

XL184 is a noncompetitive inhibitor of CYP2C8 (K_{iapp} = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (K_{iapp} = 10.4 μM) and CYP2C19 (K_{iapp} = 28.8 μM), and a weak competitive inhibitor of

CYP3A4 (estimated Ki_{app} = 282 μM) in human liver microsomal (HLM). IC_{50} values >20 μM were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes. XL184 is an inducer of CYP1A1 mRNA in human hepatocyte incubations,

Avoid grapefruit/ grapefruit juice and Seville oranges while participating in this trial.

P-glycoprotein/ MRP2:
In vitro data indicate that XL184 is unlikely to be a substrate but may be an inhibitor of P-glycoprotein transport activity (IC_{50} = 7.0 μM). Co-administration of XL184 with a P-gp substrate may result in an increase in P-gp substrate plasma concentration. Therefore, use caution when administering XL-184 with drugs known to be P-gp substrates (e.g., fexofenadine, aliskiren, ambrisentan, digoxin, colchicine, maraviroc, posaconazole, tolvaptan, etc.). In an in vitro assay, XL184 has shown to be a substrate of drug transporter MRP2, which may result in an increase plasma concentration of XL184 when administered with an inhibitor of MRP2. Use caution and monitor adverse events when administering XL184 with MRP2 inhibitors such as cyclosporine, delavirine, efavirenz, emtricitabine.

Protein bound:
XL184 is highly protein bound (≥ 99.9%). Use caution when coadministering XL184 with medications that are highly protein-bound (e.g., diazepam, furosemide, dicloxacillin, and propranolol). Avoid administration of warfarin with XL184 as warfarin is highly protein-bound and has a very narrow therapeutic index.

Antacids, H2-blockers, PPIs:
Co-administration of gastric pH modifying drugs such as PPI, H_2-blockers or antacids has no clinically-relevant effect on XL184 plasma PK in healthy volunteers; thus, concomitant use of these drugs with XL184 is allowed.

QTc prolongation:
Use caution when administering XL184 in patients with QT prolongation risk, a history of QT interval prolongation, or who are receiving antiarrhythmic drugs. Concomitant use of strong CYP3A4 inhibitors should be avoided as it may increase XL184 plasma concentrations. Refer to the protocol for QTcF criteria.

9.1.9 Potential Food Effect

The effect of food on the bioavailability of cabozantinib was evaluated in healthy adult subjects in a Phase 1, open-label, randomized, single-dose, two-treatment, two-way crossover study (Study XL184-004). Based on the preliminary PK data, a high fat meal did not appear to alter the terminal t1/2 but significantly increased the median tmax to 6 hours from 4 hours (fasted). The high fat meal also significantly increased both the cabozantinib Cmax and AUC values by 41% and 57%, respectively. Based on this result, cabozantinib should be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each cabozantinib dose).

9.1.10 Patient Care Implications: *Do not take grapefruit/ grapefruit juice or Seville oranges while participating in this trial. Inform physician and study healthcare team about current medications including over the counter drugs, herbals, or natural medicines. Refer to the protocol for management of adverse events*

9.1.11 Availability

Cabozantinib (XL184) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Cabozantinib (XL184) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Appendix I).

9.1.12 Agent Ordering and Agent Accountability (09/08/15)

NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (301) 496-5725 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

Agent Inventory Records - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9.1.13 Comprehensive Adverse Events and Potential Risks list (CAEPR) for XL184 (Cabozantinib s-malate, NSC 761968)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited

reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2438 patients.* Below is the CAEPR for XL184 (Cabozantinib s-malate).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, October 4, 2016[1]

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 4.0 Term) [n= 2438]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
ENDOCRINE DISORDERS			
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[2]	
		Gastrointestinal hemorrhage[3]	
		Gastrointestinal perforation[4]	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Oral pain		***Oral pain (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lipase increased		***Lipase increased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 3)***
Weight loss			***Weight loss (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 4.0 Term) [n= 2438]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Musculoskeletal and connective tissue disorders - Other (muscle spasms)		
		Osteonecrosis of jaw	
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
		Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
		Pneumothorax[6]	
		Respiratory fistula[7]	
	Respiratory hemorrhage[8]		
Voice alteration			***Voice alteration (Gr 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		***Dry skin (Gr 2)***
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous tissue disorders - Other (hair color changes)		***Skin and subcutaneous tissue disorders - Other (hair color changes) (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event[9]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage,

Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[5]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[6]Pneumothorax has been observed at a higher than expected frequency (15-20%) in a study treating patients with relapsed Ewing sarcoma and osteosarcoma all of whom had pulmonary metastases.

[7]Respiratory fistula includes Bronchial fistula, Bronchopleural fistula, Laryngeal fistula, Pharyngeal fistula, Pulmonary fistula, and Tracheal fistula under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[8]Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[9]Thromboembolic event includes pulmonary embolism which may be life-threatening.

