ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A021602

RANDOMIZED, DOUBLE-BLINDED PHASE III STUDY OF CABOZANTINIB VERSUS PLACEBO IN PATIENTS WITH ADVANCED NEUROENDOCRINE TUMORS AFTER PROGRESSION ON PRIOR THERAPY (CABINET)

NCI-supplied agent(s): Cabozantinib (NSC #761968, IND# 137656); IND holder: DCTD, NCI
Industry-supplied agent(s): NONE
Commercial agent(s): NONE

This is an FDA Registration Study.

ClinicalTrials.gov Identifier: NCT03375320

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Health Outcomes Co-Chair and Statistician

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Alliance GI Committee Co-Chairs

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Study Resources

Expedited Adverse Event Reporting

[redacted]

Medidata Rave® iMedidata Portal

[redacted]

OPEN (Oncology Patient Enrollment Network)

[redacted]

Biospecimen Management System (BioMS)

[redacted]

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IROC Ohio (Alliance Imaging Core Lab)

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Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modifications	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions regarding data submission, RAVE, or patient follow-up	Data Manager
Questions regarding the protocol document and model informed consent	Protocol Coordinator
Questions regarding IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting	Alliance Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions	Appropriate Alliance Biorepository
Questions regarding drug supply	Pharmaceutical Management Branch (PMB)
Questions regarding drug administration	Pharmacy Liaison

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at [redacted] and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at [redacted] Contact the CTSU Help Desk with any OPEN related questions by phone or email: [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to 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 page located on the CTSU members' website ([redacted]). 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 log in with a 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 Regulatory Support System (RSS).		
Institutions will order the following supplies from the CTSU Operations Office: patient-completed questionnaire booklets. Supplies can be ordered by downloading and completing the CTSU Supply Request Form (available on the protocol-specific page on the CTSU website) and submitting it as instructed on the form.		
For clinical questions (i.e. patient eligibility or treatment-related) see Protocol Contacts, Page 2.		
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 – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.		

RANDOMIZED, DOUBLE-BLINDED PHASE III STUDY OF CABOZANTINIB VERSUS PLACEBO IN PATIENTS WITH ADVANCED NEUROENDOCRINE TUMORS AFTER PROGRESSION ON PRIOR THERAPY

Registration Eligibility Criteria (see Section 3.2 for full descriptions)

- Histologic documentation of well- or moderately-differentiated neuroendocrine tumor of pancreatic or non-pancreatic origin
- Locally advanced/unresectable tumor(s) or metastatic disease
- Target lesion disease progression by RECIST v1.1 within 12 months
- Patients must have measurable disease per RECIST 1.1
- Progression or intolerance of ≥ 1 prior FDA approved therapy (except somatostatin analogs)
- Prior treatment must be completed ≥ 28 days prior to registration
- Prior use (and concurrent use at stable dose) of somatostatin analogs is allowed
- Prior treatment with cabozantinib is not allowed
- Resolution of toxic effects from prior therapy to grade 1 or less
- Major surgery must be completed ≥ 12 weeks and minor surgery must be completed ≥ 28 days prior to registration
- No class III or IV CHF, clinically significant cardiac arrhythmia, unstable angina, MI, or thromboembolic events (incl. stroke, TIA, DVT, and PE) within 6 months of registration
- No known history of congenital long QT syndrome
- No uncontrolled hypertension within 14 days of registration
- No clinically significant GI bleeding or GI abnormalities that may increase risk for GI bleeding or GI perforation within 6 months of registration
- No known tumor with invasion into GI tract from the outside causing increased risk of perforation or bleeding within 28 days of registration
- No radiologic or clinical evidence of pancreatitis
- No known cavitary lung lesions
- No known endobronchial lesions involving main or lobar bronchi
- No hemoptysis > 2.5 mL or signs of pulmonary hemorrhage within 3 months of registration
- No known tumor invading or encasing any major blood vessels
- No history of non-healing wounds or ulcers or history of fracture within 28 days of registration
- No active brain metastases or cranial epidural disease
- No known medical condition causing an inability to swallow oral formulations of agents
- No history of allergic reaction attributed to compounds of similar chemical or biological composition to cabozantinib/placebo
- No currently active second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ
- Other concurrent investigational agents or other tumor directed therapies (chemotherapy, radiation) are not allowed
- No full dose oral anticoagulation/antiplatelet therapy or any dose of warfarin. Aspirin ≤ 81mg and therapeutic LMWH are allowed, except in patients with brain metastases.
- Chronic concomitant treatment with strong inhibitors or strong inducers of CYP3A4 is not allowed
- Not pregnant and not nursing. Women of childbearing potential must have a negative pregnancy test ≤ 14 days prior to registration
- Age ≥ 18 Years and ECOG Performance Status: 0-2

Required Initial Laboratory Values (Section 3.2.9)
Absolute Neutrophil Count (ANC) ≥ 1500/mm^3
Hemoglobin ≥ 9 g/dL
Platelet Count ≥ 100,000/mm^3
PT/INR, PTT < 1.3 x ULN
AST/ALT ≤ 3 x ULN
Total Bilirubin ≤ 1.5 ULN*
Creatinine ≤ 1.5 mg/dL
OR
Creatinine Clearance ≥ 45 mL/min
Albumin ≥ 2.8 g/dL
Potassium, Phosphorus, Calcium, Magnesium WNL**
UPC Ratio ≤ 1
QTcF ≤ 500 msec
TSH WNL**
* Except in the case of Gilbert disease, in which case Total Bilirubin ≤ 3 x ULN
** Supplementation is acceptable to achieve WNL

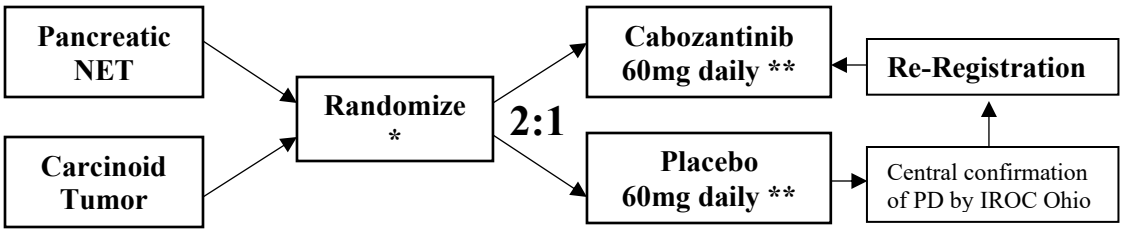
Re-Registration Eligibility Criteria (see Section 3.3 for full descriptions)

- Centrally-confirmed radiographic disease progression per RECIST v1.1
- Not pregnant and not nursing. Women of childbearing potential must have a negative pregnancy test ≤ 14 days of re-registration.

Required Laboratory Values (Section 3.3.3)
Absolute Neutrophil Count (ANC) ≥ 1500/mm^3
Hemoglobin ≥ 9 g/dL
Platelet Count ≥ 100,000/mm^3
PT/INR, PTT < 1.3 x ULN
AST/ALT ≤ 3 x ULN
Total Bilirubin ≤ 1.5 ULN*
Creatinine ≤ 1.5 mg/dL **OR** Creatinine Clearance ≥ 45 mL/min
Albumin ≥ 2.8 g/dL
Potassium, Phosphorus, Calcium, Magnesium WNL**
UPC Ratio ≤ 1
QTcF ≤ 500 msec
TSH WNL**
* Except in the case of Gilbert disease, in which case Total Bilirubin ≤ 3 x ULN
** Supplementation is acceptable to achieve WNL

Schema

1 Cycle = 28 Days



* Randomization will be done separately for the pancreatic NET and carcinoid tumor cohorts.

** Treatment is to continue until disease progression, unacceptable toxicity, or withdrawal of consent. Patients initially randomized to placebo who experience centrally confirmed progressive disease (PD) may elect to crossover to open-label cabozantinib; see Section 3.3 and Section 4.8. Patients will be followed for survival and progression every 12 weeks until progression or start of new anticancer therapy, and then for survival every 6 months until 8 years after registration or until death, whichever comes first.

NOTE: imaging scans must be submitted for real-time central review within 24 hours of local determination of PD; see Section 6.3.

Imaging after cessation of therapy may be performed at a non-registering institution. If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply. All protocol conduct must be followed, and the registering institution is responsible for ensuring all data is reported per protocol.

Please see full protocol text for a complete description of the eligibility criteria (Section 3.0) and treatment plan (Section 7.0).

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1.0 BACKGROUND

1.1 Background

The treatment of advanced neuroendocrine tumors (NET) has undergone a rapid evolution in recent years. For patients with advanced pancreatic NET, the somatostatin analog lanreotide, the mTOR inhibitor everolimus, and the tyrosine kinase inhibitor sunitinib have been shown to improve progression-free survival (PFS) compared to placebo and are approved therapies for patients with advanced disease [1-3]. For patients with advanced gastrointestinal NET, the somatostatin analogs octreotide and lanreotide have been shown to improve time to progression or PFS compared with placebo [1, 4]. In addition, ^{177}Lu-Dotatate recently was shown to improve PFS compared to high-dose octreotide in patients with midgut NET whose disease had progressed on standard-dose octreotide [5]. Everolimus also improves PFS in patients with non-functional GI and lung NET and is an approved therapy for these indications [6]. However, there currently is no standard therapy for patients with advanced NET whose disease has progressed on prior therapy. Furthermore, although everolimus and sunitinib are both approved agents for pancreatic NET, the phase III studies that demonstrated improved PFS with these agents compared with placebo were conducted primarily in patients who had not received prior molecularly targeted therapy; thus, the benefits of sunitinib following progression on everolimus have not been established.

Novel therapies to control disease in patients with progressive NET are needed. A key role for angiogenesis and the vascular endothelial growth factor (VEGF) pathway signaling in NET is suggested by clinical observations that neuroendocrine tumors are vascular tumors. Expression of VEGF has been demonstrated in carcinoid and pancreatic NET [7, 8]. Increased expression of VEGF receptor-2 (VEGFR-2) has been demonstrated in tissue from gastrointestinal carcinoid tumors and a carcinoid cell line [9, 10]. Additionally, pancreatic neuroendocrine tumors show widespread expression of VEGFR-2 and -3 in addition to platelet-derived growth factor receptors (PDGFRs) α and β, stem-cell factor receptor (c-kit) [11-13].

Sunitinib, which inhibits VEGFRs, PDGFRs, and c-kit, was evaluated in a randomized, phase III study in pancreatic NET that demonstrated improved PFS with sunitinib (median PFS 11.4 months with sunitinib, as compared with 5.5 months for placebo (HR 0.42, 95% CI 0.26-0.66)) [3].

Other tyrosine kinase inhibitors (TKIs) with activity against VEGFR, including sorafenib and pazopanib, have been evaluated in prospective phase II trials of patients with advanced carcinoid and pancreatic NET (Table 1). These studies have demonstrated evidence of activity with observed objective radiographic responses and encouraging PFS results.

Table 1

Agent	Molecular Target(s)	No. Patients	Tumor Type	Tumor Response Rate (%)	Median PFS	Reference
Sunitinib	VEGFR-1, -2, -3; PDGFR–α, -β; KIT; RET; CSF–1R; FLT3	41	Carcinoid	2	10.2 mo (TTP)	Kulke *et al.,* 2008 [14]
		66	Pancreatic NET	17	7.7 mo (TTP)	
Sorafenib	VEGFR, PDGFR, BRAF	50	Carcinoid	7	7.8 mo	Hobday *et al*., 2007 [15]
		43	Pancreatic NET	11	11.9 mo	

Agent	Molecular Target(s)	No. Patients	Tumor Type	Tumor Response Rate (%)	Median PFS	Reference
Pazopanib	VEGFR-1, -2, -3; PDGFR-α, -β; c-kit	22	Carcinoid	0	12.2 mo	Phan *et al*., 2015[16]
		33	Pancreatic NET	22	14.4 mo	
Pazopanib	VEGFR-1, -2, -3; PDGFR-α, -β; c-kit	15	Carcinoid (GI)	9	10 mo	Grande *et al*., 2015 [17]
		7	Carcinoid (lung, thymus)		3.4 mo	
		17	Pancreatic NET		12.8 mo	

Preclinical data also have demonstrated a role for mesenchymal-epithelial transition factor (MET) activation in stimulating growth of neuroendocrine tumors and a role for inhibition of MET in treatment of this disease [18-21]. Tumor expression of MET has been correlated with reduction in overall survival in patients with pancreatic NET [20]. In the *RIP-Tag2* model of spontaneous pancreatic NET, treatment with an anti-VEGF antibody or sunitinib increases hypoxia, expression of *HIF-1α*, and activation of MET. This is associated with increased tumor invasion and metastasis, which can be reduced by either combining anti-VEGF pathway therapy with an inhibitor of MET or treatment with cabozantinib, a small-molecule TKI that targets VEGFR-2 as well as c-MET [19].

1.2 Pertinent Existing Data

1.2.1 Cabozantinib

Cabozantinib is an inhibitor of tyrosine kinase receptors known to influence tumor growth, metastasis, and angiogenesis including MET, VEGFR-2, AXL, and RET [22]. MET, VEGFR-2, AXL, and RET all play important roles in cancer biology. VEGFR-2, expressed on endothelial cells, is a well-established key mediator of VEGF signaling in the process of tumor angiogenesis [23]. MET, expressed on tumor cells and endothelial cells, mediates HGF signaling leading to increased cell motility, proliferation, and survival [24]. Upregulation of MET is found in a wide range of malignancies—including thyroid, kidney, liver, prostate, ovarian, lung, and breast cancers—and is associated with more aggressive and invasive phenotypes of cancer cells in vitro and with metastases in vivo [25, 26]. MET-driven metastasis may be exacerbated by a number of factors, including tumor hypoxia caused by selective inhibition of the VEGF pathway [27, 28]. In addition, the RTK AXL has also recently been implicated in invasion and metastasis in VHL-dysregulated clear cell renal cell carcinoma (RCC) [29]. Activated forms of the RTK RET are expressed in several cancers, including medullary thyroid cancer (MTC) [30] and non-small cell lung cancer (NSCLC) [31], and are believed to play an important role in these diseases.

Clinical Experience

Cabozantinib is available as both capsules and tablets, but the two formulations are not interchangeable.

Cabozantinib as a capsule formulation was approved by the United States FDA on November 29, 2012 for the treatment of patients with progressive, metastatic MTC.

In a phase III, randomized, double-blind, placebo-controlled including 330 patients with medullary thyroid carcinoma (219 cabozantinib, 111 placebo), a significant increase in the

primary endpoint of PFS was seen in the cabozantinib arm compared with placebo (median of 11.2 vs. 4.0 months; HR = 0.28; 95 CIs: 0.19, 0.40) [32].

On April 25, 2016, cabozantinib as a tablet formulation was approved by FDA for patients with advanced RCC who had received prior anti-angiogenic therapy.

In a phase III, randomized, open-label, active-controlled study (METEOR) including 658 patients (330 cabozantinib, 328 everolimus) with advanced RCC who had received prior treatment with at least one VEGFR-TKI, cabozantinib demonstrated a statistically significant improvements in the primary endpoint, PFS, and both secondary endpoints, ORR and OS, compared with the standard-of-care control treatment (everolimus). In the primary PFS analysis performed in the first 375 subjects randomized, the hazard ratio (HR) adjusted for stratification factors was 0.58 (95% CI: 0.45, 0.74; stratified log-rank p-value < 0.0001), and the Kaplan-Meier estimates for median duration of PFS were 7.4 months in the cabozantinib arm vs. 3.8 months in the everolimus arm [33]. The PFS analysis was repeated among all randomly assigned patients assess by intention-to-treat (658 subjects), and results (stratified HR = 0.51 [95% CI: 0.42, 0.62]) were similar to those obtained for the primary PFS analysis [34]. In the primary analysis of objective response rate (ORR) at the time of the primary analysis of PFS, the ORRs for the cabozantinib and everolimus arms were 17% (95% CI: 13, 22) and 3% (95% CI: 2, 6), respectively (unstratified p-value <0.0001). A pre-specified interim analysis of OS was conducted for the intention-to-treat population at the time of the primary analysis of PFS. The interim analysis demonstrated a strong trend for improvement in duration of OS for subjects in the cabozantinib arm compared with the everolimus arm (HR = 0.68 [95% CI: 0.51, 0.90; stratified log-rank p-value = 0.006]) [33]. The final overall-survival analysis confirmed an overall-survival benefit for cabozantinib. Median overall-survival was 21.4 months (95% CI: 18.7, not estimable) with cabozantinib compared to 16.5 months (95% CI: 14.7, 18.8) with everolimus (Hazard Ratio [HR] = 0.66 [95% CI: 0.53, 0.83]; p = 0.00026) [34].

Cabozantinib also has been evaluated in clinical trials in multiple other tumor types. Detailed information for each of these studies, including pharmacokinetic data, can be found in the Investigator's Brochure.

1.2.2 Cabozantinib in Neuroendocrine Tumors

In preclinical studies, cabozantinib has demonstrated activity in NET [19, 21].

The clinical activity of cabozantinib in patients with NET has been evaluated in a phase II study that included patients with advanced pancreatic NET and carcinoid tumors, many of whom had progressed on prior therapy [35]. Patients were treated with cabozantinib starting at a dose of 60 mg daily and continued treatment until disease progression or development of unacceptable toxicity or withdrawal of consent. The primary endpoint of the study was radiographic response rate, as measured by RECIST 1.1 criteria. Objective radiographic responses to treatment were observed in 3/20 (15%) patients with pancreatic NET and 6/41 (15%) patients with carcinoid tumors. Progression-free survival was 21.8 mo (95% CI, 8.5-32.0 mo) in patients pancreatic NET and 31.4 mo (95% CI, 8.5 mo – not reached) in patients with carcinoid.

Treatment-related adverse events associated with cabozantinib in patients with NET were similar to what has been reported in other diseases [35]. Dose modification was commonly required; 81% of patients completing at least 1 cycle of therapy eventually required reduction from the starting dose of 60 mg daily to either 40 mg or 20 mg daily. Of note, a relationship between dose modification and disease control or disease progression was not observed.

1.3 Rationale for Trial Design

Because of differences in biology and potential responsiveness to treatment, it has been recommended that pancreatic NET and non-pancreatic NET (i.e. carcinoid tumors) be evaluated as separate entities in clinical trials [36]. Therefore, patients in this trial will be enrolled into two separate cohorts -- one for pancreatic NET and one for carcinoid tumors -- to independently test the hypothesis. Furthermore, at the NCI NET Clinical Trials Planning Meeting, it was recognized that OS is not a practical endpoint for most clinical trials in patients with advanced NET and that PFS be used as an endpoint in phase III studies [36].

A comparison with placebo has been chosen since there is no approved therapy for patients with pancreatic NET or carcinoid tumors whose disease has progressed on prior lines of FDA-approved therapy. Randomization to cabozantinib vs. placebo will occur in a 2:1 fashion. As of Update #02, upon disease progression confirmed by central radiology review, patients will be unblinded, and those who were receiving placebo may elect to crossover to open-label therapy with cabozantinib.

1.4 Importance and Impact of the Trial

There currently is no standard treatment for patients with advanced NET whose disease has progressed on prior lines of FDA-approved therapy. Although everolimus and sunitinib are both approved agents for pancreatic NET, the phase III studies demonstrating improved PFS compared with placebo were conducted primarily in patients who had not received prior molecularly targeted therapy; therefore, the benefits of sunitinib following progression on everolimus have not been established [2, 3]. Similarly, in patients with GI NET, there is no approved therapy following progression on a somatostatin analog and everolimus or lutetium Lu 177 dotatate. In lung NET, there is no currently approved therapy following progression on everolimus. Thus, there remains a need for clinical trials evaluating the efficacy of therapy in patients with NET whose disease has progressed on prior lines of approved therapy. There also is a need for studies examining the activity of novel agents that have the potential to improve outcomes for these patients.

If the proposed phase III study reveals significant improvement in PFS with cabozantinib compared with placebo, it could change clinical practice by establishing an effective therapy for patients with pancreatic NET and carcinoid tumors.

2.0 OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine whether cabozantinib can significantly improve progression-free survival (PFS) compared to placebo in patients with advanced pancreatic NET whose disease has progressed after prior therapy.

2.1.2 To determine whether cabozantinib can significantly improve progression-free survival (PFS) compared to placebo in patients with advanced carcinoid tumors whose disease has progressed after prior therapy.

2.2 Secondary Objectives

2.2.1 To determine whether cabozantinib can significantly improve overall survival (OS) compared to placebo in patients with advanced pancreatic NET whose disease has progressed after prior therapy.

2.2.2 To determine whether cabozantinib can significantly improve overall survival (OS) compared to placebo in patients with advanced carcinoid tumors whose disease has progressed after prior therapy.

2.2.3 To evaluate safety and tolerability of cabozantinib versus placebo in patients with advanced pancreatic NET using CTCAE and PRO-CTCAE.

2.2.4 To evaluate safety and tolerability of cabozantinib versus placebo in patients with advanced carcinoid tumors using CTCAE and PRO-CTCAE.

2.2.5 To evaluate the overall radiographic response rate of cabozantinib versus placebo in patients with advanced pancreatic NET whose disease has progressed after prior therapy.

2.2.6 To evaluate the overall radiographic response rate of cabozantinib versus placebo in patients with advanced carcinoid tumors whose disease has progressed after prior therapy.

2.3 Other Objective

Results of the primary analysis will be examined for consistency, while taking into account the stratification factors and/or covariates of baseline QOL and fatigue.

2.4 Quality of Life Substudy Objective – A021602-HO1

To compare overall quality of life (primary endpoint: HRQL scale of the EORTC QLQ-C30 post-randomization), disease-related symptoms, and other domains between the two treatment groups (cabozantinib vs. placebo) within each cohort of patients (pancreatic NET vs. carcinoid tumor); see Section 14.1.3 for detailed primary, secondary, and exploratory objectives as well as primary and secondary hypotheses.