Adverse events reported on XL184 (Cabozantinib s-malate) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that XL184 (Cabozantinib s-malate) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolytic uremic syndrome
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Myocarditis; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo
ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (hypopituitarism); Endocrine disorders - Other (thyroiditis); Endocrine disorders - Other (thyrotoxicosis); Hyperthyroidism
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (corneal epithelium defect)
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Duodenal ulcer; Dysphagia; Enterocolitis; Esophageal ulcer; Esophagitis; Flatulence; Gastric ulcer; Gastrointestinal disorders - Other (anal fissure); Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (pneumoperitoneum); Hemorrhoids; Ileus; Pancreatitis; Rectal pain; Rectal ulcer
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Fever; Gait disturbance; General disorders and administration site conditions - Other (implant site inflammation); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic cirrhosis); Hepatobiliary disorders - Other (hepatitis toxic); Portal vein thrombosis
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Autoimmune disorder
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (post procedural hemorrhage); Injury, poisoning and procedural complications - Other (tendon injury); Wound dehiscence; Wrist fracture
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; Cardiac

troponin I increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (blood lactate dehydrogenase increased); Investigations - Other (D-dimer); Investigations - Other (eosinophil count increased); Investigations - Other (glucose urine present); Investigations - Other (urine ketone body present); Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Glucose intolerance; Hyperglycemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Buttock pain; Flank pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorders - Other (muscle hemorrhage); Musculoskeletal and connective tissue disorders - Other (osteonecrosis); Musculoskeletal and connective tissue disorders - Other (rhabdomyolysis); Myalgia; Neck pain; Osteoporosis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lip and/or oral cavity cancer); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysesthesia; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders - Other (cerebral hematoma); Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (spinal cord compression); Nervous system disorders - Other (vocal cord paralysis); Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Psychiatric disorders - Other (mental status changes)
RENAL AND URINARY DISORDERS - Chronic kidney disease; Hematuria; Renal and urinary disorders - Other (azotemia); Renal and urinary disorders - Other (hemorrhage urinary tract); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (scrotal ulcer/erythema/edema); Vaginal fistula
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Aspiration; Atelectasis; Hypoxia; Laryngeal edema; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Productive cough; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (nasal septum perforation); Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (rales); Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (pain, sloughing of skin and erythema); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin and subcutaneous tissue disorders - Other (splinter hemorrhages); Skin ulceration
VASCULAR DISORDERS - Hematoma; Hypotension; Superior vena cava syndrome; Vascular disorders - Other (bleeding varicose vein); Vasculitis

Note: XL184 (Cabozantinib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10. PATHOLOGY

Patients must have recurrent or, progressive clear cell ovarian cancer not solely based on CA-125. A retrospective review of all patients entered will be performed to confirm clear cell histology. Primary tumors must be at least 50% clear cell histomorphology in order to be eligible or have a histologically documented recurrence with at least 50% clear cell histomorphology.

Stained pathology slides are required for central review by the NRG Pathology Committee to confirm eligibility for the protocol. At least one representative H&E stained slide (or slides) demonstrating primary site, histologic cell type, and grade, and **one** H&E stained slide showing the most advanced stage of disease will be required. When submitting pathology material to the NRG Statistics and Data Center individual slides must be labeled with NRG Patient ID, patient initials and the surgical / pathology accession number (e.g., S08-2355) and block identifier (e.g., A6). Do not label the slides with disease site (e.g., right ovary) or procedure date. Pack the labeled slides into plastic slide cassette(s). Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. Please include the NRG Patient ID, patient initials, and protocol number on all pages of the pathology report and black out the patient's name. Ship stained pathology slides and the official pathology report in your own shipping containing using postal mail at your own expense directly to the **Pathology Materials Coordinator at the NRG Statistics and Data Center, Roswell Park Cancer Institute, Research Studies Center, Carlton and Elm Streets, Buffalo, New York, 14263**; phone (716) 845-5702.Please see section 13.2 for additional requirements and instructions.

11. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

11.1 Reimbursement

See the Reimbursement and Case Credit Schedule found on the NRG web site (link to come).

11.2 Translational Science

Note: Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

11.2.1 Specimen Requirements **(09/08/15)**

If the patient gives permission to participate in this **optional** study component, then participating sites within the United States are required to submit the patient's specimens as outlined below.

Required Specimen (Specimen Code)	Collection Time Point	Sites Ship Specimens To
FFPE Primary Tumor (FP01)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to all treatment	NRG Oncology Biospecimen Bank-Columbus within 8 weeks of registration[1]
FFPE Metastatic Tumor (FM01)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to all treatment *(Optional if FP01, FRP01, FRM01, FPP01, or FPM01 is submitted)*	
FFPE **Recurrent Primary** Tumor (**FRP01**)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment *(Optional if FP01, FM01, FRM01, FPP01, or FPM01 is submitted)*	

FFPE **Recurrent Metastatic** Tumor (**FRM01**)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment *(Optional if FP01, FM01, FRP01, FPP01, or FPM01 is submitted)*	
FFPE **Persistent Primary** Tumor (**FPP01**)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment *(Optional if FP01, FM01, FRP01, FRM01, or FPM01 is submitted)*	
FFPE **Persistent Metastatic** Tumor (**FPM01**)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment *(Optional if FP01, FM01, FRP01, FRM01, or FPP01 is submitted)*	

*A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the NRG Oncology Biospecimen Bank-Columbus.
1 NRG Oncology Biospecimen Bank-Columbus/ Protocol NRG-GY001, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH
43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

11.2.2 Specimen Procedures

A detailed description of specimen procedures can be found in Appendix V.

11.2.3 Laboratory Testing

Details regarding the distribution of translational science specimens to investigators can be found in Appendix V.