2.5 Population Pharmacokinetics Substudy Objective – A021602-PP1

To describe the population pharmacokinetic and exposure-response relationships of cabozantinib in patients with advanced neuroendocrine tumors; see Section 14.2.2 for detailed primary objectives.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

In addition:

- Drugs that prolong the QTc interval should be avoided if possible, as cabozantinib can prolong the QTc interval. Drugs that are generally accepted to have a risk of causing Torsades de Pointes (see Appendix V) should be discontinued or replaced with drugs that do not carry this risk if at all possible. Patients who receive potential QTc-prolonging medications (see Appendix V) should be monitored closely.
- Women and men of reproductive potential must agree to use an appropriate method of birth control throughout their participation in this study and for four months after completing study treatment due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include: abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Registration Eligibility Criteria (Step 1)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ **3.2.1 Documentation of Disease**

- **Histologic Documentation**: Well- or moderately-differentiated neuroendocrine tumors of pancreatic and non-pancreatic (i.e. carcinoid) origin by local pathology.

  The pathology report must state ONE of the following: 1) well- or moderately-differentiated neuroendocrine tumor, 2) low- or intermediate-grade neuroendocrine tumor, or 3) carcinoid tumor or atypical carcinoid tumor.

  Documentation of histology from a primary or metastatic site is allowed.

  Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma without specification of differentiation status, adenocarcinoid tumor, or goblet cell carcinoid tumor are not eligible. Patients with *well-differentiated* grade 3 neuroendocrine tumor are eligible.

- **Stage**: Locally advanced/unresectable or metastatic disease.

- **Tumor Site**: Histological documentation of neuroendocrine tumor of pancreatic, gastrointestinal (GI), lung, thymus, other, or unknown primary site. GI, lung, thymus, other, and unknown primary NETs will enroll in the carcinoid tumor cohort of the study.

  Functional (i.e. associated with symptoms or a clinical syndrome related to hormone secretion by tumor) or nonfunctional tumors are allowed.

- **Radiologic Evaluation**: Target lesions must have shown evidence of disease progression by RECIST v1.1 criteria in the 12 months prior to registration. The radiologic images, imaging reports, and clinic notes indicating growth of existing lesions, development of new lesions, or treatment changes must be submitted per Section 6.1.1.

___ **3.2.2 Measurable Disease**

Patients must have measurable disease per RECIST 1.1 by computer tomography (CT) scan or magnetic resonance imaging (MRI) (see Section 11.0).

Lesions must be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 1 cm with CT or MRI (or ≥ 1.5 cm for lymph nodes). Non-measurable disease includes disease smaller than these dimensions or lesions considered truly non-measurable including: leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung. See Section 11.0 for additional details.

___ **3.2.3 Prior Treatment**

Patient must have experienced disease progression after receiving or intolerance leading to treatment discontinuation of at least one FDA-approved line of therapy (except somatostatin analogs). Prior lines of therapy must include one of the following: everolimus, sunitinib, or lutetium Lu 177 dotatate in patients with pancreatic NET; everolimus in

patients with lung NET; everolimus or lutetium Lu 177 dotatate in patients with gastrointestinal NET.

Prior treatment (except somatostatin analogs) with biologic therapy, immunotherapy, chemotherapy, investigational agent for malignancy, and/or radiation must be completed **at least 28 days prior to registration**.

Prior treatment with somatostatin analogs is allowed, and continuation of treatment with somatostatin analogs while on cabozantinib/placebo is allowed provided that the patient has been on a stable dose for at least two months.

Prior systemic treatment with radionuclide therapy must be completed at least 6 weeks prior to registration.

Prior treatment with hepatic artery embolization (including bland embolization, chemoembolization, and selective internal radiation therapy) or ablative therapies is allowed if measurable disease remains outside of the treated area or if there is documented disease progression in a treated site. Prior liver-directed or other ablative treatment must be completed at least 28 days prior to registration.

Prior treatment with cabozantinib is not allowed.

Patients should have resolution of any toxic effects of prior therapy (except alopecia and fatigue) to NCI CTCAE, version 5.0, grade 1 or less.

Patients must have completed any major surgery at least 12 weeks prior to registration and any minor surgery (including uncomplicated tooth extractions) at least 28 days prior to registration. Complete wound healing from major surgery must have occurred at least 28 days prior to registration, and complete wound healing from minor surgery must have occurred at least 10 days prior to registration.

___ **3.2.4 Patient History**

No class III or IV CHF within 6 months of registration.

No clinically significant cardiac arrhythmia within 6 months of registration.

No unstable angina or MI within 6 months of registration.

No thromboembolic events within 6 months of registration (incl. stroke, TIA, DVT, & PE).

No known history of congenital long QT syndrome.

No uncontrolled hypertension within 14 days of registration (defined as SBP ≥150 mmHg and/or DBP ≥ 90 mmHg despite optimal medical management).

No clinically significant GI bleeding within 6 months of registration.

No clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding within 6 months of registration including, but not limited to: active peptic ulcer, known endoluminal metastatic lesion(s) with history of bleeding, inflammatory bowel disease, or other gastrointestinal conditions with increased risk of perforation.

No GI perforation within 6 months of registration.

No known tumor with invasion into the GI tract from the outside causing increased risk of perforation or bleeding within 28 days of registration.

No radiologic or clinical evidence of pancreatitis.

No known cavitary lung lesions.

No known endobronchial lesions involving the main or lobar bronchi and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage. (CT with contrast is recommended to evaluate such lesions.)

No hemoptysis greater than ½ teaspoon (2.5 mL) or any other signs of pulmonary hemorrhage within the 3 months prior to registration.

No known tumor invading or encasing any major blood vessels.

No history of non-healing wounds or ulcers within 28 days of registration.

No history of fracture within 28 days of registration.

No brain metastases or cranial epidural disease unless adequately treated, stable, and off steroid support for at least 4 weeks prior to registration.

No known medical condition causing an inability to swallow oral formulations of agents.

No history of allergic reaction attributed to compounds of similar chemical or biological composition to cabozantinib/placebo.

No "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.

___ **3.2.5 Concomitant Medications**

Other planned concurrent investigational agents or other tumor directed therapies (chemotherapy, radiation) are not allowed while on this study.

Concurrent use of somatostatin analogs while on cabozantinib/placebo is allowed provided that the patient has been on a stable dose for at least two months.

Full dose oral anticoagulation/antiplatelet therapy is not permitted. Low dose aspirin ≤ 81 mg/day is allowed. Anticoagulation with therapeutic doses of LMWH is allowed in patients who are on a stable dose of LMWH for at least 6 weeks prior to registration. Treatment with warfarin is not allowed. Anticoagulation in patients with brain metastases is not permitted.

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed. Patients must discontinue the drug at least 14 days prior to registration on the study. See Section 8.1.12 for more information.

Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients must discontinue the drug at least 14 days prior to registration on the study. See Section 8.1.13 for more information.

___ **3.2.6 Not pregnant and not nursing**

Women of childbearing potential must have a negative pregnancy test done ≤ 14 days prior to registration.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months).

___ **3.2.7 Age ≥ 18 years**

___ **3.2.8 ECOG Performance Status: 0-2**

___ **3.2.9 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Hemoglobin	≥ 9 g/dL
Platelet Count	≥ 100,000/mm^3
PT/INR, PTT	< 1.3 x upper limit of normal (ULN)
AST/ALT	≤ 3 x ULN
Total Bilirubin	≤ 1.5 x ULN*
Creatinine	≤ 1.5 mg/dL **OR** Creatinine Clearance ≥ 45 mL/min
Albumin	≥ 2.8 g/dL
Potassium	within normal limits (WNL)**
Phosphorus	WNL**
Calcium	WNL**
Magnesium	WNL**
Urine Protein to Creatinine (UPC) Ratio	≤ 1
QTcF	≤ 500 msec
TSH	WNL**

*Except in the case of Gilbert disease, in which case Total Bilirubin must be ≤ 3 x ULN

**Supplementation is acceptable to achieve a value WNL. In patients with low albumin levels, a corrected calcium value WNL is acceptable. In patients with abnormal TSH, if Free T4 is normal and patient is clinically euthyroid, patient is eligible.

3.3 Re-Registration Eligibility Criteria (Step 2)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ **3.3.1 Documentation of Disease**

Patients must have centrally-confirmed radiographic disease progression per RECIST v1.1.

___ **3.3.2 Not pregnant and not nursing**

Women of childbearing potential must have a negative pregnancy test done ≤ 14 days prior to re-registration.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months).

___ **3.3.3 Required Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Hemoglobin	≥ 9 g/dL

Platelet Count	≥ 100,000/mm^3
PT/INR, PTT	< 1.3 x upper limit of normal (ULN)
AST/ALT	≤ 3 x ULN
Total Bilirubin	≤ 1.5 x ULN*
Creatinine	≤ 1.5 mg/dL **OR** Creatinine Clearance ≥ 45 mL/min
Albumin	≥ 2.8 g/dL
Potassium	within normal limits (WNL)**
Phosphorus	WNL**
Calcium	WNL**
Magnesium	WNL**
Urine Protein to Creatinine (UPC) Ratio ≤ 1	
QTcF	≤ 500 msec
TSH	WNL**

*Except in the case of Gilbert disease, in which case Total Bilirubin must be ≤ 3 x ULN

**Supplementation is acceptable to achieve a value WNL. In patients with low albumin levels, a corrected calcium value WNL is acceptable. In patients with abnormal TSH, if Free T4 is normal and patient is clinically euthyroid, patient is eligible.

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted] In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at [redacted]

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at [redacted] For questions, please contact the RCR Help Desk by email at [redacted]

4.2 Cancer Trials Support Unit Registration Procedures

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 Regulatory Support System (RSS).

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

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory

Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling [redacted]

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution'(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

Protocol-Specific Requirements for A021602 Site Registration

- This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at [redacted] Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.

4.2.1 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting

documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website [redacted] using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree; or
    - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number *A021602*.
- Click on *Documents*, *Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] in order to receive further instruction and support.

NOTE: Until institutions receive a formal notice from the Alliance regarding termination to patient follow-up, institutions must not close this trial with the IRB of record for the study without first receiving approval from Alliance Regulatory. Please contact the Alliance Regulatory team at [redacted] with any questions.

4.2.3 Checking Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the sites 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks..

4.2.4 Delegation of Task Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To

maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.3 Patient Registration Requirements

Informed Consent: the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patients with impaired decision making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

Patient Completed Booklets: patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient-completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A021602 CTSU site) and submitting it as instructed on the form. Samples of the booklets are found in Appendix I, which are to be used for reference and IRB submission only; they are not to be used for patient completion.

Protected Health Information: the H&E slide collected for this study will be sent to the Pathology Co-Chair, [redacted] at OSU from the Alliance Biorepository. The slide will be labeled with patient initials, study ID, and collection date/time. The plasma specimens collected for patients consented to the A021602-PP1 substudy will be sent to [redacted] of the Alliance Pharmacology/Pharmacokinetic Core Laboratory at the University of Pittsburgh. The specimens will be labeled with patient initials, study ID, and collection date/time. The drug company supporting this study may retrospectively review the de-identified images submitted to IROC after DSMB release.

4.4 Patient Registration/Randomization (Step 1) Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] For any additional questions, contact the CTSU Help Desk at [redacted]

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

Initial blinded, patient-specific clinical supplies of cabozantinib/placebo will be shipped from the Pharmaceutical Management Branch (PMB) to the registering investigator at the time of patient randomization and should arrive within 7 to 10 days after randomization (see Section 10.1). Treatment is to begin within 14 days of registration.

4.5 Registration to Correlative and Companion Studies

4.5.1 Registration to Substudies Described in Section 14.0

There are two substudies within Alliance A021602. The correlative studies must be offered to all patients enrolled on Alliance A021602 (although patients may opt to not participate). The substudies do not require separate IRB approval. The substudies included within Alliance A021602 are:

- Quality of Life Substudy, Alliance A021602-HO1 (Section 14.1)
- Population Pharmacokinetics Substudy, Alliance A021602-PP1 (Section 14.2)

If a patient answers "yes" to "I choose to take part in the Quality of Life study and will fill out the surveys," Question #1 in the model consent, then they have consented to participate in the substudy described in Section 14.1. The patient should be registered to Alliance A021602-HO1 at the same time they are registered to the treatment trial (A021602). Questionnaires should be submitted per Section 6.1.

If a patient answers "yes" to "I agree to have my blood collected, and I agree that my blood samples and related information may be used for the laboratory study described above," Question #2 in the model consent, then they have consented to participate in the substudy described in Section 14.2. The patient should be registered to Alliance A021602-PP1 at the same time they are registered to the treatment trial (A021602). Specimens should be submitted per Section 6.2.

4.6 Stratification and Grouping Factors and Treatment Assignments

Grouping Factors: Pancreatic NET vs. Carcinoid Tumor (i.e. non-pancreatic NET)

Randomization will be done separately within each cohort, pancreatic NET vs. carcinoid tumor.

Permuted Block

After a patient is registered, they will be assigned to one of the two treatment arms (cabozantinib vs. placebo) in a **2:1** ratio utilizing a permuted block schedule [37]. The goal of the algorithm is to maintain arm balance with respect to the following important stratification factors:

Stratification Factors for the Pancreatic NET Cohort:

- Concurrent Somatostatin Analog Use: Yes vs. No
- Prior Sunitinib Therapy: Yes vs. No

Stratification Factors for the Carcinoid Tumor Cohort:

- Concurrent Somatostatin Analog Use: Yes vs. No
- Primary Site: Midgut (jejunum, ileum, appendix, cecum, ascending, colon, hepatic flexure)/Unknown primary site vs. Non-midgut GI (stomach, duodenum, transverse colon, splenic flexure, descending colon, sigmoid colon, rectum)/Lung/Other known primary site not listed

When combined, these stratification factors create four stratum levels for each cohort, and each stratum level will have its own patient allocation schedule. The possible block size for this study is six.

4.7 Patient Re-Registration Requirements

Patient-completed Booklets: patient questionnaire booklets are to be ordered as outlined in Section 4.3.

Re-registration must occur ≤ 28 days of local determination of disease progression.

4.8 Patient Re-Registration/Crossover (Step 2) Procedures

Patients who meet the criteria for centrally-confirmed radiologic disease progression will may be unblinded to treatment assignment. If the patient was on placebo, then they will be allowed to crossover to receive open-label cabozantinib provided that all criteria in Section 3.3 are met. If the patient was on cabozantinib, then the patient should be followed per Section 5.0.

Patients receiving placebo who choose to crossover and receive open-label cabozantinib must be registered to the cabozantinib arm of the study, as follows:

1) Log into OPEN registration system and select the appropriate patient.
2) Select the next registration step.
3) Complete OPEN Enrollment Form for the patient to change arms.
4) Enter Cycle # of the last treatment received on the placebo arm, on the OPEN Enrollment Form.
5) OPEN will determine eligibility for the patient to crossover to the new arm. If patient is not eligible, OPEN will indicate this.
6) Once the new arm assignment has been successfully completed, a confirmation email will be sent to the site staff.

7) If assistance is needed with this process, contact the Alliance Registration Office at [redacted]

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all re-registration eligibility criteria within the protocol stated timeframes (see Section 3.3).

Note: The OPEN system will provide the site with a printable confirmation of re-registration and treatment information. Please print this confirmation for your records.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] For any additional questions, contact the CTSU Help Desk at [redacted]

Open-label, patient-specific clinical supplies of cabozantinib will be shipped from the Pharmaceutical Management Branch (PMB) to the registering investigator at the time of patient re-registration and should arrive within 7 to 10 days of re-registration (see Section 10.1). Treatment is to begin within 14 days of re-registration.

5.0 STUDY CALENDAR

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by oncology providers experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals:

To be completed ≤ 14 DAYS before registration: All laboratory studies, history and physical

To be completed ≤ 28 DAYS before registration: Any X-ray or scan of any type which is utilized for tumor measurement per protocol

**Calendar should be followed for both blinded therapy and for cross over patients. Crossover patients WILL NOT complete the Quality of Life and Pharmacokentic substudies. Re-registration should occur ≤ 28 days of local determination of disease progression while receiving blinded therapy with central confirmation of progressive disease.

	Prior to Registration*	Day 1 of each cycle*	Day 15 of Cycles 1 and 2 (+/- 3 days)	At progression or cessation of protocol treatment**
Tests & Observations				
History and Physical, PS	X	X	X	X
Pulse, BP, Height, Weight	X(1)	X(1)	X(1)	
ECG	X	A		
Adverse Event Assessment – CTCAE	X	X	X	B
Adverse Event Assessment – PRO-CTCAE	X(2)	X(2)		X(2)
Patient Medication Diary		X(3)		
Registration Fatigue/Uniscale Assessment	X(4)			
Laboratory Studies				
CBC w/ Differential, Platelets	X	X	X	
PT/INR, PTT	X			
Serum Creatinine	X	X	X	
Albumin, ALT, AST, Alk. Phos., Bilirubin	X	X	X	
Electrolytes (incl. Ca, Cl, CO2, K, Na, Mg, P), Glucose	X	X	X	
TSH	X	C		
Serum or Urine HCG	X(5)			
Urine Protein and Creatinine	X	D		
Serum Chromogranin A	X	C		
Hormone Assessment	E	E		
Staging				
CT Chest/Abd/Pelvis (or equiv.)	F	F		F
Real-time Central Review				X(6)
For patients who consent to participate in A021602-HO1, A021602-PP1, and A021602 Biobanking:				
Quality of Life Substudy[7]	*At registration and every 12 weeks (+/- 1 week) (i.e. every 3 cycles) until progression or start of new anticancer therapy; see Section 14.1*			

Pharmacokinetic Substudy[7]	*Submission of plasma specimens on Day 1 of Cycles 1, 2, and 3 and on Day 15 of Cycles 1 and 2; see Section 6.2, Section 14.2.*
Biobanking	*Submission of specimens within 28 days of registration, Cycle 1 Day 1, Cycle 2 Day 1, and at the time of progression; see Section 6.2*

* Labs completed prior to registration may be used for Day 1 of Cycle 1 tests if obtained ≤ 14 days prior to treatment. For subsequent cycles, all labs, scans, tests, and observations may be obtained +/- 3 days of scheduled clinic visit. Labs completed prior to re-registration must be completed ≤ 28 days.

** If protocol therapy is discontinued for reasons other than disease progression, physical examination, performance status, and radiologic imaging studies should be performed every 12 weeks (+/- 1 week) until disease progression or start of new anticancer therapy, whichever comes first. Patients who discontinue study treatment due to disease progression (or who start a new anticancer therapy after discontinuing study treatment for reasons other than disease progression) should be followed every 6 months for survival until 8 years after registration. See Section 12.0.

1 Height only collected at baseline; weight only measured at baseline, on Day 1 of Cycles 1, 2, and 3, and on Day 15 of Cycles 1 and 2.

2 Patients complete PRO-CTCAE by paper booklet ordered through the CTSU website. See Section 4.3 and Section 4.7 for ordering instructions. See Section 9.1 for administration instructions. See Appendix I for PRO-CTCAE assessments for IRB submission and review only. PRO-CTCAE booklets should be administered at the following time points: ≤ 21 days prior to treatment, Day 1 of every cycle, and at the time of progression (or cessation of protocol treatment). PRO-CTCAE should not be collected after patients crossover.

3 The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution (or compliance must be documented in the medical record by any member of the care team). See Appendix II.

4 To be completed after registration but ≤ 21 days prior to treatment.

5 For women of childbearing potential, see Section 3.2.6; must be done ≤ 14 days prior to registration and re-registration.

6 Restaging scan documenting progressive disease while on blinded therapy must be submitted for real-time central review within 24 hours of local determination; see Section 6.3 and Section 7.2.2 for instructions regarding imaging submission and IROC notification of cases when there is a local determination of progressive disease and request for real-time central review.

7. Crossover patients will not participate in the Quality of Life or the Pharmacokentic substudies.

A To be performed at baseline, on Day 1 of Cycle 2, and on Day 1 of Cycle 3.

B Any adverse events that occur within 30 days of discontinuation of study treatment should be recorded in the last treatment cycle form.

C To be performed at baseline, and then every 12 weeks (+/- 1 week) (i.e. every 3 cycles). Any measurements of biochemical response should occur in conjunction with the radiographic assessments for disease status.

D To be performed every other cycle (i.e. Cycle 1, Cycle 3, Cycle 5, etc.).

E For patients with a history of carcinoid syndrome only: perform 24-hour urine 5-HIAA at baseline and then every 12 weeks (+/- 1 week) (i.e. every 3 cycles). Other hormones, such as gastrin, insulin, glucagon, and VIP should be assessed, if clinically indicated, at baseline and then every 12 weeks (+/- 1 week) if elevated. Any measurements of biochemical response should occur in conjunction with the radiographic assessments for disease status. For patients with functional neuroendocrine tumors (i.e. patients with symptoms related to hormone production) only: perform hormone assessment, if clinically indicated, at baseline and then every 12 weeks (+/- 1 week) if elevated.

F Baseline scans and scans within the 12 months prior to registration used to determine progression for eligibility should be submitted within 3 days; see Section 3.2.1, Section 6.3, and Section 7.2.3. Restaging scans will be performed after every 12 weeks (+/- 1 week) (i.e. every 3 cycles) until evidence of progression; restaging scan used for local determination of progression while on blinded therapy must be submitted for real-time central review within 24 hours; see Section 6.3 and Section 7.2.2.

Multiphase CT scan (chest/abdomen/pelvis) is the preferred imaging modality. Equivalent modalities (MRI scan of the abd/pelvis with either CXR or non-contrast chest CT) may be used at the discretion of the treating physician. The CT component of a PET-CT is also acceptable if the CT is of diagnostic quality (using oral and IV contrast). The same imaging modality used at baseline should be used for all subsequent evaluations. CT scans should be of diagnostic quality and performed with oral and IV contrast unless there is a medical contraindication. MRI scans should be of diagnostic quality and performed with IV contrast unless there is a medical contraindication. MRI is the preferred imaging modality for patients with a medical contraindication to contrast. See Section 7.2.1 for further details. Octreotide scan or Gallium-68-Dotatate scans cannot be used for tumor measurements. Supporting documentation is to be submitted per Section 6.1.1. Imaging and reports are to be submitted per Section 6.3.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (Lab Admin), Rave SLA, or Rave Investigator.