11.2.3.1 Immunohistochemical Analysis

Unstained sections of formalin-fixed, paraffin-embedded (FFPE) tumor will be batch shipped upon trial completion to Dr. Michael Birrer (address below) for (1) immunohistochemical analysis of PTEN, pAKT, and cyclin E, and (2) fluorescence *in situ* hybridization analysis of MET amplification.

Dr. Michael Birrer
Massachusetts General Hospital
55 Fruit St, Yawkey 9072
Boston, MA 02114
Phone: 617-724-4800
Email: mbirrer@partners.org

Unstained sections of FFPE tumor will be batch shipped upon trial completion to Dr. Panagiotis Konstantinopoulos (address below) for immunohistochemical analysis of MET.

Dr. Panagiotis Konstantinopoulos
Dana-Farber Cancer Institute

450 Brookline Ave, Yawkey 1424
Boston, MA 02215
Phone: 617-632-2334
Email: panagiotisa.konstantinopoulos@dfci.harvard.edu

11.2.3.2 MET Pathway Gene Expression

Unstained sections of FFPE tumor will be batch shipped upon trial completion to Dr. Michael Birrer (address above) for MET pathway gene expression analysis.

11.2.4 Banking Specimens for Future Research

Details regarding the banking and use of specimens for future research can be found in Appendix V.

11.3 Quality of Life

Not applicable.

12. DATA AND RECORDS

12.1 Data Management/Collection

Data collection for this study will be done exclusively through Medidata Rave®. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS (Regulatory Support System). To access iMedidata/Rave, see beginning of Section 8.

Each person responsible for data entry must be on the NRG roster in order to receive access to Medidata Rave®.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Once an account is activated, eLearning modules will be available for Rave RDC instructions. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts also will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-

mail at ctsucontact@westat.com.

12.2 NRG Data Management Forms (09/08/15)

The following forms must be completed and submitted to the Statistical and Data Monitoring Center (SDMC) in accordance with the schedule below. NRG electronic case report forms **must** be submitted through the Medidata Rave Electronic Data Entry System (www.imedidata.com). All amendments to forms must also be submitted through Medidata Rave. The pathology reports can be sent to the NRG SDMC via postal mail or uploaded in Medidata Rave. The upload option is an alternative method for submitting paper reports.

Form	Comments
Baseline Folder *(Forms due within 2 weeks of registration)*	
Baseline/History Forms: - Visit Information – Baseline Form - Registration Form - History Information Form - Primary Surgery Form - Chemotherapy Information Form - Pre-Treatment Summary Form - Specimen Consent - Concomitant Medications form - ECG Information form Solid Tumor Evaluation Forms: - Target Lesions Form - Non-Target Lesions Form	The appropriate forms will load in the Baseline Folder based on the answers reported on the corresponding Baseline Visit Information form.
Visit Folder *(Forms due within 2 weeks of the completion of each cycle)*	
Cycle Information and Treatment Forms: - Visit Information Form - Cycle Drug Information Form - Labs and Chemistries Form - Vitals Form - ECG Information Form - Bio-Marker Information form	The appropriate forms will load in the Visit Folder based on the answers reported on the corresponding Visit Information forms.

Toxicity Forms: - Section 1 Form - Adverse Event Form - Adverse Event Grades Solid Tumor Evaluation Forms: - Target Lesions Form - Non-Target Form - New Target Lesions Form - Status and Response Form	

Form	Comments
Pathology Folder ***(Reports and slides due within 6 weeks of registration)***	
Primary disease: Pathology Report Stained Slides Recurrent or Persistent Disease: Pathology Report Stained Slides	Submit stained slides with two copies of the pathology report to SDC via postal mail or upload the pathology report online via RAVE. Stained pathology slides are required for central review by the GOG Pathology Committee. See Section 10 for Pathology eligibility. All stained slides MUST be submitted via postal mail.

Form	Comments
Translational Research Folder	
TR Forms: - FFPE Primary Tumor (FP01) - FFPE Metastatic Tumor (FM01) *optional* - FFPE Recurrent Primary Tumor (FRP01) *optional* - FFPE Recurrent Metastatic Tumor (FRM01) *optional* - FFPE Persistent Primary Tumor (FPP01) *optional* - FFPE Persistent Metastatic Tumor (FPM01) *optional*	An electronically completed copy of Form TR must accompany each specimen shipped to the NRG Oncology Biospecimen Bank-Columbus. Handwritten forms will not be accepted. FP01, FM01, FRP01, FRM01, FPP01, and FPM01 are due 8 weeks from registration.
Treatment Completion Folder ***(Forms due within 2 weeks of treatment completion)***	
Treatment Completion Form	
Follow-up Visit Folder ***(Forms due within 2 weeks of follow-up visits, disease progression or death)***	

Visit Information Follow-Up Form - Bio-Marker Information form Follow-Up Form Vitals form Follow-Up Period Adverse Event: - Reporting Form – Part 1 - Reporting Form – Part 2 Solid Tumor Evaluation: - Target Lesions Form - Non-Target Form - New Target Lesions Form - Status and Response Form	Follow-up visits should be scheduled quarterly for 2 years, semi-annually for 3 more years, and annually thereafter. The appropriate forms will in the Follow-up Visit Folder based on the answers reported on the corresponding Follow-up Visit Information forms.

12.3 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Sections 7.1.4 and 7.1.5 for information about expedited and routine reporting.

For reporting of secondary cancers or other report forms available in Rave:
Indicate form for reporting in Rave, timeframes, add if loading of the pathology report is required.

Summary of Data Submission: Refer to the NRG website [*Insert weblink to data submission summary]*

12.4 Global Reporting/Monitoring

This study will be monitored by the **Complete** Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design

The primary objective of this study is to assess the anti- tumor activity of cabozantinib (XL184) in women with persistent or recurrent clear cell ovarian cancer. The primary measures of efficacy will be objective response and whether the patient survived progression-free for at least 6 months.

This is a single-arm, Phase II clinical trial that will use a flexible, bivariate, three-stage design.

13.1.1 Stratification

This is a single-arm, trial with no randomization and thus no stratification.

13.1.2 Randomization

This is a single-arm, trial with no randomization.

13.1.3 Total Accrual

If the trial enters all three stages, the total accrual target will be 31 patients but will be allowed to range from 27 to 34 (due to the difficulty in accruing precise numbers of patients in a multicenter trial).

13.1.4 Justification of Design:

The biologic mechanism of the study agent is expected to impede the growth of tumors already present and inhibit the development of new metastases. Therefore, the endpoint includes progression-free survival at 6 months, which is capable of detecting stabilization of disease. In addition, there is also interest in objective tumor response as a primary measure of efficacy. So the design of the study will use both endpoints to formally draw conclusions about the activity of the drug. In particular, if either endpoint indicates activity, the drug will be considered clinically interesting and worthy of further investigation.

13.2 Study Endpoints

Primary endpoints:

- Progression-free survival at six months
- Complete or partial objective tumor response

Secondary endpoints:

- Nature, frequency and maximum degree of toxicity as assessed by CTCAE v4
- Progression-free survival
- Overall survival.

13.3 Primary Objectives Study Design

13.3.1 Primary Hypothesis and Endpoints

The primary hypothesis of this study tests the proportion of patients with objective tumor response (complete or partial) (π_r) and the proportion of patients surviving progression free for at least six months (π_s). Based on the historical data shown below, the null hypothesis is that the proportion of patients with objective tumor response will be ≤10% and the proportion of patients surviving progression free for at least six months (π_s) will be ≤15%, i.e.,:

$$H_0: \pi_r \leq 0.10 \text{ and } \pi_r \leq 0.15.$$

The alternative hypothesis is the complement of the null parameter space, and the study is powered to detect the following points in the alternative space: $\pi_r = .3$ or $\pi_s = .4$.

The primary analysis will include all eligible patients who receive study drug.

The guiding principle in selecting the design for this study is to limit the number of patients treated with clinically ineffective therapies but to estimate efficacy with reasonable precision for those agents that are clinically active. Strict adherence to a planned sample size is not practical because the accrual is complicated by the logistics of managing a multi-center phase II study. Instead, a flexible sample size will be used in which once the targeted sample size is attained, those patients who have already been approached will be permitted to register.

Historical Data and Design Parameters
The design parameters for this study arise from considering the results of three series of protocols: GOG-0126, GOG-0146, and GOG-0170. The patients entered on GOG-0126 were required to have platinum resistant disease (i.e. a platinum free interval of less than 6 months) while the patients entered on GOG-0146 were required to be GOG platinum sensitive (i.e. a platinum-free interval between 6 and 12 months). Both of these patient populations were allowed in GOG-0170 and will be allowed to enter the current protocol. Selected GOG protocols from these series are listed in Table 13.1 and were selected for historical controls because the population is similar to the current protocol and the agents investigated in the selected protocols were deemed to have minimal activity.

Table 13.1: Measures of Efficacy by Protocol and Section for All Patients and for Clear Cell Patients in the GOG 0126, 0146, and 0170 Series of Protocols Restricted to Studies with Agents Deemed Inactive or Minimally Active

Section	Evaluable (All, Clear Cell)	Response, n (%)		PFS at 6 Months, n (%)	
	N	All	Clear Cell	All	Clear Cell
GOG-126 Series					
B	26, 3	3 (12%)	1 (33%)	4 (15%)	1 (33%)
C	33, 0	3 (9%)	0 (0%)	9 (27%)	0 (0%)
D	27, 5	2 (7%)	0 (0%)	5 (19%)	0 (0%)
E	58, 7	5 (9%)	0 (0%)	10 (17%)	1 (14%)
G	27, 2	1 (4%)	0 (0%)	2 (7%)	0 (0%)
H	26, 1	1 (4%)	0 (0%)	1 (4%)	0 (0%)
K	23, 2	1 (4%)	0 (0%)	5 (22%)	0 (0%)
GOG-146 Series					
B	28, 0	3 (11%)	0 (0%)	6 (21%)	0 (0%)
E	23, 4	1 (4%)	1 (25%)	3 (13%)	1 (25%)
F	28, 1	2 (7%)	0 (0%)	8 (29%)	0 (0%)
H	54, 3	1 (2%)	0 (0%)	7 (13%)	0 (0%)
J	30, 2	0 (0%)	0 (0%)	2 (7%)	0 (0%)
L	21, 0	2 (10%)	0 (0%)	10 (48%)	0 (0%)
N	55, 0	3 (5%)	0 (0%)	11 (20%)	0 (0%)
GOG-170 Series					
C	27, 0	1 (4%)	0 (0%)	4 (15%)	0 (0%)