  Rave role requirements:

  - Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
  - Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
  - Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to [redacted] for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must either click on the link in the email or login to iMedidata via the CTSU members' website under *Data Management* > *Rave Home*, and click to *accept* the invitation in the Tasks pane located in the upper right-corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for the study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidatascreen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata

to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at [redacted] or by contacting the CTSU Help Desk at [redacted]

Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status and DQP Reports modules.

Data Submission Schedule

A Data Submission Schedule is available on the Alliance study webpage within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU website within the study-specific folders.

Patient-completed Booklets

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.3). Samples of questionnaire booklets are available in Appendix I for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff in person, and site staff will enter patient responses into Rave.

Note: There are two mandatory quality of life items included in the main study: Registration Fatigue/Uniscale and PRO-CTCAE Adverse Event Assessments; see Section 4.3 for booklet ordering instructions, Section 5.0 and Section 9.1 for administration instructions, and Appendix I for examples of the assessments for IRB submission and review. **There are two additional quality of life items included as part of the optional A021602-HO1 substudy**: EORTC Tools and Global Impression of Change Assessments; see Section 4.3 for booklet ordering instructions, Section 5.0 and Section 14.1 for administration instructions, and Appendix I for examples of the assessments for IRB submission and review.

6.1.1 Supporting Documentation to be Submitted to the Alliance

This study requires supporting documentation for diagnosis, response, and progression. Additional source documentation is required for the enhanced centralized data monitoring plan; see Section 13.6 of this protocol and the Data Submission Schedule accompanying the All Forms Packet for further guidance. Supporting documentation will include local pathology reports, radiologic images (to be submitted to IROC Ohio per Section 6.3), imaging reports, and other documents/notes/reports, and these must be submitted at the following time points:

- Prior-to-baseline – radiologic images (submit to IROC Ohio), imaging reports, and other reports/notes within the 12 months prior to registration that were used to determine progression for eligibility (see Section 3.2.1)
- Baseline – local pathology report, radiologic images (submit to IROC Ohio), and imaging reports
- Restaging – radiologic images (submit to IROC Ohio) and imaging reports
- Progression – radiologic images (submit to IROC Ohio) and imaging reports (or clinical note documenting clinical progression)

All supporting documentation is to be submitted via Rave (with the exception of radiologic images, which should be submitted to IROC Ohio per Section 6.3). Imaging reports should be submitted via Rave and to IROC Ohio per Section 6.3 along with radiologic images.

6.2 Specimen Collection and Submission

For all patients registered to Alliance A021602: Retrospective histopathology review will be conducted using the tumor tissue from the diagnostic biopsy or surgical specimens. The submission of this sample for histopathology review is required for all patients registered to this study, including those who are found to be ineligible and those who do not receive protocol therapy.

For patients consented to A021602-PP1: All participating institutions must ask patients for their consent to participate in the pharmacokinetic substudy, although patient participation is optional. Pharmacokinetic (PK) analyses will be performed; rationale and methods for the scientific components of the PK study are described in Section 14.2. For patients who consent to participate, blood will be collected at the time points below for the PK studies.

For patients consented to A021602 Biobanking: All participating institutions must ask patients for their consent to participate in the biobanking for future correlative studies, although patient participation is optional. Future biomarker studies will be performed; rationale for the scientific components of these future studies are described in Section 14.3. For patients who consent to participate, blood and tissue will be collected at the following time points for these future studies:

	Blinded Therapy							Open-label Therapy				
	Within 28 Days after Registration	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycle 2 Day 1**	**Cycle 2 Day 15**	**Cycle 3 Day 1**	**At PD/ End of Treatment***	**Cycle 1 Day 1**	**Cycle 2 Day 1**	**At PD/ End of Treatment***	**Storage/ Shipping Conditions**	**Submit to:**
Mandatory for all patients registered to A021602:												
One H&E Slide	X										Ambient/ overnight	ABOSU
For patients consented to A021602-PP1, please submit the following:**												
Plasma from Whole Blood (Lavender)[1]		1 x 5 mL	1 x 5 mL	1 x 5 mL	1 x 5 mL	1 x 5 mL					Dry ice/ overnight	PITT
For patients consented to biobanking*, please submit the following:**												
FFPE Tumor Block[2]	X						A				Ambient/ overnight	ABOSU
Plasma from Whole Blood (Lavender)[3]		2 x 10 mL		2 x 10 mL			2 x 10 mL	2 x 10 mL	2 x 10 mL	2 x 10 mL	Dry ice/ overnight	ABOSU
Whole Blood (Lavender)[4]		1 x 10 mL									Cool pack/ overnight	ABOSU

* Blood samples are to be collected in the event of progression or end of treatment; progression samples may be collected and submitted up to 60 days after progression.

** Patients who consented to A021602-PP1 are those who answered "YES" to the model consent question "I agree to have my blood collected, and I agree that my blood samples and related information may be used for the laboratory study described above."

*** Patients who consented to biobanking are those who answered "YES" to the model consent question "I agree to have my blood and tissue collected, and I agree that my blood and tissue samples and related information may be kept in a Biobank for use in future health research."

1 The Cycle 1 Day 1 sample should be collected prior to the initiation of treatment; all subsequent samples should be collected prior to the patient receiving that day's scheduled daily dose, preferably 24 hours (+/- 4 hours) after receiving the previous day's scheduled daily dose. See Section 6.2.3 for cryovial ordering suggestions. Samples will be used for the pharmacokinetic substudy detailed in Section 14.2.

2 Blocks are strongly preferred over slides, but if a block cannot be submitted due to institutional policy, then 10 unstained, uncharged slides at 5 microns cut from the FFPE primary (or metastatic) tumor are acceptable. See Section 6.2.4 for labeling and submission instructions.

3 See Section 6.2.5 for cryovial suggestions. Samples will be used for the future plasma biomarker studies detailed in Section 14.3.

4 If possible, the sample should be collected prior to the initiation of treatment, however, collection at any point during protocol treatment is acceptable. This sample will serve as a germline DNA control for the future studies described in Section 14.3.

A For patients consented to biobanking who have a biopsy or surgery performed due to tumor progression: please submit a tissue block (or alternative of 10 unstained, uncharged slides at 5 microns) from the progression sample within 60 days per Section 6.2.4. For patients consented to biobanking who have a biopsy or surgery performed due to potential treatment toxicities: please submit a tissue block (or alternative of 10 unstained, uncharged slides at 5 microns) from the potential toxicity sample within 60 days per Section 6.2.4.

6.2.1 Specimen Submission Using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers (Safari, Firefox, Internet Explorer, etc.). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Specimens for the A021602-PP1 substudy should be sent to the following address:

[redacted]

Ship specimens to the Alliance Laboratory at the University of Pittsburgh (PITT) with Priority Overnight on Monday through Thursday for next day delivery. Do not ship specimens the day before a holiday. PITT does not accept Saturday deliveries.

All other specimens should be sent to the following addresses:

[redacted]

Ship specimens to the Alliance Biorepository at Ohio State University (ABOSU) with Priority Overnight on Monday through Thursday for next day delivery. Do not ship specimens the day before a holiday. ABOSU does not accept Saturday deliveries.

6.2.2 Tumor Submission for Histopathology Review

Consistent and accurate histologic grading is important for this study. Submission of one H&E slide from the diagnostic tumor biopsy or surgery is required for all patients enrolled to this study.

While local institutional pathology interpretation will be used to determine patient eligibility, a retrospective review of the histologic slides used for diagnosis of neuroendocrine tumor on these patients will be performed. Central pathology review is not required prior to registration.

A de-identified surgical pathology report should be sent with all archival specimens. Usually, this is generated by obscuring all PHI (names and dates) with white-out or a black magic marker, labeling each page of the report with the Alliance patient ID, and photocopying the report. The surgical pathology case number and block identifier (if applicable) should be maintained on the report so that it can be matched with the physical labeling on the sample. **Please ensure neuroendocrine (chromogranin, synaptophysin) and Ki67 staining results are included in the pathology report**.

Label the H&E slide with the following information:

1) Patient Initials
2) Alliance Study Number (i.e. A021602)
3) Institutional Surgical Pathology Number/Block ID either via your institution's standard method for labeling clinical slides or using a permanent marker. Please DO NOT use sticky labels.

It is also important that H&E slides are shipped in appropriately padded and secure containers to avoid physical damage.

Ship specimens to the Alliance Biorepository at OSU with Priority Overnight on Monday through Thursday for next day delivery. Do not send specimens the day before a holiday.

6.2.3 Blood Submission for Pharmacokinetic Studies in A021602-PP1

There is **NOT** a study kit for this trial; see below for cryovial ordering suggestions.

Cryovial Ordering Suggestions: Some examples of acceptable 1.8-2.0 mL cryovials are Nalgene (Cat #5012-0020), Fisher (Cat #10-500-26), Corning (Cat #430488), and Nunc (Cat #347627).

For patients who consent to participate in the A021602-PP1 substudy, blood samples will be used for the pharmacokinetic analyses described in Section 14.2.

Plasma from Whole Blood in EDTA Lavender Top Tube:

Prior to receiving protocol therapy on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, and Cycle 3 Day 1 patients consented to the A021602-PP1 substudy will be asked to complete a Patient Pharmacokinetics Form (see Appendix IV) which will provide information about the previous 48-hours of cabozantinib/placebo dosing (i.e. details on dose and time). After completion, the form should be collected, and the data should be reported in Rave on the Specimen Submission Form for A021602-PP1.

Collect 1 x 5 mL of peripheral venous blood in a lavender top tube *prior to* the patient receiving the daily dosage of cabozantinib/placebo on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, and Cycle 3 Day 1. Invert the tubes approximately 8-10 times to mix the EDTA, and then centrifuge at room temperature for 15 minutes at ~2500

x g (in accordance with local standard operating procedure for plasma isolation). Aliquot approximately 1.0 mL of plasma into each 1.8-2.0 mL cryovial (see above for cryovial ordering suggestions).

Immediately label and freeze cryovials at –70°C or colder. If –70°C or colder freezer is not available, temporary storage on dry ice or at –20°C prior to shipping is acceptable for up to approximately 48 hours. The samples should be placed in a biohazard bag surrounded by paper toweling prior to placing them in dry ice so the plasma-containing plastic tubes will not crack. Samples should be shipped on dry ice by overnight courier service to the University of Pittsburgh within 30 days of collection. Batch shipping is acceptable when feasible. Sample handling from collection to storage should not exceed 60 minutes.

Label all plasma samples with the following identification information:

1) Date of Collection
2) Time of Collection (i.e. actual time the blood sample was obtained)
3) Alliance Patient ID Number
4) Patient Initials
5) Alliance Study Number (i.e. A021602-PP1)
6) Sample Type (e.g. Plasma)

If labels are used, please ensure labels are carefully attached to the tubes and are not likely to fall off when frozen or during shipping.

6.2.4 Collection of Paraffin Blocks of Archived Tumor Tissue for A021602 Biobanking

For patients who consent to participate in A021602 biobanking, tumor blocks from the archival, diagnostic tissue sample will be used for the analyses described in Section 14.3. For patients who consent to participate in A021602 biobanking, tissue blocks from biopsies or surgery due to tumor progression, if obtained, are also to be submitted. In addition, tissue blocks from biopsies or surgeries related to potential treatment toxicities should also be submitted.

Paraffin blocks of primary and, when available, metastatic tissue obtained from archival tumor specimens should be sent to the Alliance Biorepository at Ohio State (ABOSU). Please specify the source of the tumor block (primary or metastatic site).

Label the blocks with the following information:

1) Alliance Patient ID Number
2) Patient Initials
3) Alliance Study Number (i.e. A021602)
4) Institutional Surgical Pathology Number/Block ID

Please DO NOT use sticky labels, and DO NOT put labels/tape on top of the actual tissue.

The Alliance has instituted special considerations for the small percentage of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage of hospitals whose policies prohibit release of any block. If a block can't be submitted due to institutional policy, 10 unstained, uncharged slides at 5 microns cut from the formalin-fixed, paraffin embedded (FFPE) primary (or metastatic) tumor are required. However, blocks are strongly preferred over slides.

Label the slides with the following information:

1) Thickness (e.g. 5 microns)
2) Institutional Surgical Pathology Number/Block ID (either via your institution's standard method for labeling clinical slides or using a permanent marker). Please DO NOT use sticky labels, and DO NOT put labels/tape on top of the actual tissue.

The slide container should have a label affixed with the following information:

1) Date of Collection
2) Alliance Patient ID Number
3) Patient Initials
4) Alliance Study Number (i.e. A021602)

When shipping FFPE tissues (blocks or unstained slides) it is important to avoid extreme heat. If environmental conditions indicate, FFPE tissues should be shipped in containers containing cold packs. It is also important that tissues are shipped in appropriately padded and secure containers to avoid physical damage.

Ship specimens to the Alliance Biorepository at OSU with Priority Overnight on Monday through Thursday for next day delivery. Do not send specimens the day before a holiday.

The Alliance Biorepositories would like to maintain the integrity of the tissue so that quality histology sections may be provided to investigators sometime after the study closes when they are ready to perform their research. It is preferred that the Alliance Biorepository bank the block until the study investigator is ready to perform the research since it is best to use freshly cut tissue sections from the blocks. Please contact the Alliance Biorepository at Ohio State University if additional assurances with your hospital pathology department are required.

6.2.5 Blood Sample Submission for A021602 Biobanking

There is **NOT** a study kit for this trial; see below for cryovial ordering suggestions.

Cryovial Ordering Suggestions: Some examples of acceptable 1.8-2.0 mL cryovials are Nalgene (Cat #5012-0020), Fisher (Cat #10-500-26), Corning (Cat #430488), and Nunc (Cat #347627).

For patients who consent to participate in A021602 biobanking, blood samples will be used for the biomarker analyses described in Section 14.3.

Plasma from Whole Blood in EDTA Lavender Top Tubes:

Collect 2 x 10 mL of peripheral venous blood in lavender top tubes on Cycle 1 Day 1, Cycle 2 Day 1, and at the time of progression/end of treatment during both blinded and open-label therapy. Invert the tubes approximately 8-10 times to mix the EDTA and then centrifuge at room temperature for 15 minutes at ~2500 x g (in accordance with the centrifuge manufacturer's instructions). Transfer the upper layer of plasma from the two tubes into a 15 mL conical tube. Repeat the centrifugation of the plasma in the 15 mL conical tube at room temperature for 15 minutes at ~2500 x g (in accordance with the centrifuge manufacturer's instructions). Aliquot approximately 1.0 mL of plasma into each 1.8-2.0 mL cryovial (see above for cryovial ordering suggestions).

Immediately label and freeze cryovials at –70°C or colder. If –70°C or colder freezer is not available, temporary storage on dry ice or at –20°C prior to shipping is acceptable for up to approximately 48 hours. The samples should be placed in a biohazard bag and **shipped**

according to IATA Guidelines within approximately 30 days of the blood draw on dry ice by overnight courier service to the Alliance Biorepository at Ohio State University. Batch shipping is acceptable when feasible.

Whole Blood in EDTA Lavender Top Tube:

Collect 1 x 10 mL of peripheral venous blood in one lavender top tube on Cycle 1 Day 1 during blinded therapy (preferably collected prior to the initiation of treatment, however, collection at any point during protocol treatment is acceptable). The tube should be inverted approximately 8-10 times to mix the EDTA. Refrigerate sample until shipping. The blood sample should be placed in a biohazard bag and **shipped the same day as the blood is drawn** on a cold pack by overnight courier service to the Alliance Biorepository at Ohio State University, where it will then be processed for germline DNA.

Label all blood samples with the following identification information:

1) Date of Collection
2) Alliance Patient ID Number
3) Patient Initials
4) Alliance Study Number (i.e. A021602)
5) Sample Type (e.g. Whole Blood, Plasma)

6.3 Imaging Submission

Collection of CT or MRI and CXR (or MRI and non-contrast CT chest) images is required for all patients consented on A021602. Quality images will be collected digitally for archival and retrospective purposes (see Section 7.2.1 for definitions of quality images). The same imaging modality (i.e. multiphase CT or MRI [and CXR or non-contrast chest CT]) used at baseline for each patient should be used for all subsequent evaluations to ensure accurate comparison. Images and local interpretation reports will be collected digitally at the following time points:

- Prior-to-baseline (scan within the 12 months prior to registration that was used to determine progression for eligibility; see Section 3.2.1)
- Baseline (completed within 28 days prior to patient registration)
- Restaging* (performed every 12 weeks until disease progression)
- Progression

* For patients who discontinue protocol treatment prior to disease progression, continue to submit every 12 weeks until disease progression (or start of new anticancer therapy).

- For patients who cross-over to receive open-label therapy, continue to submit ever 12 weeks until progression on open-label therapy.

The complete CT or MRI (and CXR or non-contrast CT) scan data in digital DICOM format should be submitted electronically to the Imaging and Radiation Oncology Core at Ohio (IROC Ohio) within no more than **3 business days** upon patient registration (baseline and prior-to-baseline scans) or upon image acquisition completeness (restaging), and **within no more than 24 hours upon local determination of progression** (for real-time central review, see Section 7.2.2). BMP files, JPG files, or hard copies (films) are not acceptable.

Imaging data should be submitted electronically to IROC Ohio via TRIAD (Section 6.3.1). The standard TRIAD based data transfer approach will be provided separately through IROC efforts

via the specific trial e-mail, [redacted], per the request of participating sites before their first imaging data submission.

If the TRIAD approach is not achievable at a site, alternatively the site needs to de-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number (e.g. 112136) and protocol number (e.g. A021602), and use the following electronic approaches for data submission:

1) Web Transfer [redacted]

   Any PCs with internet access and web browser (e.g. Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to IROC Ohio. The standard Web Transfer information will be provided separately through the specific trial e-mail, [redacted] per the request of participating sites before the first imaging data submission.

2) FTP Transfer

   Any FTP software can be used to initiate access to the secure FTP Server of IROC Ohio. The standard FTP access information will be provided separately through the specific trial e-mail, [redacted] per the request of participating sites before the first imaging data submission.

3) Mail/CD Shipment

   If neither of the electronic data transfer approaches can be achieved, then the de-identified images in digital DICOM format may be burned to a CD and mailed to IROC Ohio (however, electronic submission is preferred). Submit only one of the patient's images per CD, with the Alliance patient ID number, study type, date of scans, and name of submitting institution.

   Submit these data to:

   [redacted]

If the imaging data submission is done via web transfer, FTP transfer, or mail/CD shipment, send an e-mail to IROC Ohio at the specific trial email, [redacted] to inform them that the study has been submitted from the institution. Please include the following basic information of submitted data sets:

1) Alliance Patient ID Number
2) Scan Time Point (i.e. Baseline)
3) Date of Scans
4) Institution Name

IROC Ohio will notify the site within 2 business days of the data receipt and within 3 business days following the data receipt of the quality check report via the trial specific email [redacted]

For any questions about or problems with data submission to IROC Ohio, please call the IT Group at [redacted] for help.

6.3.1 Digital Imaging Data Submission Using Transfer of Images and Data

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

6.3.1.1 TRIAD Access Requirements

TRIAD Access Requirements:

- A valid CTEP-IAM account.
- Registration and Credential Repository (RCR) registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR) registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

6.3.1.2 TRIAD Installation

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at [redacted]

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email [redacted] or [redacted]

6.3.1.3 Procedures for Data Submission via TRIAD

The standard TRIAD-based data transfer approach will be provided separately through IROC efforts via the specific trial e-mail, [redacted] per the request of participating sites before their first imaging data submission.

7.0 TREATMENT PLAN/INTERVENTION

7.1 Cabozantinib/Placebo

Protocol treatment is to begin ≤ 14 days of registration or re-registration.

For questions regarding treatment, please see the study contacts page.

Blinded Therapy

This is a 2:1 randomized, double-blind trial. The initial blinded, patient-specific clinical supplies of cabozantinib/placebo will be requested by the Alliance Statistics and Data Management Center at the time of randomization and should arrive at the clinical site ≤ approximately 7-10 days after randomization (see Section 10.1).

Protocol therapy will consist of 60 mg oral cabozantinib/placebo (three 20 mg tablets) taken once daily during each 28-day treatment cycle. Patients should not eat for at least 2 hours before and for at least 1 hour after taking cabozantinib/placebo.

Treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent. Crossover from placebo to open-label cabozantinib at the time of centrally-confirmed radiologic disease progression is permitted; see Section 3.3, Section 4.8, Section 6.3, and Section 7.2. Patients will be monitored for treatment response and toxicity.

Open-label Therapy

The open-label, patient-specific clinical supplies of cabozantinib will be requested by the Alliance Statistics and Data Management Center at the time of re-registration and should arrive at the clinical site ≤ approximately 7-10 days after re-registration (see Section 10.1).

Protocol therapy will consist of 60 mg oral cabozantinib (three 20 mg tablets) taken once daily during each 28-day treatment cycle. Patients should not eat for at least 2 hours before and for at least 1 hour after taking cabozantinib.

Treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent. Patients will be monitored for treatment response and toxicity.

7.2 Imaging

Collection of CT or MRI and CXR (or MRI and non-contrast CT chest) images is required for all patients consented on A021602. Quality images will be collected digitally for archival and retrospective purposes (see Section 7.2.1 for definitions of quality images). The same imaging modality (i.e. multiphase CT or MRI [and CXR or non-contrast chest CT]) used at baseline for each patient should be used for all subsequent evaluations to ensure accurate comparison. Images and local interpretation reports will be collected digitally at the following time points:

- Prior-to-baseline (scan within the 12 months prior to registration that was used to determine progression for eligibility; see Section 3.2.1)
- Baseline (completed within 28 days prior to patient registration)
- Restaging* (performed every 12 weeks until progression)
- Progression

* For patients who discontinue protocol treatment prior to disease progression, continue to submit every 12 weeks until disease progression (or start of new anticancer therapy).

If diagnostic CT imaging is performed in conjunction with a PET/CT, that is allowable.

Images submitted for the progression time point (i.e. local determination of progressive disease) while patient is on blinded therapy will be reviewed by the A021602 Imaging Central Review Panel **in real time**; see Section 7.2.2. Images submitted for the progression time point while the patient is on open-label therapy are being collected for documentation purposes and will not be reviewed by the A021602 Imaging Central Review Panel at this time.

Images submitted for the baseline time point and the restaging time points while patient is on blinded therapy will be reviewed by the A021602 Imaging Central Review Panel retrospectively in batches; see Section 7.2.3. Images submitted for the progression time point while the patient

is on open-label therapy are being collected for documentation purposes and will not be reviewed by the A021602 Imaging Central Review Panel at this time.

Images submitted for the prior-to-baseline time point are being collected for documentation purposes and will not be reviewed by the A021602 Imaging Central Review Panel at this time.

See Section 6.3 for digital image submission instructions.

If a patient discontinues protocol therapy prior to disease progression, then the follow-up imaging required per Section 5.0 may be performed at a non-registering institution. All protocol conduct must be followed, and the registering institution is responsible for ensuring all data is reported per protocol. Please refer to the Alliance policy and procedures document posted on the Alliance website for the policy on engagement in research by non-registering institutions. If the NCTN Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

7.2.1 Definition of Quality Imaging

CT Scan Recommendations

Optimal Technique: The recommendations listed below should be followed if possible for the multiphase CT scan of chest/abdomen/pelvis, whenever possible:

- Scanning Mode: Helical
- Patient Position: Supine, arms up
- Scan Extent: Thoracic inlet through pubic symphysis
- Scan Time: Single breath-holding period, in full inspiration
- Section Thickness: 2.5 mm or less
- Enhancement: Intravenous contrast unless medical contraindication
- Reconstruction: Contiguous or overlapping sections; no gaps
- Consistency: Same technique is to be used between baseline and restaging scans

Minimum Technique: The recommendations listed below should be followed if possible for the multiphase CT scan of the chest/abdomen/pelvis, whenever possible (any CT scan that does not meet these minimal recommendations should be repeated):

- Scanning Mode: Helical
- Patient Position: Supine, arms up if possible
- Scan Extent: Thoracic inlet through pubic symphysis
- Scan Time: Single breath-holding period, in full inspiration
- Section Thickness: 5 mm or less
- Enhancement: Required if not clinically contraindicated.
- Reconstruction: Contiguous or overlapping sections; no gaps
- Consistency: Same technique is to be used between baseline and restaging scans

Note: For both optimal and minimum CT recommendations, if contrast is used for baseline scans but it is contraindicated at a restaging time point while on protocol therapy, then the scans

obtained at all future restaging time points should be obtained as both contrast and non-contrast in order to maintain consistency, unless there is a medical contraindication.

MRI Scan Recommendations

MRI may be performed instead of CT, and it is the preferred imaging modality for patients with a medical contraindication to contrast. It is of the utmost importance that the same imaging modality be used at baseline and for all subsequent follow up visits if clinically able.

The MRI should be performed with routine slice thickness generally not to exceed 5 mm. T1-weighted, T2-weighted as well as pre- and post-contrast enhanced T1-weighted images should be obtained. The precise TR and TE values as well as other pulse sequence parameters can be determined based upon local site preferences. At subsequent time points, the same imaging technique and sequences should be consistently used unless the patient can no longer receive IV contrast. The MRI should be performed of the abdomen and pelvis, and the chest should be scanned with CT chest or alternatively, AP and lateral CXR.

CXR Scan Recommendations

At minimum, AP chest should be optimal. PA and lateral views are preferred if CT chest is not obtained.

If there is a need to switch imaging modalities, for example, from CT to MRI, then a best attempt should be made to account for differences in imaging techniques and care should be taken not to progress a patient because of a potentially more sensitive imaging test.

7.2.2 Real-time Imaging Central Review

The following images and local interpretation reports will be collected and submitted for centralized, **real-time review** by the A021602 Imaging Central Review Panel:

- Local determination of progressive disease (PD) while on blinded therapy
    - **NOTE:** Participating sites must notify IROC Ohio of local radiology assessment at the time of site determination of PD (either by trial email at [redacted] and submit locally-determined PD scans **within no more than 24 hours** (see Section 6.3), and all imaging studies will be centrally reviewed to evaluate for efficacy on a per time point basis and to confirm the presence of PD.

Sites must notify IROC Ohio preferrable by email, alternate by phone. Please indicate in your message to IROC that the scans demonstrate progressive disease to trigger the real-time review of scans and include the patient ID and scan date of the images. To perform the real-time read of scans with local determinations of PD, IROC Ohio must have all prior imaging in addition to the PD scan.

IROC Ohio will contact the A021602 Imaging Central Review Panel within 24 hours (except weekends and holidays) of images being received for scheduling a real-time remote review. The Imaging Central Review Panel will be blinded to the patient's treatment assignment. IROC Ohio notifies both the participating site and Alliance of the central review results within 24 hours after receiving the results from the Imaging Central Review Panel. The overall turn-around time between imaging data receipt and central review results notification is within 24-72 hours after the imaging data receipt (except weekends and holidays). The radiology reviewer or designated team member will enter the central review results into Rave. Local review results in Rave should NOT be changed based on the results of the central review.

The patient should continue taking cabozantinib/placebo while the results of the central review are pending, unless the treating investigator believes a change in therapy is medically necessary.

The final treatment decision (remaining blinded versus crossing over to open label) is determined by the central review.

- If radiographic progressive disease is the final determination by the central review, then protocol treatment will be discontinued, and the patient should be followed for survival per Section 5.0.
- If radiographic progressive disease is not the final determination by the central review, then protocol treatment should be continued. Sites should communicate with IROC Ohio if there are questions regarding the real-time central review results.

Per protocol, the real time central review readers will be blinded to patients' treatment assignment but may have access to clinical history. Reviewers will evaluate the provided imaging based on RECIST 1.1, basing lesion involvement and target selection on their individual expertise with this disease, and therefore differences in interpretation may arise.

Central review results will be reported back to the site PI for further evaluation and determination of patient status.

In the event of disagreement between the local and central reads, adjudication may be requested by the local site. Notify the IROC Ohio and the Alliance study team that an adjudication is requested. Provide relevant clinical documentation as well as information regarding how the local determination was recorded to IROC Ohio for further review, and IROC Ohio will assign an adjudicator. If requested locally or centrally, the adjudicator may be put in touch with the local treating physician. This process may take an additional 24-72 hours of turnaround time, and the result will be used as the final central review decision for the interpretation and treatment/response determinations.

The A021602 Imaging Central Review Panel will initially consist of [redacted] of the University of California, San Francisco and [redacted] of The Ohio State University; other qualified radiologists may be added to the panel in the future upon approval by IROC Ohio, the Alliance, and the Study Chair.

For any questions related to central review, participating sites may directly contact IROC Ohio instead of the central reviewer(s), preferably by the trial email at [redacted]

7.2.3 Retrospective Imaging Central Review

To ensure the highest standards and consistency, the following complete CT or MRI (and CXR or non-contrast CT) imaging data sets will be collected and submitted for quality checks and retrospective centralized primary endpoint assessment image reviews by the A021602 Imaging Central Review Panel:

- Baseline scan
- Restaging scans with local determination of CR, PR, or SD during blinded therapy

The centralized image reviews by the A021602 Imaging Central Review Panel will be performed every 6 months for each patient starting from the date of patient registration until the date of centrally-confirmed radiographic disease progression or start of new anticancer therapy, whichever comes first. At minimum, the central reviewer will assess

the scans from the two time points within the 6-month period, however, scans from any previous periods may also be reviewed if desired by the central reviewer to ensure an accurate interpretation. Scans will be reviewed in batches every quarter for any patients who have reached the 6-month benchmark within the preceding three calendar months.

IROC Ohio will contact the A021602 Imaging Central Review Panel 3 days ahead (except weekends and holidays) for scheduling the batched centralized image reviews. Reviewers' availabilities should be sent (at least quarterly) to IROC Ohio in advance for this purpose. The batched centralized image reviews will be performed using an IROC Ohio established thin-client remote review approach.

In the event there is disagreement between central reviewers with previously recorded central review measurements, a blinded adjudication by another central reviewer will occur; the adjudicator will not be the same radiologist that performed either of the central reviews in question. The adjudicator's decision will be used as the retrospective, batched central review decision for the purposes of the primary study endpoint.

Results of the batched centralized image reviews will not be reported back to the site PI.

There will be no comparison between the real-time image central review results and the retrospective image central review results.

The A021602 Imaging Central Review Panel will initially consist of [redacted] of the University of California, San Francisco and [redacted] of The Ohio State University; other qualified radiologists may be added to the panel in the future upon approval by IROC Ohio, the Alliance, and the Study Chair.

For any questions related to central review, participating sites may directly contact IROC Ohio instead of the central reviewer(s), either by the trial email at [redacted]

8.0 DOSE AND TREATMENT MODIFICATIONS, UNBLINDING

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint.

8.1.2 Patients should receive full supportive care while on this study.

This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose must be recorded in the medical records.

8.1.3 Treatment with other chemotherapeutic agents is not permitted.

8.1.4 Antiemetics may be used at the discretion of the treating physician.

Antiemetic agents, along with supportive care, may be used as clinically appropriate at the first sign of nausea and vomiting. 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone due to possible CYP3A4 interactions.

8.1.5 Diarrhea management is per the discretion of the treating physician.

Diarrhea may need to be managed conservatively with medications such as loperamide, diphenoxylate/atropine, deodorized tincture of opium, or octreotide as clinically

appropriate at the first sign of diarrhea. Treating physicians may wish to instruct patients to notify their physician immediately at the first signs of poorly-formed or loose stool or an increased frequency of bowel movements.

Patients with severe diarrhea may need to be assessed for intravenous hydration, correction of electrolyte imbalances, and dietary adjustments.

8.1.6 Prevention of Skin Toxicity

Patients could be advised to use prophylactic measures for skin care. These measures may include: 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. Treating physicians may wish to carefully monitor patients with skin disorders 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. Treating physicians may wish to consider adequate interventions to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas, including aggressive management of symptoms and an early dermatology referral.

Recommendations for treatment of palmar-plantar erythrodysesthesia (hand-foot) syndrome include urea 20% cream twice daily and clobetasol 0.05% cream once daily. Analgesics (e.g. NSAID, GABA agonist, narcotic) can be used for pain control if needed.

8.1.7 Prevention of GI Perforation/Fistula and Non-GI Fistula Formation

Treating physicians may wish to consider carefully monitoring patients for episodes of abdominal pain, especially in patients with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis.

8.1.8 Prevention of Mucositis and Stomatitis

Comprehensive dental examination may be used as a preventative measure to identify any potential complications prior to initiation of protocol therapy, and, if indicated, the appropriate correction may need to be implemented such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with cabozantinib/placebo, treating physicians may wish to advise patients to maintain 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), as well as noting that the oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque.

8.1.9 Prevention of Osteonecrosis of the Jaw (ONJ)

Patients using concomitant antiangiogenic drugs, bisphosphonates, or denosumab may need to be monitored for ONJ more frequently, and treating physicians may wish to advise patients who have previously been treated with or concomitantly receive these medications to avoid invasive dental procedures if possible. In cases where dental procedures are unavoidable, treating physicians may wish to consider the risks and benefits of a dental procedure, the extent of the procedure, as well as the risk of developing osteonecrosis of the jaw when deciding how long to hold protocol therapy.

8.1.10 Palliative radiation therapy may not be administered while on protocol therapy.

Patients who require radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression.

8.1.11 Alliance Policy Concerning the Use of Growth Factors

The following guidelines are applicable unless otherwise specified in the protocol.

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 33: 3199-3212, 2015 and American Society of Clinical Oncology – American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. J Clin Oncol 28:4996-5010, 2010.

Epoetin (EPO): Use of epoetin in this protocol is permitted at the discretion of the treating physician. The use of FDA-approved biosimilar WBC growth factor products is acceptable.

White Blood Cell Growth Factors and other FDA-approved White Blood Cell Growth Factor biologics):

- White Blood Cell Growth Factor may not be used:
    - To avoid dose reductions, delays or to allow for dose escalations specified in the protocol.
    - For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy.
    - If white blood cell growth factors are used, they must be obtained from commercial sources. Selection of white blood cell growth factor products should be per institutional guidelines.

8.1.12 CYP3A4 Inhibitors

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed during on this trial. The following drugs are EXAMPLES of strong inhibitors of CYP3A4 and are not allowed during treatment with cabozantinib.

- Indinavir
- Clarithromycin
- Ketoconazole

CYP3A4 inhibiting foods such as grapefruit/grapefruit juice and Seville oranges may increase plasma concentrations of cabozantinib and should be avoided during treatment with cabozantinib.

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.13 CYP3A4 Inducers

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed during on this trial. The following drugs are EXAMPLES of strong inducers of CYP3A4 and are not allowed during treatment with cabozantinib

- Rifampin

- Carbamazepine

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.14 Concomitant Medications

Concurrent use of somatostatin analogs is allowed, given that the patient has been on a stable dose for at least two months.

Full dose oral anticoagulation/antiplatelet therapy is not permitted. Low dose aspirin ≤ 81mg/day is allowed. Anticoagulation with therapeutic doses of LMWH is allowed in patients who are on a stable dose of LMWH for at least 6 weeks. Treatment with warfarin is not allowed. Anticoagulation in patients with brain metastases is not permitted.

Bisphosphonates should be used with caution due to the nephrotic potential of these agents.

Drugs that prolong the QTc interval should be avoided if possible, as cabozantinib can prolong the QTc interval. Drugs that are generally accepted to have a risk of causing Torsades de Pointes (see Appendix V) should be discontinued or replaced with drugs that do not carry this risk if at all possible. Patients who receive potential QTc-prolonging medications (see Appendix V) should be monitored closely.

Drugs known to be P-glycoprotein substrates (e.g. fexofenadine, aliskiren, ambrisentan digoxin, colchicine, maraviroc, posaconazole, tolvaptan, etc.) should be used with caution as cabozantinib can cause increased P-glycoprotein substrate plasma concentrations.

MRP2 inhibitors such as cyclosporine, delavirine, efavirenz, and emtricitabine should be used with caution during treatment with cabozantinib as coadministration can cause increased cabozantinib plasma concentrations.

Highly protein-bound medications (e.g. diazepam, furosemide, dicloxacillin, propranolol, etc.) should be used with caution during treatment with cabozantinib.

8.2 Dose Modifications

- As a general approach, it is suggested that, when possible, all toxicities be managed with supportive care at the earliest sign of toxicity and modifying the dose as necessary.
- No dose reductions below level -2 are allowed. If dose reductions below 20 mg once daily are required (i.e. level -2), then cabozantinib/placebo will be discontinued.
- Cabozantinib/placebo will not be re-escalated once reduced.
- **If cabozantinib/placebo is held for more than 4 weeks, then patients must discontinue protocol treatment**. Any missed or delayed doses should be considered skipped, and the Study Calendar requirements in Section 5.0 should be maintained.
- If multiple adverse events are seen, administer dose based on the greatest reduction required for any single adverse event observed. Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- If more than one of these apply, use the most stringent (i.e. the greatest dose reduction).
- AERS reporting may be required for some adverse events (see Section 9.0).

- **NOTE**: PRO-CTAE data should not be used for determining attribution, dose modifications, or reporting serious adverse events.

8.2.1 Dose Levels

Dose Level	Cabozantinib/Placebo
0*	60 mg once daily
-1	40 mg once daily
-2	20 mg once daily

*Dose level 0 refers to the starting dose

8.2.2 Hematologic Toxicities

For **grade 3 neutropenia with documented infection, grade 3 neutropenia ≥ 5 days, or grade 4 neutropenia**, delay cabozantinib/placebo until toxicity resolves to grade ≤ 1, then resume cabozantinib/placebo with one dose level reduction.

For **grade 3 febrile neutropenia**, delay cabozantinib/placebo until ANC grade ≤ 1 and temperature to ≤ 38.0°C, then resume cabozantinib/placebo with one dose level reduction.

For **grade 4 febrile neutropenia**, discontinue cabozantinib/placebo.

For **grade 3 thrombocytopenia with clinically significant bleeding or grade 4 thrombocytopenia**, delay cabozantinib/placebo until platelet count ≥ 100,000/mm^3, then resume cabozantinib/placebo with one dose level reduction.

For **grade 4 anemia**, delay cabozantinib/placebo and use supportive care (e.g. red blood cell transfusions) as clinically indicated according to institutional guidelines until toxicity resolves to grade ≤ 1, then resume cabozantinib/placebo with one dose level reduction.

For **grade 4 hematologic toxicities other than anemia**, discontinue cabozantinib/placebo.

8.2.3 Hepatic Toxicities

8.2.3.1 For patients with ALT or AST ≤ ULN at the time of registration:

For **grade 1 ALT or AST**, continue cabozantinib/placebo and consider checking LFTs in two weeks.

For **grade 2 ALT or AST**, consider checking LFTs weekly. If **ALT or AST continues to rise within grade 2**, delay cabozantinib/placebo (and consider checking LFTs weekly) until grade ≤ 1, then resume cabozantinib/placebo with one dose level reduction.

For **grade 3 ALT, AST, or bilirubin**, delay cabozantinib/placebo and check LFTs weekly until grade ≤ 1, then resume cabozantinib/placebo with one dose level reduction. If LFT abnormalities are related to a biliary obstruction that has resolved and have returned to grade ≤ 1, cabozantinib/placebo treatment may be resumed with the previous dose.

For **grade 3 bilirubin recurring after a dose level reduction or grade 4 bilirubin without biliary obstruction**, discontinue cabozantinib/placebo. If LFT abnormalities are related to a biliary obstruction that has resolved and values have returned to grade ≤ 1, cabozantinib/placebo treatment may be resumed with the previous dose.

For **grade 4 ALT or AST**, discontinue cabozantinib/placebo.

For **grade 3 or 4 hepatic failure**, discontinue cabozantinib/placebo.

8.2.3.2 For patients with ALT or AST above the ULN but ≤ 3.0 x ULN (i.e. grade 1) at the time of registration:

For **≥ 1.5 fold increase of ALT or AST <u>and</u> both ALT and AST are ≤ 5.0 x ULN**, continue cabozantinib/placebo and consider weekly monitoring of LFTs. If LFTs continue to rise, delay cabozantinib/placebo (and consider checking LFTs weekly) until grade ≤ 1, then resume cabozantinib/placebo with one dose level reduction.

For **≥ 1.5 fold increase of ALT or AST <u>and</u> 5.0 < ALT or AST ≤ 20.0 x ULN (i.e. either ALT or AST is grade 3)**, delay cabozantinib/placebo (and consider checking LFTs weekly) until grade ≤ 1, then resume cabozantinib/placebo with one dose level reduction.

8.2.3.3 For <u>all</u> patients:

For **ALT or AST increases accompanied by progressive elevations of total bilirubin and/or elevations of coagulation tests**, delay cabozantinib/placebo (and consider checking LFTs weekly) until total bilirubin < 1.5 x ULN, INR < 1.5 x ULN, and ALT or AST grade ≤ 1, then resume cabozantinib/placebo with one dose level reduction.

For **ALT or AST increases accompanied by bilirubin > 2 x ULN in the absence of biliary obstruction or other explanation**, discontinue cabozantinib/placebo.

8.2.4 Proteinuria

The UPC (urine protein to creatinine) Ratio directly correlates with the grams of protein found in a 24-hour urine. The UPC ratio based on a random urine sample can be used in place of a 24-hour urine. If the UPC Ratio is > 1, then a repeat UPC Ratio and a 24-hour urine protein and creatinine may need to be performed to confirm the result.

$$\textbf{UPC Ratio} = \frac{\textbf{Urine Protein Concentration (mg/dL)}}{\textbf{Creatinine Concentration (mg/dL)}}$$

For **UPC Ratio < 3.5 or urine protein < 3.5 g/24 hours**, continue the same dose of cabozantinib/placebo.

For **UPC Ratio ≥ 3.5 or urine protein ≥ 3.5 g/24 hours**, delay cabozantinib/placebo and check UPC weekly until proteinuria resolves to UPC < 1.5 or urine protein < 1.5 g/24 hours, then resume cabozantinib/placebo with one dose level reduction. If treatment is delayed for more than one cycle (4 weeks) due to proteinuria, discontinue cabozantinib/placebo.

For **Nephrotic Syndrome (proteinuria ≥ 3.5 g/24 hours in combination with hypoalbuminemia, edema, and hyperlipidemia) or other relevant renal disease**, discontinue cabozantinib/placebo.

8.2.5 Hypertension (HTN)

- For **patients who require a delay of greater than 4 weeks for management of hypertension**, discontinue cabozantinib/placebo.
- Patients may have up to 3 agents for management of hypertension prior to any dose reduction in cabozantinib/placebo.
- 24 to 48 hours should elapse between modifications of anti-hypertensive therapy.

- Treating physicians should not add antihypertensive medications that are strong inducers or inhibitors of CYP3A4.

8.2.5.1 Persistent Grade 2 HTN (Systolic 140-159 mmHg, Diastolic 90-99 mmHg)

Continue cabozantinib/placebo at the same dose level without interruption; however, please see below for recommendations on adding anti-hypertensive therapy agents.

Recommended Antihypertensive Therapy

1. Increase existing antihypertensive therapy or initiate a new antihypertensive agent if needed after 24-48 hours of treatment; increase dose in stepwise fashion every 24-48 hours until BP is controlled or at the maximum dose of therapy.
2. If BP is still not controlled, add another antihypertensive agent; increase dose of this drug as described in Step 1.
3. If BP is still not controlled, add a 3rd agent; increase dose of this drug as described in Step 1.
4. If BP is still not controlled after maximal medical management, proceed with one dose level reduction.

8.2.5.2 Persistent Grade 3 HTN (Systolic ≥ 160 mmHg, Diastolic ≥ 100 mmHg)

Delay cabozantinib/placebo until systolic BP ≤ 159 mmHg and diastolic BP ≤ 99 mmHg. Once blood pressure is controlled to this level, resume cabozantinib/placebo with one dose level reduction and consider the recommended antihypertensive therapy outlined above in Section 8.2.5.1. However, if the patient requires hospitalization for management of symptomatic systolic BP >180 or diastolic BP >110, then discontinue cabozantinib/placebo and recommend inpatient management as clinically indicated with IV medications.