E	57, 0	1 (2%)	0 (0%)	10 (18%)	0 (0%)
G	26, 0	0 (0%)	0 (0%)	2 (8%)	0 (0%)
H	27, 1	1 (4%)	0 (0%)	2 (7%)	0 (0%)

13.3.2 Definitions of Primary Endpoints and How These Will Be Analyzed

To evaluate the hypothesis stated above, we will utilize a modification of the bivariate two-stage design of Sill, et al (2012), which uses the numbers of patients progression-free at 6 months and the number with objective responses to make inferences about the efficacy of the study drug. We will add an additional stage to the study—preceding the Sill design. In the first stage, if all patients have increasing disease (progression) at their first scan (which will be done after 2 cycles or 8 weeks), the trial will be stopped, and the agent will be not considered worthy of further investigation in this patient population. The trial will be suspended for this first stage decision; however, if at any point, any of these patients do *not* have increasing disease, it would not be necessary to suspend the trial.

If the trial enters the second stage and third stage, the following decision rules will be applied where

- $X_{r(1)}$ is the number of patients with objective tumor responses (partial or complete) within four months of starting treatment in stage 1,
- $X_{s(1)}$ is the number of patients progression-free at 6 months after stage 1,
- $X_{r(2)}$ is the number of patients with objective tumor responses after stage 2,
- $X_{s(2)}$ is the number of patients progression-free at 6 months after stage 2,
- X_r is the cumulative number of patients with objective tumor responses after stage 3,
- X_s is the cumulative number of patients progression-free at 6 months after stage 3,
- $C_{r(1)}$ is the critical value for $X_{r(1)}$,
- $C_{r(2)}$ is the critical value for $X_{r(2)}$,
- $C_{s(2)}$ is the critical value for $X_{s(2)}$,
- C_r is the critical value for X_r, and
- C_s is the critical value for X_s.

Decision Rules:

1) If $X_{r(1)} > C_{r(1)}$ after the first stage, then the study will open to a second stage of accrual to further evaluate the activity of the drug,
   a. or if $X_{s(1)} > C_{s(2)}$, the trial will open to the third stage of accrual (because the number of patients with PFS≥6 months in the first stage will be greater than that required in the second stage).
2) If either $X_{r(2)} > C_{r(2)}$ or $X_{s(2)} > C_{s(2)}$ after the second stage, then the study will open to a third stage of accrual to further evaluate the activity of the drug.
3) If either $X_r > C_r$ or $X_s > C_s$ after the third stage and clinical judgment indicates, then the agent will be deemed clinically interesting and worthy of further investigation.

13.3.3 Sample Size and Power Calculations

The targeted accrual for the first stage will be 12 eligible and treated patients but will be permitted to range from 10 to 14. If all patients have increasing disease on their first scan, the trial will be terminated for futility. The cumulative targeted accrual for the second stage will be 19 eligible and evaluable patients but permitted to range from 15 to 22 for administrative reasons. The cumulative targeted accrual for the third stage will be 31 eligible and evaluable patients. Critical values for each stage are provided in Table 13.2, Table 13.3, and Table 13.4, respectively.

We acknowledge that a three-stage trial may lengthen the trial beyond what is normally expected; therefore, we will follow the following plan for the first stage. After eight patients have been followed for response for four months (which is required for the $X_{r(1)}$ endpoint), if no responses have been seen, we will suspend the trial; otherwise, we will continue to stage 2. If the trial is suspended, we will then follow any additional patients for the response endpoint; given the anticipated accrual rate of 1/month, this should be approximately four or less. If no responses are seen, the trial will end.

The operating characteristics of each stage's decision rules are provided in Table 13.5 and Table 13.6 under the assumption of independence of response and PFS and under an assumption of a high association between response and PFS, respectively. To assess the operating characteristics when the two primary endpoints are not independent, the probability calculations (carried out as outlined above) were done with the assumption that the joint probability (π_{11}) of response and PFS at 6 months is equal to $0.90 \cdot \min\{\pi_r, \pi_s\}$, which would carry a fairly high degree of association.

Table 13.2: Stage 1 critical values for the number of patients with objective responses within four months of starting treatment

n_1 †	10	11	12	13	14
$C_{r(1)}$	0	0	0	0	0
† n_1 is the sample size for the first stage of accrual.					

Table 13.3: Stage 2 critical values for the number of patients with objective responses and the number who survive progression-free for 6 months

	n_2 †							
	15	16	17	18	19	20	21	22
$C_{r(2)}$	1	1	2	2	2	2	2	2
$C_{s(2)}$	3	3	3	3	4	4	4	5
† n_2 is the cumulative sample size for the second stage of accrual								

Table 13.4: Stage 3 critical values for the number of patients with objective responses and the number who survive progression-free for 6 months

Stage 3 (C_r, C_s)	
n_2 †	n‡

	27	28	29	30	31	32	33	34
15	(4,7)	(5,7)	(5,7)	(5,8)	(5,8)	(5,8)	(6,8)	(6,9)
16	(4,7)	(5,7)	(5,7)	(5,8)	(5,8)	(5,8)	(6,8)	(6,9)
17	(4,7)	(5,7)	(5,7)	(5,8)	(5,8)	(5,8)	(6,8)	(6,9)
18	(4,7)	(5,7)	(5,7)	(5,8)	(5,8)	(5,8)	(6,8)	(6,9)
19	(4,7)	(5,7)	(5,7)	(5,8)	(5,8)	(5,8)	(6,8)	(6,9)
20	(4,7)	(5,7)	(5,7)	(5,8)	(5,8)	(5,8)	(6,8)	(6,9)
21	(4,7)	(5,7)	(5,7)	(5,8)	(5,8)	(5,8)	(6,8)	(6,9)
22	(4,7)	(5,7)	(5,7)	(5,8)	(5,8)	(5,8)	(6,8)	(6,9)

† n_2 is the cumulative sample size for the second stage of accrual
‡ n is the cumulative sample size after the third stage of accrual.