NOTE: Discontinuing or reducing the dose of cabozantinib/placebo is expected to cause a decrease in BP. The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly.

8.2.5.3 Grade 4 HTN (Life-threatening Consequences of Hypertension)

Discontinue cabozantinib/placebo. Recommended management is in inpatient setting with ICU support and IV medication as clinically indicated; notify the hospital staff that discontinuing cabozantinib/placebo may result in a decrease in BP.

8.2.6 Thrombosis

For **grade 2 or 3 venous thrombosis requiring anticoagulation**, delay cabozantinib/placebo. If the planned duration of full dose anticoagulation is ≤ 2 weeks, then delay cabozantinib/placebo until anticoagulation is completed. If the planned duration of full dose anticoagulation is > 2 weeks, then resume cabozantinib/placebo during anticoagulation therapy if all of the following are met:

- The patient must have been on a stable dose of LMWH prior to restarting cabozantinib/placebo. Warfarin or a novel oral anticoagulation drug may not be used for anticoagulation.
- The patient must not have any pathological condition that carries a high risk of bleeding.
- The patient must not have had any hemorrhagic events while on study.

For **recurrent/worsening venous thromboembolic events after resuming cabozantinib/placebo**, discontinue cabozantinib/placebo.

For **grade 4 venous thromboembolic events**, discontinue cabozantinib/placebo.

For **any grade arterial thromboembolic events including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia**, discontinue cabozantinib/placebo.

8.2.7 Hemorrhage

For **grade 2 CNS or pulmonary hemorrhage**, discontinue cabozantinib/placebo.

For **any other grade 3 or 4 hemorrhage**, discontinue cabozantinib/placebo.

8.2.8 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

For **signs and symptoms suggestive of RPLS (e.g. confusion, headache, seizures, cortical blindness)**, delay cabozantinib/placebo. Suspected RPLS should be investigated with MRI. If RPLS is confirmed, discontinue cabozantinib/placebo.

If RPLS is ruled out via MRI, then the decision to resume cabozantinib/placebo should be based on the signs and symptoms:

- For **grade 3 events**, if symptoms resolve, resume cabozantinib/placebo with one dose level reduction.
- For **grade 4 events considered at least possibly related to cabozantinib/placebo**, discontinue cabozantinib/placebo.

8.2.9 Fistula, Perforation, Bowel Obstruction, or Wound Dehiscence

For **any grade perforation of any organ, GI leak, or any fistula**, discontinue cabozantinib/placebo.

For **any grade bowel obstruction requiring medical intervention**, delay cabozantinib/placebo until obstruction resolves completely, then resume cabozantinib/placebo at the previous dose.

For **any grade bowel obstruction requiring surgery**, delay cabozantinib/placebo for 28 days (with full healing for at least 10 days), then resume cabozantinib/placebo at the previous dose.

If cabozantinib/placebo is delayed for > 28 days due to any grade of bowel obstruction, discontinue cabozantinib/placebo.

For **wound dehiscence requiring medical or surgical intervention**, discontinue cabozantinib/placebo.

8.2.10 Gastrointestinal Toxicities

For **grade 2 diarrhea or nausea/vomiting that worsens or lasts ≥ 10 days**, delay cabozantinib/placebo until toxicity improves to grade ≤ 1, then resume cabozantinib/placebo with one dose level reduction.

For **grade 3 diarrhea or nausea/vomiting**, delay cabozantinib/placebo until toxicity improves to grade ≤ 1, then resume cabozantinib/placebo with one dose level reduction.

For **grade 4 diarrhea or nausea/vomiting**, discontinue cabozantinib/placebo.

8.2.11 Thyroid Dysfunction

For **grade 3 hyper- or hypothyroidism**, delay cabozantinib/placebo until toxicity improves to grade ≤ 2, then resume cabozantinib/placebo with one dose level reduction.

For **grade 4 hyper-or hypothyroidism**, discontinue cabozantinib/placebo.

8.2.12 Pancreatic Enzyme Increase/Pancreatitis

For **grade 2 pancreatitis, lipase, or amylase (see CTCAE version 5.0, Gastrointestinal Disorder)**, continue cabozantinib/placebo and consider more frequent monitoring of lipase and amylase and radiographic evaluation.

For **grade 3 pancreatitis, lipase, or amylase**, delay cabozantinib/placebo until toxicity improves to grade ≤ 2, then resume cabozantinib/placebo with one dose level reduction.

For **grade 4 pancreatitis, lipase, or amylase**, discontinue cabozantinib/placebo.

8.2.13 Skin Toxicity

Refer to Section 8.1.6 for guidance regarding supportive management of skin toxicity.

For **grade 1 palmar-plantar erythrodysesthesia (PPE) syndrome (hand-foot syndrome) that does not improve within 2 weeks or grade 2 PPE syndrome**, continue cabozantinib/placebo with one dose level reduction and consider delaying cabozantinib/placebo treatment until PPE syndrome improves to grade ≤ 1.

For **grade 2 PPE syndrome that does not improve within 2 weeks or grade 3 PPE syndrome**, delay cabozantinib/placebo until PPE syndrome improves to grade ≤ 1, then resume cabozantinib/placebo with one dose level reduction.

For **grade 3 PPE syndrome that does not improve within 4 weeks**, discontinue cabozantinib/placebo.

8.2.14 Mucositis and Stomatitis

Refer to Section 8.1.8 for guidance regarding supportive care of mucositis and stomatitis.

For **grade 2 mucositis or stomatitis that is subjectively tolerable**, continue cabozantinib/placebo and consider providing supportive care.

For **grade 2 mucositis or stomatitis that worsens, lasts ≥ 10 days, or interferes with adequate nutrition (and supportive care is insufficient)**, delay cabozantinib/placebo until toxicity improves to grade ≤ 1, then resume cabozantinib/placebo with one dose level reduction.

For **grade 3 mucositis or stomatitis that interferes with adequate nutrition (and supportive care is insufficient)**, delay cabozantinib/placebo until toxicity improves to grade ≤ 1, then resume cabozantinib/placebo with one dose level reduction.

For **grade 4 mucositis or stomatitis that interferes with adequate nutrition (and supportive care is insufficient)**, discontinue cabozantinib/placebo.

8.2.15 Osteonecrosis of the Jaw

To minimize the risk of osteonecrosis of the jaw, it is recommended that, if possible, cabozantinib/placebo be stopped at least 4 weeks prior to dental procedures such as tooth extractions, implants, and major jaw surgery whenever possible. In this scenario, cabozantinib/placebo may be held for up to 8 weeks. Cabozantinib/placebo does not need to be held for routine dental fillings and cleanings.

8.2.16 Cardiac Toxicity

For **QTc interval > 500 msecs**, delay cabozantinib/placebo, stop any medications that may prolong the QTc interval (if possible), and consider checking calcium, potassium, and magnesium levels and correcting any abnormalities. Once QTc interval ≤ 500 msecs, correction of electrolyte abnormalities has been considered, and symptoms have resolved, cabozantinib/placebo may be resumed with one dose level reduction.

8.2.17 Other Non-Hematologic Grade 3 or 4 Toxicity

For **other grade 3 non-hematologic toxicity not described above and considered at least possibly related to protocol treatment**, delay cabozantinib/placebo until toxicity improves to grade ≤ 1, then resume cabozantinib/placebo with one dose level reduction.

For patients on **dose level -2 who experience recurrent other grade 3 non-hematologic toxicity (not described above)**, discontinue cabozantinib/placebo.

For **other grade 4 non-hematologic toxicity (not described above)**, discontinue cabozantinib/placebo.

8.3 Unblinding Procedures

Unblinding can be done only in the event of an emergency or upon centrally-confirmed disease progression. Follow the directions below to unblind patient treatment. Please note that if a treatment assignment is unblinded due to an emergency, the patient must discontinue protocol therapy.

8.3.1 Emergency Unblinding Procedures

Examples of emergencies include:

- A life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions
- A medication error, such as accidental overdose

Expected adverse events are listed in Section 9.0.

Contact the Alliance Executive Officer on call by calling [redacted]

The institution must provide the following information to the Alliance Executive Officer:

- Alliance Study ID (i.e. “A021602”)
- Alliance Patient ID Number (e.g. “999999”)
- Patient Initials (e.g. “L,FM”)
- Institution Name
- Name and telephone number of treating physician
- Name and contact information of person requesting the unblinding procedure
- Name and contact information of person to inform of treatment assignment
- Reason for emergency unblinding

Please remember that emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence

management of the medical situation. After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

8.3.2 Protocol-specified Unblinding Procedures

The steps for unblinding a patient upon progression are as follows:

1) Patient has an imaging scan that shows progression by RECIST v1.1 (except symptomatic deterioration)
2) Site submits the radiologic images and local imaging report documenting progression to IROC Ohio within 24 hours of local determination of disease progression. Scans with a local determination of progressive disease should be labeled as "progression" when submitted to IROC. Sites should also communicate with IROC via email to inform IROC of the need for real-time radiology review for a case of progressive disease. IROC contact information can be found on the Study Resources page.
3) IROC Ohio confirms disease progression by RECIST v1.1.
4) The confirmation of disease progression is received by the site and the Alliance Statistics and Data Management Center.
5) Site emails the Alliance Registration Office to unblind the patient; Registration Office confirms receipt of central confirmation of disease progression with Statistics and Data Management Center in order to communicate patient treatment assignment to site.

Contact the Alliance Registration Office at [redacted]. Upon confirmation by the Primary Statistician (or designee) that the criteria for progression have been met, the treatment assignment may be unblinded. No Alliance Executive Officer (or designee) approval is required.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

To complement CTCAE reporting, patients will self-report their side effects using the PRO-CTCAE. The specific PRO-CTCAE items for this protocol can be found in Appendix I. They can also be found at: [redacted]

NOTE: PRO-CTCAE data should not be used for determining attribution, dose modifications, or reporting of serious adverse events.

9.1 Routine Adverse Event Reporting (Rave-CTEP-AERS)

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 according to the Study Calendar in Section 5.0. For this trial, Adverse Events: Solicited is the Form used for routine AE reporting in Rave.

PRO-CTCAE paper booklets ordered from the CTSU website are to be administered by a nurse/CRA and completed by the patient at scheduled times according to the Study Calendar in Section 5.0, and then entered into Rave by site staff.

9.1.1 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period and used to collect AEs that start during the period or persist from the previous reporting period. CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at [redacted] Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents> Education and Promotion; and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information> User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at [redacted]

9.1.2 Solicited Adverse Events

The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment by CTCAE, PRO-CTCAE, or both (with the exception of Day 15 of Cycles 1 and 2 for CTCAE).

CTCAE v5.0 Term	PRO-CTCAE v1.0 Term	CTCAE v5.0 System Organ Class (SOC)
Neutrophil count decreased		Investigations
Platelet count decreased		Investigations
Alanine aminotransferase increased		Investigations
Aspartate aminotransferase increased		Investigations
Palmar-plantar erythrodysesthesia syndrome	Hand-foot syndrome (a rash of the hands or feet that can cause cracking, peeling, redness, or pain)	Skin and subcutaneous tissue disorders
Rash maculo-papular	Rash	Skin and subcutaneous tissue disorders
Hyperglycemia		Metabolism and nutrition disorders
Hypothyroidism		Endocrine disorders
Hypertension		Vascular disorders
Fatigue	Fatigue, tiredness, or lack of energy	General disorders and administration site conditions
Diarrhea	Loose or watery stools (diarrhea)	Gastrointestinal disorders
Mucositis oral	Mouth or throat sores	Gastrointestinal disorders
	Problems with tasting food or drink	Gastrointestinal disorders
	Decreased appetite	Gastrointestinal disorders
	Nausea	Gastrointestinal disorders

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Management Center. Questions about routine reporting should be directed to the Data Manager.

NOTE: PRO-CTCAE data should not be used for determining attribution, dose modifications, or reporting of serious adverse events.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated		a	a	a	a
Unlikely		a	a	a	a
Possible		a, b	a, b	a, b	a, b
Probable		a, b	a, b	a, b	a, b
Definite		a, b	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (Rave-CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: [redacted]All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

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

NOTE: PRO-CTCAE data should not be used for determining attribution, dose modifications, or reporting of serious adverse events.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE ≤ 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 **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** 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 **<u>ANY</u>** 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 electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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 submitted electronically 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 electronically 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.

Effective Date: May 5, 2011

9.3.2 Expedited AE Reporting Timelines Defined

"24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.

"10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 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 (see below).

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.

9.3.3 Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND

All adverse events reported via CTEP-AERS (i.e. serious adverse events) should also be forwarded to your local IRB.

Alliance A021602 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.

Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.

Death due to progressive disease should be reported as Grade 5 “Disease progression” in the system organ class (SOC) “General disorders and administration site conditions.” Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE version 5.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, or (3) Treatment-related secondary malignancy. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available. New primary malignancies should also be reported using study Form, Notice of New Primary.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

Pregnancy loss:

- Pregnancy loss is defined in CTCAE as "Death in utero."
- Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.
- A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

9.4 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Cabozantinib

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' [redacted] for further clarification. *Frequency is provided based on 3219 patients*. Below is the CAEPR for XL184 (Cabozantinib).

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 2.4, December 17, 2018[1]

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			**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]	

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<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		
	Hypophosphatemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Generalized muscle weakness		
	Muscle cramp		
		Osteonecrosis of jaw	
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
		Reversible posterior leukoencephalopathy syndrome	
		Stroke	

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Transient ischemic attacks	
RENAL AND URINARY DISORDERS			
	Hematuria		
		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)***
	Hair color changes		***Hair color changes (Gr 1)***
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
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 [redacted] 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, Hemoptysis, 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) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that XL184 (Cabozantinib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Eosinophilia; Febrile neutropenia; Hemolytic uremic syndrome
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (hypokinetic cardiomyopathy); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Myocarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo
ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (thyroiditis); Endocrine disorders - Other (thyrotoxicosis); Hyperthyroidism; Hypopituitarism
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (corneal epithelium defect)
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal fissure; Anal mucositis; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Duodenal ulcer; Dysphagia; Enterocolitis; Esophageal ulcer; Esophagitis; Flatulence; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (pneumoperitoneum); Gastrointestinal pain; Gingival pain; Hemorrhoids; Ileus; Pancreatitis; Periodontal disease; Rectal pain; Rectal ulcer; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema face; Fever; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (implant site inflammation); Hypothermia; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Budd-Chiari syndrome; Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic cirrhosis); Hepatobiliary disorders - Other (hepatic thrombus); Hepatobiliary disorders - Other (hepatitis toxic); Hepatobiliary disorders - Other (hepatorenal syndrome); 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; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (D-dimer); Investigations - Other (urine ketone body present); Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; Thyroid stimulating hormone increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Glucose intolerance; Hyperglycemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Buttock pain; Chest wall pain; Flank pain; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle hemorrhage); Myalgia; Neck pain; Osteonecrosis; Osteoporosis; Rhabdomyolysis

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); Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysesthesia; Dysphasia; Encephalopathy; Lethargy; Memory impairment; Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (vocal cord paralysis); Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Seizure; Somnolence; Spinal cord compression; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Psychiatric disorders - Other (mental status changes)
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Glucosuria; Renal and urinary disorders - Other (hemorrhage urinary tract); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain; Reproductive system and breast disorders - Other (scrotal ulcer/erythema/edema); Scrotal pain; Vaginal fistula; Vaginal inflammation; Vaginal perforation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Aspiration; Atelectasis; Hoarseness; Hypoxia; Laryngeal edema; Oropharyngeal pain; 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 (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (rales); Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Nail changes; Pain of skin; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (pain, sloughing of skin and erythema); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin hypopigmentation; 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.

10.0 DRUG INFORMATION

10.1 Cabozantinib (Cabometyx, XL184, IND# 137656, NSC #761968, IND Holder: DCTD, NCI)

Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, 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 participating investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Availability

Cabozantinib and matching placebo will be provided free of charge by Exelixis and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Cabozantinib (NSC 761968) is supplied as 20 mg tablets. The 20 mg and matching placebo tablets are round, yellow film coated containing microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and Opadry yellow film coating. Cabozantinib and placebo tablets are packaged as 30 tablets per bottle.

Each blinded, patient-specific bottle will be labeled with:

- The protocol number (i.e. A021602)
- The bottle number (i.e. “Bottle 1 of 6”, “Bottle 2 of 6”, etc.)
- The number of tablets (i.e. “30 tablets”)
- The patient ID number (e.g. "999999")
- The patient initials (i.e. Last initial, First initial, Middle initial [e.g. “L, FM”])
- The agent identification (i.e. “Cabozantinib 20 mg or Placebo”)
- A blank line for the pharmacist to enter the patient’s name
- Administration instructions (i.e. “Take ____ tablets daily.”)
- Storage instructions (i.e. “Store at Controlled Room Temperature 20° to 25°C.”)
- Emergency contact instructions
- A Julian date

Julian Dating

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g. 2017 = 17, 2018 = 18) and a day count (e.g. January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2017 would have a Julian date of ‘17001’ and a bottle labeled and shipped on December 31, 2017 would have a Julian date of ‘17365’. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e. both cabozantinib and placebo) shipped on or before that date thus eliminating any chance of breaking the blind. The Julian Date – Order number (e.g. 17352-0003) from the patient-specific label must be used as the Lot number on the NCI Oral DARF.

Storage and Stability

Store intact bottles at controlled room temperature, 20^0C to 25^0C; excursions permitted from 15^0C to 30^0C (59^0F to 86^0F). Stability testing of the intact bottles is on-going. Dispense cabozantinib (XL 184)/placebo in the original container. Cabozantinib/placebo is stable for up to 24 hours when dispensed in an open container, such as a pill cup, and for up to 7 days when dispensed in a closed container, such as a pharmacy bottle other than the original container.

Administration

Cabozantinib/placebo is taken orally on an empty stomach. Fasting is required for at least 2 hours before and at least 1 hour after each dose of cabozantinib/placebo. Do not crush or chew. Do not take a missed dose within 12 hours of the next dose. Cabozantinib/placebo should not be taken with grapefruit/grapefruit juice or Seville oranges.

Initial Supply

No blinded starter supplies will be available for this study. Blinded, patient specific clinical supplies will be sent to the registering investigator at the time of randomization and should arrive within approximately 7 to 10 days. This randomization will be performed by the Alliance Statistics and Data Management Center. The assigned Alliance patient ID number must be recorded by the registering institution for proper bottle dispersion. Once a patient has been registered, the Alliance Statistics and Data Management Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the Alliance Statistics and Data Management Center the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day. Shipments within the United States will be sent by FedEx Ground and shipments to Canada (if participating) will be sent by FedEx (generally one to two day delivery). For example, if a patient is randomized on Monday, PMB will receive the order Tuesday and ship Wednesday. Shipments to United States sites can be expedited (i.e. receipt on Thursday in example above) by the provision of an express courier account name and number to the Alliance Statistics and Data Management Center at the time the patient is registered. Orders to destinations within the United States are shipped Monday through Thursday. Orders to destinations within Canada are shipped Monday through Wednesday.

The initial request will be for 6 bottles of cabozantinib/placebo 20 mg. Approximately 2 weeks after Cycle 2 begins (2 weeks before needed), sites may reorder an additional 6 bottles [a 2 cycle (8 week) supply at a dose of 3 tablets given once daily] of cabozantinib/placebo 20 mg using the PMB Online Agent Order Processing (OAOP) application [redacted] Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account [redacted] the maintenance of an “active” account status, and a “current” password. The assigned patient ID number (e.g. "999999") and the patient initials (e.g. "L, FM") must be entered in the "Patient or Special Code" field. A separate order is required for each patient ID number (e.g. "999999") being ordered. All drug orders will be shipped directly to the physician responsible for treating the patient.

Study drug cannot be shipped post-distribution.

In the event of a patient institution transfer, the site to which the patient transferred cannot order study drug until the patient is officially transferred through the CTSU.

Initial Supply – Open-Label (Unblinded): For Crossover Patients Only

No open-label starter supplies will be available for this study. Open-label (unblinded), patient specific clinical supplies will be sent to the registering investigator at the time of re-registration and should arrive within approximately 7 to 10 days. Once a patient has been re-registered, the Alliance Statistics and Data Management Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the Alliance Statistics and Data Management Center the day the patient is re-registered and will be processed by the PMB the next business day and shipped the following business day. Shipments within the United States will be sent by FedEx Ground and shipments to Canada (if participating) will be sent by FedEx (generally one to two day delivery). For example, if a patient is reregistered

on Monday, PMB will receive the order Tuesday and ship Wednesday. Shipments to United States sites can be expedited (i.e. receipt on Thursday in example above) by the provision of an express courier account name and number to the Alliance Statistics and Data Management Center at the time the patient is re-registered. Orders to destinations within the United States are shipped Monday through Thursday. Orders to destinations within Canada are shipped Monday through Wednesday.

The initial request will be for 6 bottles of cabozantinib 20 mg. Approximately 2 weeks after the second cycle begins (2 weeks before needed), sites may reorder an additional 6 bottles [a 2 cycle (8 week) supply at a dose of 3 tablets given once daily] of cabozantinib 20 mg using the PMB Online Agent Order Processing (OAOP) application [redacted] Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account [redacted] the maintenance of an "active" account status, and a "current" password. The assigned patient ID number (e.g. "999999") and the patient initials (e.g. "L, FM") must be entered in the "Patient or Special Code" field. A separate order is required for each patient ID number (e.g. "999999") being ordered. All drug orders will be shipped directly to the physician responsible for treating the patient.

Study drug cannot be shipped post-distribution.

In the event of a patient institution transfer, the site to which the patient transferred cannot order study drug until the patient is officially transferred through the CTSU.

Drug Transfers

Tablets MAY NOT be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g. a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB [redacted] a Transfer Investigational Agent Form available on the CTEP home page [redacted] or by calling the PMB at [redacted] The patient ID number (e.g. "99999"') and the patient initials (e.g. "L, FM") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e. "A021602").

Drug Returns

When it is necessary to return **undispensed** study drug (e.g. sealed or partial bottles remaining when a patient permanently discontinues protocol treatment, expired bottles recalled by the PMB), Investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page [redacted] or by calling the PMB at [redacted] The patient ID number (e.g. "99999") and the patient initials (e.g. "L, FM") should be entered in the "Lot Number" field.

Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing, and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation, and ordering investigator on this protocol.

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a

CTEP IAM account and the maintenance of an "active" account status, and a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: [redacted]
- NCI CTEP Investigator Registration: [redacted]
- PMB Online Agent Order Processing (OAOP) Application: [redacted]
- [redacted]
- CTEP Associate Registration and IAM Account Help: [redacted]
- IB Coordinator: [redacted]
- PMB Email: [redacted]
- PMB Phone and Hours of Service: [redacted] Monday through Friday between 8:30 am and 4:30 pm (ET)

Drug Interactions

Cabozantinib is a substrate of CYP3A4. Coadministration of cabozantinib with medications that are strong inhibitors/inducers of CYP3A4 should be avoided. Administration of a strong CYP3A4 inducer, rifampin (600 mg daily for 31 days), to healthy subjects decreased single-dose plasma cabozantinib exposure (AUC) by 77%. Examples of strong CYP3A4 inducers are carbamazepine, dexamethasone, phenobarbital, phenytoin, rifabutin, rifampentin, rifampin, and St. John's Wort. Administration of a strong CYP3A4 inhibitor, ketoconazole (400 mg daily for 27 days), to healthy subjects increased single-dose plasma cabozantinib exposure (AUC) by 38%. Strong CYP3A4 inhibitors are boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, and voriconazole. Avoid grapefruit/grapefruit juice and Seville oranges while participating in this trial.

Coadministration of gastric pH modifying drugs such as PPIs, H_2-blockers, or antacids has no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers; thus, concomitant use of these drugs with XL184 (cabozantinib) is allowed.

Cabozantinib is highly protein bound, 99.9%. Use caution when coadministering cabozantinib with medications that are highly protein-bound (e.g. diazepam, furosemide, dicloxacillin, and propranolol). Administration of warfarin with cabozantinib is not allowed as warfarin is highly protein-bound and has a very narrow therapeutic index.

Drugs that prolong the QTc interval should be avoided or replaced if possible, as cabozantinib can prolong the QTC interval. Patients who receive potential QTc-prolonging medications (see Appendix V) should be monitored closely.

P-glycoprotein (P-gp) substrates (e.g. fexofenadine, aliskiren, ambrisentan digoxin, colchicine, maraviroc, posaconazole, tolvaptan, etc.) should be used with caution during treatment with cabozantinib as coadministration can cause increased P-gp substrate levels.

MRP2 inhibitors (e.g. cyclosporine, delavirine, efavirenz, emtricitabine, etc.) should be used with caution during treatment with cabozantinib as coadministration can cause increased cabozantinib plasma concentrations.

Pharmacokinetics

Distribution: V_d: ~319 L

Protein Binding: ≥ 99.7% to plasma proteins

Metabolism: Hepatic via CYP3A4

Half-life Elimination: ~99 hours

Time to Peak: ~2-5 hours

Excretion: Feces (54%); urine (27%)

Adverse Events

Please refer to the CAEPR in Section 9.4.

Nursing Guidelines

Instruct patients to take on an empty stomach. They should be fasting 2 hours prior and 1 hour after taking the agent.

Instruct patients to not crush or chew tablets.

Do not take the agents with grapefruit/grapefruit juice or Seville oranges.

The agent has many drug-to-drug interactions. Assess patient's medication list including OTC and herbal products. Instruct patient to report any new medications to the study team immediately.

Surgery (including dental work) should be avoided with 28 days of last dose of agent, if at all possible.

Patients may experience hypertension. Monitor BP as required per protocol and instruct patients to make sure they continue any prescribed antihypertensives.

Warn patients of possible changes to hair color.

Monitor electrolytes closely, especially calcium as hypocalcemia is common.

Patients may experience GI side effects including, but not limited to: abdominal pain, constipation, anorexia, dysgeusia, diarrhea, and nausea/vomiting. Treat symptomatically and monitor for effectiveness of any intervention. Diarrhea may be treated with loperamide 4 mg po at the first onset of diarrhea, and then with loperamide 2 mg po every 2 hours until the patient is diarrhea-free for 12 hours.

Monitor CBC with diff. as cytopenias are common. Instruct patients to report any signs or symptoms of infection and/or bruising/bleeding to the study team immediately.

Monitor LFTs.

Warn of possible hand-foot syndrome (PPE). Instruct patient to report pain, skin changes, etc. to the study team.

Rarely, pulmonary embolism and other arterial thromboembolism has been reported.

11.0 MEASUREMENT OF EFFECT

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) guidelines (version 1.1).

Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline [38].

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated every 12 weeks (+/- 1 week).

Supporting documentation of response should be submitted per Section 6.1.1, and radiologic images and local interpretation reports should be submitted per Section 6.3.

11.2 Definitions of Measurable and Non-Measurable Disease

11.2.1 Measurable Disease

A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥ 2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan or MRI.

A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) on imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

A malignant lymph node is considered measurable if its short axis is >1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Tumor lesions in a previously irradiated area are considered measurable disease if there has been evidence of disease progression in the previously irradiated area in the 6 months prior to registration.

11.2.2 Non-measurable Disease

Non-measurable disease includes disease smaller than these dimensions or lesions considered truly non-measurable including: leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung.

11.3 Guidelines for Evaluation of Measurable Disease

11.3.1 Measurement Methods

All measurements should be recorded in metric notation (i.e. decimal fractions of centimeters) using a ruler or calipers.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during restaging. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.3.2 Acceptable Modalities for Measurable Disease

- 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.

- 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. The lesions should be measured on the same pulse sequence. 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.

- 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 scans are preferable.

11.3.3 Measurement at Follow-up Evaluation

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.

Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g. residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Treatment/Intervention Effect

11.4.1 Target Lesions & Target Lymph Nodes

Measurable lesions (as defined in Section 11.2.1) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in Section 11.2.1), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should

be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.4.2 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with Section 11.4.3.

11.4.3 Response Criteria

All target lesions and target lymph nodes followed by CT/MRI/Chest X-ray must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

- Evaluation of Target Lesions
    - Complete Response (CR): All of the following must be true:
        - Disappearance of all target lesions.
        - Each target lymph node must have reduction in short axis to < 1.0 cm.
    - Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.4.1).
    - Progression (PD): At least one of the following must be true:
        - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
        - At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
    - Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.
- Evaluation of Non-Target Lesions & Non-target Lymph Nodes
    - Complete Response (CR): All of the following must be true:
        - Disappearance of all non-target lesions.
        - Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes
- Progression (PD): At least one of the following must be true:
  - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  - Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

11.4.4 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following table:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	Nontarget Lesions & Nontarget Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

* See Section 11.4.3

11.4.5 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as "symptomatic deterioration" on the corresponding Case Report Form in Rave. Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration, and radiologic imaging should continue to be collected every 12 weeks until disease progression (or start of a new anticancer therapy); see Section 5.0.

11.5 Definitions of Analysis Variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section (Section 13.0) of the protocol.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

Patients will receive treatment until disease progression, unacceptable toxicity, or withdrawal of consent. Patients initially randomized to placebo who experience centrally-confirmed progressive disease (PD) may elect to crossover to open-label cabozantinib; see Section 3.3 and Section 4.8.

12.1.1 CR, PR, or SD

Patients who are in CR, PR or SD will continue treatment at the highest tolerable dose until the appearance of disease progression, unacceptable toxicity, or withdrawal of consent.

After treatment is discontinued, patients will be followed per Section 12.1.3.

12.1.2 Disease Progression

Patients should be given a minimum of 3 cycles of protocol therapy.

Patients who progress on blinded therapy may be unblinded, and, if randomized to placebo, they will be allowed to crossover to open-label cabozantinib; see Section 8.3.

Document details of progression, including tumor measurements, on data forms.

Patients who progress on blinded therapy who do not crossover and patients who experience disease progression on open-label cabozantinib should be followed for survival per Section 5.0.

12.1.3 Discontinuation of Study Agent

If the patient discontinues cabozantinib/placebo due to disease progression, then the patient should crossover to open-label cabozantinib (if applicable) or the patient should be followed for survival per the Study Calendar (Section 5.0). If the patient discontinues cabozantinib/placebo for a reason other than disease progression, then the patient should be followed every 12 weeks (+/- 1 week) for progression and survival per Section 5.0.

12.2 Follow-up for Patients Who Stop Protocol Therapy

If the patient discontinues cabozantinib/placebo due to disease progression and does not crossover to open-label therapy, then the patient should be followed for survival every 6 months per the Study Calendar (Section 5.0).

If the patient discontinues open-label cabozantinib due to disease progression, then the patient should be followed for survival every 6 months per the Study Calendar (Section 5.0).

12.2.1 Withdrawal of Consent

If the patient no longer wishes to continue cabozantinib/placebo and withdraws his/her consent for protocol therapy, then the patient should be asked if he/she may be followed for disease progression and survival per Section 5.0. The reason for discontinuation and the patient's response should be documented.

If the patient no longer wishes to continue disease progression follow-up and withdraws his/her consent for follow-up, then the patient should be asked if he/she may be followed for survival per Section 5.0. The reason for discontinuation and the patient's response should be documented.

If the patient no longer wishes to continue survival follow-up and withdraws his/her consent, then no additional follow-up is required. The reason for discontinuation should be documented.

If the patient is consented to either the optional substudies or biobanking (Section 14.0) and no longer wishes to have his/her specimens collected or quality of life reported and withdraws his/her consent for future collections, then no additional collections should occur. The reason for discontinuation should be documented.

If the patient is consented to either the optional substudies or biobanking (Section 14.0) and no longer wishes to have his/her specimens biobanked for use in future research or quality of life responses analyzed and withdraws his/her consent for future use, then no future analyses should occur, and his/her related health information should no longer be collected. The reason for discontinuation should be documented.

12.2.2 Stopping Study Treatment due to Toxicity

If the patient discontinues cabozantinib/placebo due to unacceptable toxicity, then the patient should be followed for disease progression and survival per the Study Calendar in Section 5.0. The date on which the patient begins a new treatment should be recorded.

12.3 Managing Ineligible Patients and Registered Patients Who Never Receive Protocol Intervention

Definition of Ineligible Patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for Ineligible Patients Who Continue with Protocol Treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, Study Chair, and Executive Officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for Ineligible Patients Who Discontinue Protocol Treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for Patients Who are Registered, but Never Start Study Treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are as follows: Baseline, off-treatment,

and post-treatment follow up (i.e. progression and survival) data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS

This study is a two-arm randomized, double-blinded, placebo-controlled phase III trial comparing the outcomes of treatment with 1) cabozantinib or 2) placebo in patients with advanced neuroendocrine tumors after progression on prior therapy. Patients will be separated into 2 cohorts: pancreatic NET vs. carcinoid tumors. Patients will be randomized in 2:1 fashion to either cabozantinib or placebo. The randomization will be done separately within each cohort. Efficacy analyses will be based on the intention to treat principle, and all randomized patients will be included for the analysis, i.e. patients will be assigned to the treatment group they were randomized to regardless of the actual treatment received. Analysis related to adverse events will be based on the safety population. All patients who were randomized and received any amount of protocol therapy will be considered in the safety population, and patients will be assigned to the treatment group they actually received.

13.1 Accrual Time and Study Duration

Pancreatic NET Cohort

We aim to accrue 6 patients per month for 31 months for a total of 185 patients, which translates to an accrual rate of 72 patients per year. After a minimum follow-up of 8 months, the total time to primary analysis is 3.25 years (39 months).

CALGB 80701, a randomized phase II study of everolimus and octreotide with or without bevacizumab in advanced pancreatic NET, enrolled 150 patients from October 2010-October 2012. This translates to enrollment of 6.25 patients per month on average. ECOG 2211, a randomized phase II study of temozolomide plus capecitabine versus temozolomide in advanced pancreatic NET, accrued as many as 6 patients per month. Both of these studies included a patient population that is similar to the pancreatic NET cohort in this study.

Carcinoid Tumor Cohort

We aim to accrue 6 patients per month for 35 months for a total of 210 patients, which translates to an accrual rate of 72 patients per year. After a minimum follow-up of 11 months, the total time to primary analysis is 3.8 years (46 months).

Alliance A021202 (NCT 01841736), a randomized phase II study of pazopanib versus placebo in patients with progressive carcinoid tumors, enrolled 171 patients from June 2013-October 2015. A021202 included patients similar to the carcinoid tumor cohort in this study.

13.2 Sample Size

Pancreatic NET Cohort

The best historical data available on the outcome of patients with pancreatic NET and progressive disease comes from the results of the placebo arms of the RADIANT-3 study and

the randomized study of sunitinib vs. placebo. In these studies, the progression-free survival (PFS) in patients receiving placebo was approximately 5 months.

We assume an accrual period of 2.6 years (31 months), 6 patients per month, 4.32% of dropout, minimum follow-up in all other patients of 8 months, exponential survival, and that a one-sided log-rank test for superiority will be conducted at level 0.025. We also assume PFS of 5 months for patients receiving placebo. Based on these assumptions, a sample size of 185 patients (124 in cabozantinib arm and 61 in placebo arm) will result in 149 events which are required to provide 90% power to detect a hazard ratio (HR) of 0.568 between the two treatment arms. The PFS estimate corresponding to this HR is 8.8 months.

Carcinoid Tumor Cohort

The best historical data available on the outcome of patients with carcinoid tumors and progressive disease comes from the results of the placebo arms of the RADIANT-2 and RADIANT-4 studies. In the RADIANT-2 study, the PFS according to investigator review in patients receiving placebo was 8.6 months. In the RADIANT-4 study, the PFS in patients receiving placebo was 3.9 months.

We assume an accrual period of 2.9 years (35 months), 6 patients per month, 4.286% of dropout, minimum follow-up in all other patients of 11 months, exponential survival, and that a one-sided log-rank test for superiority will be conducted at level 0.025. We also assume PFS of 7 months for patients receiving placebo. Based on these assumptions, a sample size of 210 patients (141 in cabozantinib arm and 69 in placebo arm) will result in 164 events which are required to provide 90% power to detect a hazard ratio (HR) of 0.583 between the two treatment arms. The PFS estimate for the cabozantinib corresponding to this HR is 12 months.

For Both Cohorts

The rate of PFS events and censoring will be monitored over the course of the study; if it appears that the study will not reach the requisite number of PFS events within the planned study timeframe, the protocol may be amended to increase the total sample size.

13.3 Study Endpoints

13.3.1 Primary Endpoint

For both cohorts: The primary endpoint of this trial is progression-free survival (PFS), defined as the time from randomization to the first radiographic documentation of disease progression, per RECIST 1.1 determined by retrospective independent central review (i.e. IROC; see Section 7.2.3), or death from any cause. Symptomatic deterioration alone does not constitute a PFS event. Patients who do not have a PFS event will be censored for PFS at the last disease assessment date which is prior to initiation of new anticancer therapy.

13.3.2 Secondary Endpoints

For both cohorts: overall survival, adverse events, and radiographic response rate.

Overall Survival (OS)

The secondary endpoint of this study is overall survival, defined as the time from randomization to death, from any cause. Patients who do not have an OS event will be censored for OS at the date they were last known to be alive.

Adverse Events (AEs)

CTCAE AEs and the maximum grade for each type of AE will be recorded for each patient. Similarly, scores (0-4) and the maximum score for each PRO-CTCAE item will be recorded for each patient.

Radiographic Response Rate

A secondary endpoint of this study is (confirmed) radiographic response rate, defined as the proportion of patients in each arm whose best response is either complete response (CR) or partial response (PR) prior to crossover.

13.4 Stratification

The analysis will be done separately for the pancreatic NET and carcinoid tumor cohorts and will be stratified by the stratification factors listed in Section 4.6.

13.5 Analysis Plan

13.5.1 Primary Endpoint

Treatment Efficacy Decision Rules

Interim analysis for both cohorts: Two interim analyses for futility only will be performed at the time at which 33% and 66% of the projected number of events have occurred. Gamma family spending function with parameter -6 will be used for futility boundary. The futility boundary will be considered non-binding. The specific critical p-values for declaring futility at each analysis are specified in the tables below. Specifically, at 2nd interim analysis in the pancreatic NET cohort: if p-value > 0.343, then the cabozantinib will be considered inefficacious. When progression-free survival (PFS) crosses futility boundary, the accrual will be suspended (if still ongoing), the enrolled patients will be followed per protocol, and the data will be reported.

Final analysis for both cohorts: The primary efficacy analysis will be performed at the time at which 100% of the projected number of events have occurred (149 PFS events for the pancreatic NET cohort, and 164 PFS events for the carcinoid tumor cohort). The specific critical p-values for declaring superiority or futility at each analysis are specified in the tables below. Specifically, at the final analysis for the pancreatic NET cohort: if the p-value $\leq$ 0.023, then the cabozantinib will be deemed effective; if not, then the cabozantinib will be considered to have not met the criteria for efficacy. Per FDA instruction, the critical p-value of 0.023 is used for analysis, even though the statistical design has a Type I error of 0.025; therefore, we are spending 0.001 alpha for efficacy at each of the two interim analyses.

Pancreatic NET Cohort – Decision Boundary

Analysis time point (% events)	Number of events	Critical p-value for efficacy	HR for efficacy	Critical p-value for futility	HR for futility
33%	50	N/A	N/A	0.856	1.375
66%	99	N/A	N/A	0.343	0.917
100% (Final)	149	0.023*	0.711	0.023*	0.711

Carcinoid Tumor Cohort – Decision Boundary

Analysis time point (% events)	Number of events	Critical p-value for efficacy	HR for efficacy	Critical p-value for futility	HR for futility
33%	55	N/A	N/A	0.856	1.356
66%	109	N/A	N/A	0.343	0.921
100% (Final)	164	0.023*	0.723	0.023*	0.723

* Alpha spending of 0.001 (for efficacy) per interim analysis (overall level = 0.025) is employed per FDA instruction.

Operating characteristics for both cohorts: The tables below show the operating characteristics assuming the PFS follows exponential survival functions, and they include the operating characteristics according to the monitoring plan outlined above. The proportion of times that: 1) the study would stop early at 1st or 2nd interim analyses due to futility of cabozantinib, and 2) the study would conclude the cabozantinib is superior to placebo at the final analysis, are tabulated by true median PFS and equivalent true hazard ratio for PFS by treatment groups.

Pancreatic NET Cohort – Operating Characteristics

True median PFS (months) †		True Hazard Ratio	%‡ of times the study will be stopped early for futility		%‡ of times the study will be stopped early for efficacy		%‡ of times that cabozantinib is declared superior
Placebo	Cabozantinib		1st interim analysis	2nd interim analysis	1st interim analysis	2nd interim analysis	
5	8.8	0.568	0.12	1.04	NA	NA	90.89
5	8	0.625	0.36	3.4	NA	NA	77.92
5	7	0.714	1.34	10.53	NA	NA	50.15
5	6	0.833	4.61	28.04	NA	NA	18.92
5	5	1	14.47	51.1	NA	NA	2.58

† Although we use median PFS to illustrate each scenario, the hypothesis testing is based on the entire survival curve.

‡ Proportions are based on 10,000 replicates in the simulation study.

Carcinoid Tumor Cohort – Operating Characteristics

True median PFS (months) †		True Hazard Ratio	%‡ of times the study will be stopped early for futility		%‡ of times the study will be stopped early for efficacy		%‡ of times that cabozantinib is declared superior
Placebo	Cabozantinib		1st interim analysis	2nd interim analysis	1st interim analysis	2nd interim analysis	
7	12	0.583	0.14	1.04	NA	NA	90.67
7	11	0.636	0.38	3.23	NA	NA	78.55
7	9	0.778	2.74	18.07	NA	NA	34.02
7	8	0.875	6.47	33.6	NA	NA	12.70
7	7	1	14.25	51.63	NA	NA	2.42

† Although we use median PFS to illustrate each scenario, the hypothesis testing is based on the entire survival curve.

‡ Proportions are based on 10,000 replicates in the simulation study.

Analysis plan for both cohorts: PFS will be compared between treatment arms using the stratified log rank test at one-sided level 0.023. The stratification factors listed in Section 4.6, as collected on the OPEN Enrollment Form, will be used for the analysis. The HR for PFS will be estimated using a stratified Cox proportional hazards model, and the 95% CI for the HR will be provided. Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves will be produced. Brookmeyer Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm [39].

Sensitivity analysis plan for both cohorts:

- The PFS according to investigator assessment will be used as the endpoint for a sensitivity analysis.
- For patients with a PFS event related to the results of a scan performed prior to the time of scheduled restaging, the PFS event will be dated on the date of the next scheduled radiology restaging assessment.

Carcinoid Tumor Cohort – Pre-planned Subgroup Analysis

In the carcinoid tumor cohort, we will perform the subgroup analysis by the subgroups specific below to evaluate whether the treatment effect is consistent across different subgroups. Interaction p-value (interaction between treatment arms and specific subgroups) will be used to determine whether the treatment effect is consistent. A p-value of < 0.1 will indicate that there is a differential treatment effect across different subgroups.

The pre-planned subgroups are:

- Prior Anti-VEGF Therapy: Yes vs. No
- Prior Targeted Radionucleotide Therapy (PRRT): Yes vs. No

13.5.2 Secondary Endpoints

Overall survival (OS) for both cohorts: The analyses for OS will follow ITT principle and will be conducted separately within each cohort (pancreatic NET and carcinoid tumor).

The distribution of OS will be estimated using the method of Kaplan-Meier. The median OS, along with the 95% confidence intervals, will be estimated for the two treatment groups. Additionally, 3-year OS rate, along with the 95% confidence intervals, will be estimated for the two treatment groups.

Overall survival will be compared between treatment arms using the stratified log-rank test at a one-sided cumulative 2.3% level of significance. The stratified Cox regression will be used to estimate the hazard ratio (HR) of OS, along with the 95% confidence interval. A hierarchical approach will be used to control for family-wise type-I error rate, therefore OS will be formally statistically tested only if the primary efficacy endpoint, PFS, is statistically significantly different between the two treatment groups.