Table 13.5: Average power of testing procedure when accrual guidelines are met and under the assumption that response and surviving progression-free for 6 months are independent events

Scenario (probabilities)			Probability of†		
	π_r	π_s	Stopping at Stage 1	Stopping at Stage 2	Rejecting H_0
Null	0.10	0.15	0.260	0.308	0.097
Alternative Response Only	0.30	0.15	0.014	0.026	0.906
Alternative PFS Only	0.10	0.40	0.072	0.022	0.867
Alternative Both	0.30	0.40	0.004	0.002	0.989

† Probabilities are averaged across all possible combinations of n_1, n_2, and n_3; and are computed from 10,000 simulations for each sample size combination.

Table 13.6: Average power of testing procedure when accrual guidelines are met and under the assumption that response and surviving progression-free for 6 months are not independent events‡

Scenario (probabilities)			Probability of†		
	π_r	π_s	Stopping at Stage 1	Stopping at Stage 2	Rejecting H_0
Null	0.10	0.15	0.284	0.342	0.083
Alternative Response Only	0.30	0.15	0.016	0.032	0.900
Alternative PFS Only	0.10	0.40	0.111	0.023	0.833
Alternative Both	0.30	0.40	0.013	0.012	0.954

‡ Joint probability $\pi_{11} = 0.90 \cdot \min\{\pi_r, \pi_s\}$.
† Probabilities are averaged across all possible combinations of n_1, n_2, and n_3; and are computed from 10,000 simulations for each sample size combination.

13.4 Study Monitoring of Primary Objectives

Monitoring of the primary objectives is an inherent part of the three-stage design and is described fully in sections 13.3.2 and 13.3.3.

13.5 Accrual Considerations

13.5.1 Accrual Rate

We expect to accrue approximately one patient per month. This is based on the accrual to study GOG-0254, which accrued 35 patients over 34 months of active accrual in the same patient population.

13.5.2 Accrual Goal

Ten patients are required for the first stage, a cumulative target of 19 (allowable range 15-22) in the second stage, and a cumulative target of 31 (allowable range 27-34) in the third stage.

13.5.3 Study Duration

Approximately sixteen months are expected to be required for the first stage, ten months for the second stage, and twelve months for the third stage.

13.5.4 Estimated Duration for Completion of Primary Endpoint:

Completion of the primary endpoints is expected approximately 52 months after activation.

13.6 Dose Level Guidelines

Not applicable.

13.7 Secondary or Exploratory Elements (including correlative science aims)

If there are secondary or exploratory aims, they must be addressed in the Statistical Considerations section.

13.7.1 Secondary Hypotheses and Endpoints:

Below are the secondary objectives and endpoints. These are focused on estimation and description; there are no associated hypotheses.

Objective: To determine the nature, frequency and maximum degree of toxicity as assessed by CTCAE v4 for cabozantinib (XL184)
Endpoint: Adverse events based on CTC AE v 4.

Objective: To determine the PFS and OS for patients with persistent or recurrent clear cell ovarian cancer treated with cabozantinib (XL184).
Endpoints: Progression-free Survival and Overall Survival

13.7.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Adverse events are based on CTC AE v 4. Events will be tabulated using maximum grade for each AE term regardless of attribution to study drug.

Overall survival and PFS of patients on this study will be characterized graphically and using descriptive statistics such as median survival based on Kaplan-Meier estimates.

13.7.3 Interim Analysis for All Other Endpoints (Goals): Optional
No interim analyses are planned for secondary endpoints.

13.7.4 Power Calculations:
As there are no hypotheses for the secondary endpoints, no power calculations are done.

13.7.5 Expected Sample Size or Patient Cohorts:
Not applicable.

13.7.6 Data and Safety Monitoring (09/08/15)
Data sheets from studies on this protocol will be reviewed before each semi-annual meeting and will also be reviewed by the Study Chairperson in conjunction with the NRG Statistics and Data Management Center (SDMC). In some instances, because of unexpectedly severe toxicity, the NRG SDMC may elect, after consultation with the Study Chairperson and the Medical Oncology Committee, to recommend early closure of a study.

The frequency and severity of all toxicities are tabulated from submitted case report forms and summarized for review by the study chairperson, Gynecologic Rare Tumor Committee, and NRG Safety Review Committee (SRC) in conjunction with each semi-annual NRG meeting. For studies sponsored by CTEP of the National Cancer Institute (NCI), standardized toxicity reports are also submitted to the drug and disease monitors at the Investigational Drug Branch (IDB) and Clinical Investigation Branch (CIB). As this is a multi-stage multi-institutional phase II protocol, the initial overall review of toxicity is usually performed after completion of the first stage of accrual, at which point accrual is generally suspended pending formal analysis of response.