The best historical data related to OS outcome in patients with pancreatic NET and progressive disease comes from the results of the placebo arms of the RADIANT-3 study and the randomized study of sunitinib vs. placebo. In the RADIANT-3 study, median OS was 37.7 months in patients who received placebo. In the phase III study of sunitinib vs. placebo in patients with pancreatic NET, median OS was 29.1 months in patients who received placebo.

The best historical data available related to OS outcome in patients with carcinoid tumors and progressive disease comes from the results of the placebo arm of the RADIANT-2 study. In the RADIANT-2 study, median OS was 35.8 months in patients who received octreotide with placebo. The final OS analysis has not been reported for the RADIANT-4 study, which included patients with nonfunctional carcinoid tumors who were randomized to receive everolimus or placebo.

Because patients in this trial are required to have experienced disease progression on at least one line of prior systemic therapy not including somatostatin analogs, we anticipate that the median OS time in patients receiving placebo in both cohorts of this trial may be shorter than what has been reported in the clinical trials mentioned above.

The OS analyses within each cohort will be conducted when approximately 155 OS events have been observed. Based on the assumed accrual rate and target sample size specified in previous sections, the anticipated analysis times for the final OS analysis are approximately 86 months and 68 months for the pancreatic NET and carcinoid tumor cohorts, respectively.

13.5.3 Adverse Events (AEs)

AEs and the maximum grade for each type of adverse event will be recorded for each patient. Similarly, scores (0-4) and the maximum score for each PRO-CTCAE item will be recorded for each patient. For patients who elect to crossover to open-label cabozantinib at centrally-confirmed PD, only adverse events that occur prior to crossover will be considered for endpoint. Any AEs that occur after crossover for these patients will be analyzed separately in a descriptive fashion.

For CTCAE data, the frequency tables will be reviewed to determine the patterns. The overall adverse event rates will be compared between treatment groups using Chi-square test (or Fisher's exact test if the data in contingency table is sparse).

PRO-CTCAE data will, at minimum, be analyzed similarly to CTCAE data. Reasons for missed PRO-CTCAE assessments will be collected, and we will describe the extent of

missing data as well as its patterns and causes. The initial analysis of each PRO-CTCAE item will use all available scores in an analysis which mirrors the approach used for the CTCAE data. Supplemental analysis will use model-based multiple imputation incorporating baseline patient characteristics and physician-rated performance status (which is collected at each cycle). CTCAE data may be incorporated as auxiliary data into multiple imputation models for AEs which are captured by both PRO-CTCAE and CTCAE. Results from supplemental analysis will be descriptively compared to the results of the initial analysis to assess the robustness of results to missing data. Since a preferred or optimal statistical methodology for PRO-CTCAE data is yet to be determined, additional analyses of PRO-CTCAE data beyond those specified above may be undertaken based on the current state of the science at time of data maturity for this study.

13.5.4 Radiographic Response Rate

Radiographic response rate for both cohorts: the analyses for (confirmed) radiographic response rate will follow the ITT principle and will be conducted separately within each cohort (pancreatic NET and carcinoid tumor).

The proportion of patients with either (confirmed) CR or (confirmed) PR as their best response will be estimated using point estimates and 95% confidence intervals . For patients who elect to crossover to open-label cabozantinib at centrally-confirmed PD, only disease assessments prior to crossover will be considered for this endpoint. Any radiographic responses that occur after crossover will be analyzed separately in a descriptive fashion. Radiographic response rate will be compared between treatment arms using the 2-sample z-test to compare sample proportion at a one-sided 2.5% level of significance.

13.6 Monitoring

Safety Monitoring:

This study will be monitored by the Alliance Data and Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines. In addition, the Study Chair and Study Statistician will review the accrual and safety data periodically, as well as the Alliance Group Meeting Reports, in order to identify any feasibility problems associated with accrual rates and adverse events.

Any data release, whether at the time of interim analysis or at the time of final analysis, must be approved by the Alliance DSMB prior to execution.

CDUS Monitoring: This study has been assigned CDUS Abbreviated monitoring.

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site [redacted]

Note: If your study has been assigned to CDUS-Complete reporting, all adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

Enhanced Centralized Data Monitoring: This trial will utilize central monitoring in order to ensure complete and consistent data collection.

Enhanced centralized data monitoring will be performed for the first two cycles of treatment for all patient cases enrolled from each site (as identified by a unique NCI Institution Code). The cases selected for central monitoring will be reviewed for completeness and consistency with the eligibility criteria via source data verification (SDV) with source documents compared to data reported via the electronic Case Report Forms in Rave. Centralized data monitoring with SDV will be performed for all patients for key eligibility and response/disease outcomes.

A source document is a document in which data collected for a clinical trial is first recorded. This data is usually later entered in the Case Report Forms. The ICH-GCP guidelines define source documents as original documents, data, and records.

The pretreatment documents that should be uploaded within two weeks after registration for central review include:

1) Pathology report
2) Baseline imaging reports used to confirm radiographic progression for eligibility
3) Documentation of one or more prior lines of FDA-approved systemic therapy (as specified in Section 3.2.3) not including somatostatin analogs and documentation of disease progression or treatment intolerance
4) Labs to include baseline CBC, chemistry, urine protein to creatinine (UPC) ratio, TSH
5) ECG
6) Clinic source documents to verify initial performance status
7) Deidentified last page of the signed and dated informed consent document including any pages with responses indicated by patient for optional studies (with patient's full signature and any other PHI redacted, but date should be retained)
8) Documentation of the first two courses of treatment (submitted within two weeks of completion) to include, medication orders, medication compliance records

See the Data Submission Schedule, available on the Alliance and CTSU websites, for additional details regarding source data verification of key eligibility criteria.

Sites should ensure that patient identifiers have been removed from all pages that will be uploaded and add study-specific identifying information (i.e. Alliance Patient ID) and then scan and upload all document into Rave. Please ensure that all pages are legible and correct.

In the event that enhanced central monitoring or review of key performance indicators (KPIs) identifies unacceptable enrollment procedures or significant deviations from eligibility criteria, treatment administration, or other significant protocol requirements, then the site will need to submit a corrective and preventative action plan (CAPA) within two weeks of being notified of the findings of the central monitoring.

Additional cases may be selected for centralized monitoring or an audit visit may be conducted when deviations are noted or for sites will high enrollment (note: audit visits will be conducted according to the NCI Clinical Trials Monitoring Branch guidelines). Deficiencies or KPIs that may elicit one of these responses include, but are not limited to:

- Accrual rate
- Eligibility
- Early termination
- Data submission timeliness
- Outstanding forms
- Outstanding queries
- Query responsiveness
- Protocol deviations

13.7 Descriptive Factors

Tumor Grade: grade 1 vs. grade 2 vs. grade 3 vs. unknown

Functional (Hormone Secretion) Status: functional vs. non-functional

Tumor Site: pancreatic vs. lung vs. stomach vs. duodenum vs. jejunum vs. ileum vs. appendix vs. cecum vs. ascending colon vs. hepatic flexure vs. transverse colon vs. splenic flexure vs. descending colon vs. sigmoid colon vs. rectum vs. unknown vs. other

13.8 Inclusion of Women and Minorities

Pancreatic NET Cohort

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	2	2	0	0	4
Asian	6	7	0	0	13
Native Hawaiian or Other Pacific Islander	8	10	0	0	18
Black or African American	3	3	1	1	8
White	63	66	5	4	138
More Than One Race	2	2	0	0	4
Total	84	90	6	5	185

Carcinoid Tumor Cohort

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	3	3	1	1	8
Asian	6	7	0	0	13
Native Hawaiian or Other Pacific Islander	8	10	0	0	18
Black or African American	4	4	2	2	12
White	69	73	6	5	153
More Than One Race	2	2	1	1	6
Total	92	99	10	9	210

14.0 CORRELATIVE AND COMPANION STUDIES

There will be one substudy and one biobanking for future correlative science studies, and all patients are encouraged to participate.

14.1 Quality of Life Substudy (Alliance A021602-HO1)

14.1.1 Background

We will evaluate quality of life and disease-related symptoms in patients with advanced pancreatic NET and carcinoid tumors treated with cabozantinib versus placebo. For patients who opt in, patients will complete the EORTC QLQ-C30 and EORTC QLQ-GI.NET21 at baseline and every 12 weeks until disease progression or the start of a new anticancer therapy. The hypothesis is that cabozantinib will improve quality of life and decrease disease-related symptoms as compared to placebo and will be important in the current study to investigate potential treatment benefits in the setting where no effective treatments exist. We are using the same tools as were used in A021202 (randomized phase II study of pazopanib versus placebo in patients with progressive carcinoid tumors) to allow for cross-study comparison and to further our current work in understanding quality of life and disease symptomatology of these patients. In A021202, the EORTC QLQ-C30, GI.NET21, and Linear Analog Self-Assessment (LASA) items were administered at baseline, weekly during the first cycle of treatment, at 3 months, and at 1 year with a plan to compare the longer questionnaires (EORTC QLQ-C30 and GI.NET21) to a brief approach (LASA items). We have modified our approach somewhat in the present study maintaining the longer questionnaires (as results indicating comparability of approaches is not available at this time) but capturing less acute data and more frequent long-term data on the same schedule as disease assessments to better estimate and compare the trajectory of disease impact over time as well as to begin to explore possible symptom response endpoints for use in future clinical trials. Note, patient-reported treatment-related toxicities will be captured in the main body of the protocol using PRO-CTCAE on a more frequent interval.

Recently, Pearman et al. [40] reported a large cross-sectional study using the PROMIS-29 questionnaire reported on the quality of life outcomes of patients with NET. The authors report that increased frequency of bowel movements and presence of flushing symptoms

are correlated with decreased quality of life. Also, patients with recurrent disease reported poorer physical, social, and mental functions. This study was consistent with a previous study reported by Beaumont et al. [41].

A major limitation of these studies was their cross-sectional approaches in heterogeneous patient populations. Investigation of quality of life in this patient population in the setting of therapeutic clinical trials remains lacking. The present study allows us to estimate the within-patient trajectory of disease impact over time and compare trajectories between arms in a well-defined clinical trial population. We also aim to explore possible symptom response endpoints to begin to develop criteria for evaluating future therapies in clinical trials in this patient population.

14.1.2 Methods

For the schedule of assessments for this quality of life study, see Section 5.0. All participating institutions must ask patients for their consent to participate in this quality of life study (A021602-HO1), although patient participation is optional. Paper booklets will be used for this study. For information regarding ordering the booklets, see Section 4.3. For all patients who consent to participate in the quality of life study (A021602-HO1), a booklet will be given to the patient to complete at the specified, planned clinic visits before any procedures/tests are initiated at the site visit and prior to any discussion of their status with healthcare personnel at the site. For assessments after cessation of protocol-treatment but prior to disease progression or the start of a new anticancer therapy, a member of the site study staff may administer the booklet over the phone if no clinic visit is available for in-person completion. Booklets will be collected at the following time points: at baseline and every 12 weeks until disease progression or initiation of new anticancer therapy (i.e. every 3 cycles approximately coinciding with disease assessments). The booklet contains 52 questions, and it is anticipated that the booklet will take approximately 10-15 minutes for the patient to complete at each administration time point. The questionnaires will be available in pre-printed booklets in English at time of study activation. Booklets containing other languages may be added depending on patient demand. Patients who consent to participate in this quality of life study (A021602-HO1) may decline to complete a booklet at any time. The primary reason for each missed booklet will be collected on a case report form.

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) is a 30-item questionnaire about patient ability to function (measured via five functional scales), symptoms related to the cancer and its treatment (via eight symptom scales/items), overall health and quality of life, and perceived financial impact of the cancer and its treatment. Each item is measured on a 1-4 scale (1=not at all; 4=very much). Seven of nine scales had Cronbach's alpha greater than 0.70 and the test-retest reliability for all scales and one single item was 0.78 or higher. These instruments are available in other languages upon request.

The GI.NET21 module is intended for use among patients with gastrointestinal-related neuroendocrine tumors, who vary in disease stage and treatments. The module comprises 21 questions assessing disease symptoms, side effects of treatment, body image, disease-related worries, social functioning, communication and sexuality. The questionnaire results in the following scale scores: endocrine symptoms [3 questions], gastrointestinal symptoms [5 questions], treatment-related side effects [3 questions], bone/muscle pain [1 question], concern about weight loss [1 question], social function [3 questions], disease-related worries [3 questions], sexuality [1 question], and communication [1 question]. The measure is presently in phase IV validation testing as set out in the EORTC module

development process, indicative that initial content and construct validity has been achieved, but that further data are needed to demonstrate responsiveness and discriminant validity. Given the lack of an alternative fully validated NET-specific questionnaire, and the EORTC's rigorous development process and high rate of ultimately successful validation, we have selected to use this questionnaire for the current study. We believe that this questionnaire will become the gold standard for assessment of quality of life issues in patients with NET.

Perception of change will be evaluated with a Patient Global Impression of Change item. Global Impression of Change Scale (also called the Subjective Significance Scale) has been used as an anchor for determination of minimally clinically significant differences in numerous oncology clinical trials within Alliance legacy trials (N00C3, N01C3, N01CB, and N03CA) and beyond [42-44]. The patient rates the change in his/her overall status (ranging from very much improved, much improved, minimally improved, no change, minimally worse, much worse, to very much worse).

14.1.3 Objectives/Hypotheses

Primary Objective

Compare health-related quality of life (HRQL) as assessed by the EORTC QLQ-C30 between patients randomized to cabozantinib vs. placebo by patient cohort (pancreatic NET vs. carcinoid tumor).

Hypothesis: HRQL (based on the EORTC QLQ-C30 HRQL summary score) will be better in patients randomized to cabozantinib compared to placebo from initiation of protocol-treatment until disease progression or start of new anticancer therapy.

Secondary Objective

Compare NET disease-related symptoms and other domains as assessed by EORTC QLQ-GI.NET21 between patients randomized to cabozantinib vs. placebo by patient cohort (pancreatic NET vs. carcinoid tumor).

Hypothesis: NET disease-related symptoms and other domains (based on the EORTC QLQ-GI.NET21 scale scores excluding treatment-related side effects and communication) will be better in patients randomized to cabozantinib compared to placebo from initiation of protocol-treatment until disease progression or start of new anticancer therapy.

Exploratory Objectives

1) Assess the relationship between EORTC QLQ-GI.NET21 symptoms, EORTC QLQ-C30 functioning domains, and EORTC QLQ-C30 Global Health Status/Quality of Life score.
2) Explore possible symptom response definitions through estimation of meaningful changes in EORTC QLQ-GI.NET21 scale and summary scores and compare rates of symptom response between arms.

14.1.4 Statistical Considerations

All questionnaires will be scored according to published scoring algorithms. The primary analysis will involve a mixed model of the EORTC QLQ-C30 HRQL summary score within each patient cohort. The mixed model will compare the post-randomization HRQL between randomized arms. In addition to a randomized arm covariate, each model will include a covariate for baseline HRQL and will use the planned month of assessment as the categorical time value. Unstructured covariance will initially be used, though alternative covariance structures will be investigated with the final covariance structure

selected based on minimization of the Akaike information criterion. The statistical significance of the randomized arm covariate between arms will be employed for hypothesis testing. Within this model, this covariate represents the estimated average difference between randomized arms across post-randomization time points. We have chosen this approach to reduce the number of hypothesis tests to one for each patient cohort. We feel that this is a reasonable approach because we anticipate a consistent effect across time points. In supplemental analysis, we will modify this approach to include a time-by-arm interaction effect and report time-specific comparisons between arms as well as model-based estimation of the area-under-the-curve throughout treatment based on mixed model contrasts.

Primary patient-reported outcome analysis will be conducted at the time that all consented patients have completed 24 weeks of treatment (or are no longer being followed for quality of life). Release of the data for presentation will be at the discretion of the DSMB. Patients will be analyzed according to the randomized treatment arm assignment. All patients who consent for participation in the HO1 component with a baseline endpoint value and at least one endpoint value post-randomization will be included in the primary analysis. In the primary analysis, all observations available will be used. See below for information regarding analyses to account for missing data.

In secondary analysis, similar mixed model comparisons of EORTC QLQ-GI.NET21 scale scores will be conducted within each patient cohort. Graphical procedures will include plots of average values over time by arm for each primary and secondary endpoint. Exploratory analysis will include computation of Pearson correlations among patient-reported endpoints at fixed time points and univariate and multivariate linear mixed models of EORTC QLQ-C30 Global Health Status/Quality of Life score to investigate the impact of symptoms and functioning on quality of life.

Possible symptom response endpoints will be explored. Candidate summary scores include the average of all EORTC QLQ-GI.NET21 scale scores and the average of all EORTC QLQ-GI.NET21 scale scores excluding treatment-related side effects and communication. Meaningful change for each will be explored using common distribution-based and anchor-based approaches. Data will be pooled across patient cohorts for this analysis. For distribution-based approaches, meaningful changes will be estimated as 0.5 and 0.3 times the baseline standard deviation, 12-week standard deviation, 24-week standard deviation, standard deviation of the change-from-baseline scores at 12 weeks, and standard deviation of the change-from-baseline scores at 24 weeks. The anchor-based approach will employ the global impression of change items at 12 and 24 weeks. Candidate symptom response endpoints with triangulated meaningful change criteria will be applied to each treatment arm and rates of symptom response will be compared between arms within each patient cohort using a chi-squared test. Finally, cumulative distribution plots will be used to visually simultaneously assess arm comparisons across all possible meaningful change criteria within each patient cohort.

For all statistical analyses, p-values <0.05 will be considered statistically significant (though interpretation will take into consideration that the type I error is not strictly controlled across primary and secondary endpoints). For interpreting the clinical significance of effects, 0.2, 0.5, and 0.8 standard deviation (SD) effects will be considered as small, moderate, and large based on Cohen throughout [45].

Missing data will be handled in a number of ways. Missing items within a summary or scale score will be handled according to each questionnaire's published scoring algorithms. Missing data at the summary or scale score level will be handled as follows. Baseline

patient/disease characteristics will be compared between patients who do and do not provide data for the primary analysis. We will also graphically explore patterns of missing data. All analyses will be completed using all available data, followed by analyses completed using a range of imputation methods. Lastly, we will employ pattern mixture models for longitudinal analyses. Output from all analyses will be tabulated and descriptively compared to assess the degree to which missing data impacts study results.

Power

Within the **pancreatic NET cohort**, we assume that 138 of the 185 enrolled patients will be progression-free at 12 weeks (based on median PFS of 5 months in the placebo arm and 8.8 months in the cabozantinib arm). Allowing up to 15% additional missing data due to non-compliance, we based power estimation on having baseline and at least one follow-up assessment in 117 patients (83 on the cabozantinib arm, 34 on the placebo arm) in this cohort. The primary analysis in this cohort has 80% and 90% power to detect a 0.58 and a 0.67 standard deviation difference between arms, respectively, assuming no correlation between baseline and follow-up HRQL (conservatively based on a power calculation for a two-sample t-test). With correlation of 0.5 between baseline and a single follow-up HRQL, the detectable effect size shrinks to 0.52 and 0.61, respectively, which can still be thought of as a conservative estimate based on a single follow-up time point.

Within the **carcinoid tumor cohort**, we assume that 169 of the 210 enrolled patients will be progression-free at 12 weeks (based on median PFS of 7 months in the placebo arm and 12 months in the cabozantinib arm). Allowing up to 15% additional missing data due to non-compliance, we based power estimation on having baseline and at least one follow-up assessment in 143 patients (100 on the cabozantinib arm, 43 on the placebo arm) in this cohort. The primary analysis in this cohort has 80% and 90% power to detect a 0.51 and a 0.60 standard deviation difference between arms, respectively, assuming no correlation between baseline and follow-up HRQL (conservatively based on a power calculation for a two-sample t-test). With correlation of 0.5 between baseline and a single follow-up HRQL, the detectable effect size shrinks to 0.47 and 0.55, respectively, which can still be thought of as a conservative estimate based on a single follow-up time point.

The planned analyses will incorporate all available data to maximize power. Thus, we anticipate having 80% power for detecting an effect size between 0.4 and 0.5 standard deviations within each cohort which is considered as clinically meaningful based on the work of Cohen.

Overall power across both cohorts is expected to be 81% (i.e. 0.90 x 0.90 = 0.81) for effect sizes of 0.67 and 0.60 in the pancreatic NET and carcinoid tumor cohorts, respectively, assuming no correlation between baseline and follow-up HRQL, and for effect sizes of 0.61 and 0.55 in the pancreatic NET and carcinoid tumor cohorts, respectively, assuming a correlation of 0.5 between baseline and follow-up HRQL. These effect sizes are considered moderate to large and clinically-meaningful based on the work of Cohen.

14.2 Population Pharmacokinetics of Cabozantinib (Alliance A021602-PP1)

14.2.1 Background

The absolute bioavailability of cabozantinib tablet or capsule formulations has not been determined. As noted by Lacy et al., the median time to maximum plasma concentration (T_{max}) values across healthy volunteer (HV) studies was 3 to 5 hours, although individual subjects did show prolonged absorption phases with maximum plasma concentration (C_{max}) occurring as late as 120 hours after dosing [46]. Following the absorption peak, plasma concentrations declined slowly with a mean terminal half-life of 111–131 hours across the

studies. Cabozantinib accumulates approximately fivefold by day 15 following daily dosing based on area under the plasma concentration-time curve (AUC). A population pharmacokinetics (PK) analysis was performed on pooled data for 289 cabozantinib-treated cancer patients (including medullary thyroid cancer [MTC]) receiving daily administration of the cabozantinib capsule formulation at a dose of 140 mg FBE/day (FBE, free base equivalents), except for five subjects that were dosed at 200 mg FBE/day. The data were adequately described by a one-compartment model with first-order absorption and first-order elimination with a small lag time. The mean clearance of distribution (CL/F) and apparent volume of distribution (Vc/F) were estimated to be 106 L/day (standard error % [SE%] = 2.98%) and 349 L (SE% = 2.73%), respectively, resulting in an estimated effective half-life of 2.28 days (55 hours).

Hepatobiliary elimination appears to be the major route of elimination of cabozantinib and its inactive metabolites, while urinary excretion is a route of elimination exclusively for cabozantinib metabolites. Four identified inactive metabolites constitute approximately 65% of total cabozantinib-related AUC following a single 140-mg FBE dose.