All serious and/or unexpected events are communicated to the Study Chair, sponsor, and regulatory agencies as mandated in the protocol. These reports are reviewed by the Study Chair (or designated co-chair) within two working days for consideration of investigator notification, amendment, or immediate study suspension. All participating institutions will then receive notification of the toxicities and reason for study suspension. Under these circumstances, accrual cannot be re-activated until the study is reviewed by the NRG SRC. However, patients currently receiving treatment may continue to receive treatment in accordance with protocol guidelines at the discretion of their physicians, unless directed otherwise.

13.8 Exploratory Hypothesis and Endpoints
There are no exploratory objectives.

13.9 Gender/Ethnicity/Race Distribution
The distribution below is based on the maximum, two-stage sample size of 34 patients.

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	2	0	2
Not Hispanic or Latino	32	0	32

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Ethnic Category: Total of all subjects	34	0	**34**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	1	0	1
Asian	2	0	2
Black or African American	1	0	1
Native Hawaiian or other Pacific Islander	1	0	1
White	29	0	29
Racial Category: Total of all subjects	34	0	**34**

14. PUBLICATION INFORMATION AND ADMINISTRATIVE AGREEMENTS

TBD

15. EVALUATION CRITERIA

15.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

15.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment on study.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

15.1.2 *Disease Parameters*

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 by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy. Thus, a confirmed biopsy in an irradiated area at a date longer than 90 days post-completion of radiation can be considered a target lesion to assess progression and response.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated

measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

15.1.3 *Methods for Evaluation of Measurable Disease*

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

CA125 (Ovarian, fallopian tube and primary peritoneal cancer trials): CA125 alone cannot be used to assess response. If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response. Specific guidelines for CA-125 response (in recurrent ovarian cancer) have been published [*JNCI* 96:487-488, 2004]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer

[*JNCI* 92:1534-1535, 2000].

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

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 mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

15.1.4 Response Criteria

15.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

15.1.4.2 Evaluation of Non-Target Lesions

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

Note: If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of CA125 level above the normal limits.

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

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).

15.1.4.3 Progression Based on Serum CA-125

1. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart

OR

2. Patients with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart

OR

3. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart

When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks that such progression is documented. The patient should continue therapy, as per protocol, until progressive disease is documented by imaging.

15.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The

patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

15.1.5 Duration of Response

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

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

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

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

15.1.6 Progression-Free Survival

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

15.1.7 Survival

Survival is defined as the duration of time from start of treatment to time of death or the date of last contact.

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APPENDIX I - GENERAL CHEMOTHERAPY GUIDELINES:

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.
- It will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of 21 or 28 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).
- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.
- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).
- Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.
- Maximum body surface area used for chemotherapy dose calculations will be 2.0 m2. For chemotherapy dose calculations that use mg/kg, there will be no maximum kilogram amount used (doses will be calculated on actual weight in kg).

APPENDIX II - CRADA

NCI/ DCTD Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA) a Cooperative Research and Development Agreement (CRADA) or a Clinical Supply Agreement, hereinafter referred to as Collaborative Agreement:

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data":

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborators confidential proprietary information.

APPENDIX III - CONGESTIVE HEART FAILURE – NEW YORK HEART ASSOCIATION CLASSIFICATION

Class	Definition
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even with rest. With any physical activity, increased discomfort is experienced.

Source: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964: 114.

APPENDIX IV - PATIENT'S PILL DIARY: CABOZANTINIB

NRG-GY001 – A Phase II Trial of Cabozantinib (XL-184) (NSC #761968) in Women with Recurrent Clear Cell Carcinoma of the Ovary, Fallopian Tube, or Peritoneum

Today's date _____

Patient Name_____Patient Study ID _____
Cycle #_____ (*initials acceptable for patient's name)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle (28 days).
2. You will take ___ tablets each morning.
   Do not eat for at least 2 hours before and at least 1 hour after taking cabozantinib.
3. Record the date, the number of pills you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottle and this form to your physician when you go for your next appointment.
6. If you miss a dose of Cabozantinib, take it as soon as you remember (as long as it is not within 12 hours of the time for your next dose). If it is within 12 hours of the time for your next dose skip the missed dose. Do not take a missed dose within 12 hours of the next dose. Vomited doses will not be made up.

Date	Day	# pills and when taken: Cabozantinib 20mg	60 mg	Time	Comments	Date	Day	# pills and when taken: Cabozantinib 20mg	60 mg	Time	Comments
	1						15				
	2						16				
	3						17				
	4						18				
	5						19				
	6						20				
	7						21				
	8						22				
	9						23				
	10						24				
	11						25				
	12						26				
	13						27				
	14						28				

Patient's Signature: _____ Date: _____

APPENDIX V - TRANSLATIONAL SCIENCE

I. Obtaining a Bank ID for Translational Science Specimens

Only one Bank ID (# # # # - # # - G # # #) is assigned per patient. All translational science specimens and accompanying paperwork must be labeled with this coded patient number.

A Bank ID is automatically assigned once the Specimen Consent is completed and indicates that a patient has agreed to participate in the translational science component.

A Bank ID can also be obtained online via the Tissue Bank Portal link on the NRG Oncology website. Obtain the patient's study ID for all protocols with translational science specimen requirements before requesting a Bank ID from the Tissue Bank Portal. **Be sure to indicate if the patient has a legacy GOG ID when registering.** This will ensure the patient is only assigned one Bank ID. The GOG ID – Bank ID Lookup on the Tissue Bank Portal can be used to search for an existing Bank ID.

Please contact User Support if you need assistance or have assigned more than one Bank ID to a patient (Email: support@gogstats.org; Phone: 716-845-7767).

II. Requesting Translational Science Specimen Kits

Kits are not provided for this protocol.

III. Formalin-Fixed, Paraffin-Embedded Tissue Shipped to the GOG Tissue Bank

Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the specimen type (primary, metastatic, recurrent, persistent). **Primary** and **metastatic** tumor should be collected prior to all treatment. **Recurrent** and **persistent** tumor should be collected prior to the study treatment. Recurrent or persistent tumor collected from the site of primary disease should be labeled **recurrent primary** or **persistent primary**, respectively. Recurrent or persistent tumor collected from a site other than the site of primary disease (e.g., lymph node) should be labeled **recurrent metastatic** or **persistent metastatic**, respectively. Only one block may be submitted per tissue type.

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then 20 unstained slides (10 charged, 5µm and 10 uncharged, 10 µm) should be submitted. All tissue sections should be cut sequentially from the same block.

Note: Stained slides to confirm patient eligibility by central pathology review are required for this protocol, but are NOT sent to the GOG Tissue Bank. If these slides will be cut from the same block that will be submitted for translational science, your pathology department should cut these slides prior to submitting the block for translational science.

The type of specimen (block or slides) should be specified on Form TR. If submitting slides, the slide type, thickness, and count should also be specified.

All FFPE tissue should be submitted with the corresponding pathology report.

Labeling Translational Science Specimens
A waterproof permanent marker or printed label should be used to label each translational science specimen with:

Bank ID (# # # # - # # - G # # #)
protocol number (NRG - GY - # # #)
specimen code (e.g., WB01)
collection date (mm/dd/yyyy)
surgical pathology accession number (tissue specimens only)
block number (tissue specimens only)

Note: If labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

IV. Submitting Form TR
An electronically completed copy of Form TR must accompany each specimen shipped to the GOG Tissue Bank. Handwritten forms will not be accepted.

Note: A copy does not need to be sent to the GOG Tissue Bank if specimens are not collected.

Retain a printout of the completed form for your records.

Please contact User Support if you need assistance (Email: support@gogstats.org; Phone: 716-845-7767).

V. Shipping Translational Science Specimens
An electronically completed copy of Form TR must be included for each translational science specimen.

A. FFPE Tissue
FFPE tissue, an electronically completed copy of Form TR, and a copy of the corresponding pathology report should be shipped using your own container at your own expense to:

GOG Tissue Bank / Protocol NRG-GY-001
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205
Phone: 614-722-2865
FAX: 614-722-2897
Email: GOGBank@nationwidechildrens.org

Do not ship FFPE tissue for Saturday delivery.

VI. Distributing Translational Science Specimens
Note: Testing of banked specimens will not occur until an amendment to this treatment protocol

(or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

The NRG Oncology Statistics and Data Management Center-Buffalo Office and GOG Tissue Bank (or alternate laboratory) will coordinate the distribution of translational science specimens to approved investigators.

Investigators will not be given access to any personal identifiers.

Investigators will be responsible for the direct supervision and oversight of the translational science and for keeping accurate records.

Investigators will ensure the results are linked to the appropriate translational science specimen-specific identifiers and are responsible for transferring relevant laboratory data to the NRG Oncology Statistics and Data Management Center-Buffalo Office.

At the discretion of the Chair of the Translational Science-GYN Committee and the Director of the GOG Tissue Bank, investigators may be required to ship any specimens (or by-products) remaining after the completion of the translational science to the GOG Tissue Bank.

VII. Banking Translational Science Specimens for Future Research
Specimens will remain in the GOG Tissue Bank and made available for approved research projects if the patient has provided permission for the use of her specimens for future health research. The patient's choices will be recorded on the signed informed consent document and electronically via Specimen Consent. At the time of specimen selection for project distribution, the most recent consent information will be used.

Sites can amend a patient's choices regarding the future use of her specimens at any time if the patient changes her mind.

If the patient revokes permission to use her specimens, the GOG Tissue Bank will destroy or return any remaining specimens. The patient's specimens will not be used for any <u>further</u> research; however, any specimens distributed for research prior to revoking consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her specimens distributed prior to revoking consent.

Note: If return of specimens is requested, shipping will be at the site's expense.

APPENDIX VI - ECOG PERFORMANCE SCALE (09/08/15)

GRADE	KARNOFSKY SCALE	PERFORMANCE
0	90 & 100	FULLY ACTIVE
1	70 & 80	RESTRICTED IN PHYSICALLY STRENUOUS ACTIVITIES, BUT AMBULATORY.
2	50 & 60	AMBULATORY; CAPABLE OF SELF CARE; UNABLE TO WORK; UP 50% OF WAKING HOURS.
3	30 & 40	LIMITED SELF CARE; CONFINED TO BED OR CHAIR 50% OF WAKING HOURS.
4	10 & 20	COMPLETELY DISABLED; NO SELF-CARE