The protein binding of cabozantinib is approximately 99.77%. The percentage of cabozantinib unbound to plasma protein appeared to be correlated with serum albumin concentration; subjects with low serum albumin concentrations exhibited a higher percentage of unbound plasma protein and lower total C_{max}. The mean values of systemic exposures, $AUC_{0–24}$ and $AUC_{0–72}$, in plasma were around 1.6 times higher than those in whole blood.

Single doses of cabozantinib tablets at 20-, 40-, and 60-mg FBE dose strengths showed dose-proportional increases in mean plasma cabozantinib C_{max} and $AUC_{0–t}$ values, suggesting linear pharmacokinetics.

Cabozantinib AUC was increased by 63-81% or 7-30% in subjects with mild/moderate hepatic or renal impairment, respectively, by 34-38% with concomitant administration of the CYP3A4 inhibitor ketoconazole, and by 57% following a high-fat meal. Cabozantinib AUC was decreased by 76-77% with concomitant administration of the CYP3A4 inducer rifampin and was unaffected following administration of the proton pump inhibitor esomeprazole. Cabozantinib is a potent *in vitro* inhibitor of P-glycoprotein and multidrug and toxin extrusion transporters 1 and 2-K, and it is a substrate for multidrug resistance protein 2.

Patients with medullary thyroid cancer with low model-predicted apparent clearance were more likely to dose hold/reduce cabozantinib early and had a lower average dose through day 85. However, longitudinal tumor modeling suggests that cabozantinib dose reductions from 140 to 60 mg/day did not markedly reduce tumor growth inhibition in medullary thyroid cancer patients.

PK parameter values at a single 140-mg FBE dose were generally consistent for capsule and tablet formulations administered in HVs and for the capsule formulation administered in subjects with advanced malignancies.

In a population pharmacokinetic analysis, no clinically significant covariates affecting cabozantinib pharmacokinetics were identified. Sex and body mass index (BMI) on oral clearance were the only covariates retained in the final model. Cabozantinib CL/F was shown to decrease by approximately 22% at the 95th percentile of BMI relative to the median, which translates to an approximately 28% increase in steady-state AUC. Female individuals cleared cabozantinib slower than male individuals by 22%, resulting in a predicted increase in steady-state AUC of 28% for female individuals. Sex and BMI

combined contributed to 15% of the variability in cabozantinib CL/F. Cabozantinib pharmacokinetics were not affected by age (20-86 years). The effect of race on cabozantinib pharmacokinetics could not be concluded based on the low percentages of non-white patients in the study population. Inter-individual variability in CL/F was modest (coefficient of variability [CV] = approximately 35%).

The inter-subject variability (%CV) in HVs following a single capsule or tablet dose ranged from 20-59% for AUC values and from 28-72% for C_{max} values across the studies. The %CV was estimated to be 39% for C_{max} and 28% for AUC values in the capsule-tablet bioequivalence study. The %CV in cancer patients was 42-43% for C_{max} and 34% for AUC after a single dose, and 37-43% for C_{max} and 38-43% for AUC at steady state.

In the pivotal phase III study for MTC, 79% of patients who received the 140-mg FBE cabozantinib dose eventually dose reduced. Forty-two percent of subjects received 60 mg/day as their final dose. Exposure-response analyses showed an increased risk for time-to-first-cabozantinib-dose-modification to be highly correlated with higher $AUC_{ss,\ pred}$. However, Kaplan–Meier analyses of progression-free survival (PFS) stratified by time-to-first-dose-modification (tertiles) showed no clear association between early and late cabozantinib dose modifications and reduced PFS. These findings suggest that, although MTC patients who clear cabozantinib slower may have a higher risk of early dose reduction relative to the faster-clearing patients, the dose reduction paradigm used in the phase III study allowed individual MTC patients to ultimately attain a tolerated exposure providing clinical benefit [46].

14.2.2 Objectives

To determine the intra-patient and inter-patient variability of cabozantinib exposure (C_0) in patients with advanced neuroendocrine tumors receiving cabozantinib.

To correlate cabozantinib exposure (C_0) and AUC, as determined by population pharmacokinetic analysis, with toxicity and efficacy in patients with advanced neuroendocrine tumors.

14.2.3 Methods

Approximately 5 mL of peripheral blood for cabozantinib trough concentrations will be obtained from consenting patients prior to receiving their first cabozantinib dosage on Cycle 1 Day 1 and then obtained during clinic visits on Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, and Cycle 3 Day 1 while still on protocol therapy but before receiving the scheduled daily dose (trough sample). The time of day the samples were obtained will be documented. Plasma will be extracted by local hospitals and shipped to the Alliance Pharmacology/Pharmacokinetic Core Laboratory at the University of Pittsburgh in a frozen condition. During the clinic visits, a Patient Pharmacokinetics Form (see Appendix IV) will be completed which will collect information about the timing of the previous 48-hours of cabozantinib dosing; this will detail the time the last two doses of study drug were received.

Drug concentrations will be measured in plasma using an LC-MS/MS assay implemented by the Alliance Pharmacology/Pharmacokinetic Core Laboratory at the University of Pittsburgh using a modification of the assay published by Su et al. [47].

Both frequentist and population modeling approaches will be employed.

14.2.4 Analyses

For the first objective, we will calculate the intra- and inter-subject variability in exposure. Population pharmacokinetic approaches will be employed to achieve this.

For the second objective, population pharmacokinetic approaches will be used to explore the relationships of exposure versus dose modification, toxicity, and efficacy.

Factors such as patient weight, height, albumin levels, etc. will be used as covariants in the analyses.

The data collected from the samples, as outlined above, will be sent using encrypted secure spreadsheets to the Alliance SDC A021602 Statistician. Statistical analyses will be a collaboration between the Alliance SDC and Alliance Pharmacology/Pharmacokinetic Core Laboratory teams.

14.3 Biobanking for Future Correlative Science Studies

NOTE: Testing of banked samples 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.

Note: All laboratory correlates are classified as exploratory, and the specimens requested for submission in Section 6.2 will be collected for banking-only at this time.

14.3.1 Potential Plasma Biomarkers of Cabozantinib

Background

Previous phase II studies in patients with breast cancer and cholangiocarcinoma treated with cabozantinib have evaluated baseline and on-treatment levels of pro-angiogenic and pro-inflammatory biomarkers [48, 49]. Treatment with cabozantinib was associated with significant increases in VEGF, PlGF, and SDF1α and decreases in Ang-2 and sVEGFR2. Cabozantinib also led to decreases in HGF and TIMP-1, both of which are associated with stellate cell activation and fibrosis and decreases in the inflammatory cytokines IFN-c, TNF- α, IL-8, and IL-10.

These studies have also demonstrated that baseline biomarker levels may be associated with patient outcomes. In patients with cholangiocarcinoma treated with cabozantinib, a low baseline plasma TIMP-1 level was associated with longer PFS, and a low IL-6 level and a high soluble MET (sMET) level were correlated with longer OS [49]. In patients with breast cancer treated with cabozantinib, a high baseline sMET level was also correlated with longer PFS [48]. In contrast, data from a phase II study of patients with castrate resistant prostate cancer did not reveal a relationship between plasma biomarkers and radiographic response to cabozantinib [50].

Other studies examining on-treatment changes in biomarker levels in patients treated with anti-VEGF pathway inhibitors have demonstrated that changes may correlate with outcome. For example, in patients with renal cell carcinoma treated with the anti-VEGF antibody bevacizumab, elevated HGF levels at baseline were associated with worse OS. Patients experiencing a decline in HGF level following 4 weeks of treatment had improved OS compared to those with persistently elevated HGF levels [51].

Based on this data, there is a strong biological rationale to examine the association of circulating biomarkers both at baseline and in the setting of response and resistance to cabozantinib. We hypothesize that baseline levels of plasma inflammatory and angiogenic markers will predict likelihood of response to cabozantinib in NET. Similarly, treatment-related changes in biomarker levels will predict outcomes.

Although assessment of biomarker levels at baseline may identify factors that predict benefit or lack of benefit from cabozantinib, evaluation of changes in biomarker levels following initiation of therapy may identify responders to treatment. Reassessment of

biomarkers at the time of progression also may reveal markers and mechanisms of resistance. As such, it may be possible to use such biomarkers to risk-stratify individuals and their response to treatment, providing a more personalized approached to therapy.

Methods

Peripheral blood will be collected at baseline (Cycle 1 Day 1), during treatment (Cycle 2 Day 1), and at the time of disease progression. To identify blood-based markers of anti-angiogenic inhibition, the Duke multiplex ELISA-based plasma angiome panel will be tested. Results of prior studies utilizing this platform have identified strong candidate predictors of benefit for bevacizumab, including VEGF-D in patients with pancreatic cancer and IL-6 in patients with clear cell renal carcinoma. We anticipate being able to identify and validate or refute candidate plasma biomarkers of benefit that are specific for cabozantinib using this methodology.

Table 1 below lists the panel of key angiogenic and inflammatory markers currently optimized. The "Angiome" multiplex array has gone through a rigorous evaluation to ensure data quality and has recently been approved by the NCI Biomarker Review Committee (BRC) as an integrated biomarker for use in two phase III studies of cediranib and olaparib in both platinum-sensitive and platinum-resistant ovarian cancer. Because cabozantinib also inhibits the activity of MET and AXL, we also aim to examine levels of members of these families, including s-MET, s-AXL, and GAS6.

Table 1 – Plasma-based Marker Identification

Soluble Angiogenic Factors		**Matrix-derived Factors**	**Markers of Vascular Activation and Inflammation**
ANG-2	VEGF-A	BMP-9	CD73
bFGF	VEGF-C	OPN	ICAM-1
HGF	VEGF-D	TGFβ1	IL-6
PDGF-AA	sVEGFR1	TGFβ2	IL-6R
PDGF-BB	sVEGFR2	TGFβR3	IL-6ST (GP130)
PlGF	sVEGFR3	TIMP1	SDF-1
		TSP2	VCAM-1

14.3.2 Determination of Mutation Spectrum in ct-DNA

Background

Mutations in pancreatic neuroendocrine tumors are well established and include alterations in MEN1, DAXX, ATRX, and SETD2, among other genes [52, 53]. Far less understood are GI carcinoid genetics, but mutations in CDKN1B are found most commonly [54, 55]. Investigation of the mutational spectrum in lung carcinoid tumors has disclosed mutations in chromatin remodeling genes [56]. Drug sensitivity based on genotype in NET is unknown at this time. Additionally, mechanisms of resistance to cabozantinib have not been well studied.

Changes in the mutational profile of circulating tumor DNA (ctDNA) may provide an opportunity to better understand tumor biology and genetic mechanisms of response and resistance to therapy. In a study examining the mutational profile in ctDNA in patients with metastatic renal cell carcinoma, ctDNA was observed to be altered between first- and second-line treatments [57]. The highest disparity in genomic alteration frequencies in post-first-line versus first-line were in TP53 (49% vs. 24%), VHL (29% vs. 18%), NF1 (20% vs. 3%), EGFR (15% vs. 8%), and PIK3CA (17% vs. 8%). Restricting the analysis to later lines versus first-line vascular endothelial growth factor inhibitors, these

differences were even more prominent, particularly for TP53 (64% vs. 31%) and NF1 (29% vs. 4%). These results suggest that events leading to these changes may underlie unknown mechanisms of resistance. In addition, assessment of ctDNA may reveal relevant biomarkers to facilitate selection of novel targeted therapies.

In this study, we aim to characterize changes in the tumor mutation profile that occur in NET following therapy with cabozantinib and at the time of disease progression. These results will be correlated with response and resistance to cabozantinib. Sequencing results from ctDNA will also be compared to results from FFPE tumor tissue when available.

Methods

Peripheral blood will be collected at baseline (Cycle 1 Day 1), during treatment (Cycle 2 Day 1), and at progression. Circulating tumor DNA (ctDNA) and DNA from buffy coat will be extracted using standard methods. Select samples (representative responders, non-responders, and those with acquired resistance) will undergo sequencing and copy number assessment with a 410 CLIA-certified gene panel test (MSKCC-IMPACT) to determine changes in the mutation spectrum with drug treatment. The MSKCC-IMPACT platform has been used on over 16,000 patients to assess somatic and germline mutations.

14.3.3 Evaluation of *c-MET* and *phospho-c-MET* Expression in FFPE Tumor Tissue

The receptor tyrosine kinase *MET* is known target of cabozantinib. To determine baseline *MET* expression and phosphorylation of the receptor, FFPE tissue sections will be deparaffinized prior to antigen retrieval, blocking, and incubation with primary antibodies. Patients will be dichotomized as to whether or not their tumor expresses *c-MET* and the association between expression and response to cabozantinib will be evaluated.

14.3.4 Next-Generation Sequencing (NGS) of Tumor DNA and of Matching Germline DNA Collected from Peripheral Blood

Background

NGS of tumor DNA is crucial to obtain a comprehensive genetic molecular basis to inform hypotheses related to the biology of this disease and its treatment. Among the different approaches for NGS, whole-exome sequencing (WES) of tumor DNA combined with that of germline DNA from a matching peripheral blood sample is the most cost-effective one. WES will provide a systematic analysis of the tumor genome of each patient, thus establishing genomic signatures for testing of their predictive and prognostic value. The WES output from the germline DNA will allow, in addition to providing novel candidate genes for outcome testing, new genes associated with the side effects of the study drug.

Methods

This analysis is very comprehensive and exploratory and will be used to generate a set of novel hypotheses and test their clinical significance.

Whole exome libraries will be prepared in the Pre-Clinical Genomic Pathology (gPATH) laboratory at UNC. We will use a DNA input of 750 ng. For WES, we will utilize the Agilent SureSelect All-Exon bait set, which is optimized to target uniform coverage of the human exome, followed by the Illumina DNA TruSeq library preparation kit. Currently, we are using a 150 base paired-end sequencing strategy. To accurately identify somatic gene variants, we sequence cancer samples to an average depth of 200x coverage. With current computational protocols, this depth achieves 100% sensitivity for SNPs and small indels and >90% sensitivity for large indels, assuming the allele is present in at least 10% of the sample. At this depth, specificity for somatic events is also very high (>99.999%) when a paired normal is available.

Targeted sequencing in this manner is fast, reproducible, economical, and has excellent performance characteristics (sensitivity and specificity). Sequencing of DNA from FFPE and frozen samples is generally performed using the same protocol with the following minor modifications: FFPE samples will be sequenced using the paired end protocol with PCR duplicates removed to address the greater problem of lower complexity and PCR artifacts in paraffin samples. The UNC laboratory has extensive experience with WES from tumor samples and matching germline DNA [58-61].

Sequencing data are routed through an automated pipeline, SeqWare, managed by the UNC Bioinformatics Core Facility. SeqWare initiates processing of the raw data based on the protocols specified in gPATH's Laboratory Information Management System. Initial alignment to the genome is performed using Stampy, a highly-sensitive DNA alignment algorithm [62]. Currently, the resulting alignments are then processed with UNCseqR to generate somatic mutation calls, all while following standard quality control procedures [63].

Once mutations, structural variations, or copy number variations are detected, they are annotated. High-quality variants will be carried on to annotate for genomic features, including known genes, exonic function, predicted amino acid changes, predicted allele frequencies based upon the 1,000 Genomes Project [64] and the NHLBI Exome Sequencing Project [65], variant functions (loss of function, gain of function, no change), and COSMIC IDs etc. by Variant Effect Predictor (VEP) [66] combined with the UniPort database [redacted]Specifically, the call on loss-of-function or gain-of-function will be based on existing experimental data from the UniPort database, while harmful or tolerated effects on protein structure will be predicted using SIFT [redacted] embedded in the VEP analysis. In addition, other bioinformatic analyses will be conducted to detect regulatory changes potentially affecting gene expression using publicly-accessible repositories such as ENCODE, as well as other repositories that have been utilized in the past [67-70].

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69. Innocenti, F., et al., *A genome-wide association study (GWAS) of overall survival (OS) in 609 metastatic colorectal cancer (mCRC) patients treated with chemotherapy and biologics in CALGB 80405.* Journal of Clinical Oncology, 2015. **33**(15_suppl): p. 3599-3599.
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APPENDIX I QUALITY OF LIFE MEASURES

Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and entered into Medidata Rave at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

National Cancer Institute PRO-CTCAE

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' and the side effects you are experiencing as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains one set of questions:
    a. National Cancer Institute PRO-CTCAE (12 questions)
2. Please follow the directions at the top of this questionnaire.
3. You may choose not to answer any questions that make you feel uncomfortable.
4. Please complete the booklet during your scheduled clinical visit and return it to your nurse, physician, or research coordinator.

Thank you for taking the time to help us.

NCI PRO-CTCAE™ ITEMS
Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an X in the one box that best describes your experiences over the past 7 days…

1.	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

2.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

4.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

5.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

6.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

7.	In the last 7 days, what was the SEVERITY of your HAND-FOOT SYNDROME (A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS, OR PAIN) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

The PRO-CTCAE™ items and information herein were developed by the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO-CTCAE™ is subject to NCI's Terms of Use.

8.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

The PRO-CTCAE™ items and information herein were developed by the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO-CTCAE™ is subject to NCI's Terms of Use.

Patient Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' and the side effects you are experiencing as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains three sets of questions:

    a. EORTC QLQ-C30 (30 questions)
    b. EORTC QLQ-GI.NET21 (21 questions)
    c. Patient Global Impression of Change (1 question)

2. Please follow the directions at the top of each questionnaire.

3. You may choose not to answer any questions that make you feel uncomfortable.

4. Please complete the booklet during your scheduled clinical visit and return it to your nurse, physician, or research coordinator.

Thank you for taking the time to help us.

EORTC QLQ - C30 (Version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

Please go to next page

EORTC QLQ - C30 (Version 3)

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Please go to next page

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31. Did you have hot flushes?		1	2	3	4
32. Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33. Did you have night sweats?		1	2	3	4
34. Did you have abdominal discomfort?		1	2	3	4
35. Did you have a bloated feeling in your abdomen?		1	2	3	4
36. Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37. Have you had acid indigestion or heartburn?		1	2	3	4
38. Have you had difficulties with eating?		1	2	3	4
39. Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40. Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41. Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42. Were you concerned about disruption of home life?		1	2	3	4
43. Have you worried about your health in the future?		1	2	3	4
44. How distressing has your illness or treatment been to those close to you?		1	2	3	4
45. Has weight loss been a problem for you?		1	2	3	4
46. Has weight gain been a problem for you?		1	2	3	4
47. Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48. Have you had aches or pains in your muscles or bones?		1	2	3	4
49. Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:					
50. Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51. Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

Please go to next page

If you **have not** started treatment on this study, please stop here. 

If you **have** started treatment on this study, please complete the one question below. 

Patient Global Impression of Change (PGIC)

---

1. **Since the start of the study, my overall status is:**

   X *one box only:*

- ☐ Very Much Improved
- ☐ Much Improved
- ☐ Minimally Improved
- ☐ No Change
- ☐ Minimally Worse
- ☐ Much Worse
- ☐ Very Much Worse

Thank you for taking the time to help us.

APPENDIX II PATIENT MEDICATION DIARY

Patient Initials: _____ Patient ID Number: _____ Study Number: _____

Cycle #: _____ Dose: _____ Blinded ☐ Open-label ☐

Patient Instructions

- Please fill in on the table below *every* day that you take your study medication by writing in the number of tablets you take, and the date on which you take them. Please bring this sheet with you to all appointments.
- Cabozantinib/placebo should be taken by mouth (orally) without food. Do not eat for at least 2 hours before and at least 1 hour after each dose of cabozantinib/placebo. Grapefruit/juice and Seville oranges should be avoided while on cabozantinib/placebo.
- If you miss a dose, please take the missed dose as soon as possible, but only if there are 12 or more hours remaining before the next scheduled dose.
- If you miss a dose and the next dose is due (scheduled) in less than 12 hours, then place a "**0**" for the "Number of Tablets" you took that day, and do not take the "missed" dose. Please take the next dose as scheduled.
- If vomiting occurs after taking cabozantinib/placebo (even if it appears that an intact or whole tablet has been vomited), then do NOT take a replacement dose on that day. Start taking cabozantinib/placebo again with the next scheduled dose. If consistent vomiting occurs, please notify your study doctor.
- Cabozantinib/placebo tablets should be stored at room temperature; do not crush or chew tablets.

Cabozantinib/Placebo	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Number of Tablets							
Date							

Cabozantinib/Placebo	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Number of Tablets							
Date							

Cabozantinib/Placebo	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Number of Tablets							
Date							

Cabozantinib/Placebo	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
Number of Tablets							
Date							

Comments: _____

Patient Signature: _____ Date: _____

The table below is to be completed ONLY by Site Staff (Nurse/CRP) after the cycle is completed:

Pill Bottle Returned (Circle)	Yes No
Date of Pill Count (MM/DD/YYYY)	/ /
Number of Tablets Given	
Number of Tablets Returned	
Discrepancy (Circle)	Yes No
Site Staff Initials	

APPENDIX III PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers, and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **XL184 (cabozantinib).** This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

XL184 (cabozantinib) interacts with a specific enzyme in your liver, certain transport proteins that help move drugs in and out of cells, and the heart's electrical activity (QTc prolongation).

- The enzyme in question is **CYP3A4**. XL184 (cabozantinib) is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme.
- The proteins in question are **P-glycoprotein (P-gp) and MRP2.** XL184 (cabozantinib) is an inhibitor of P-gp and may be affected by other drugs that are "substrates." XL184 is also a substrate of MRP2 and may be affected by other drugs that are "inhibitors" or "inducers" of MRP2.
- XL184 (cabozantinib) may affect the heart's electrical activity causing QTc prolongation. The study doctor may be concerned about QTc prolongation and any other medicine that is associated with greater risk for having QTc prolongation.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

XL184 (cabozantinib) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

XL184 (cabozantinib) must be used very carefully with other medicines that use certain **liver enzyme transport proteins to be effective or to be cleared from your system or that may affect your heart's electrical activity.** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors of CYP3A4, substrates of P-gp, or any medicines associated with greater risk for having QTc prolongation."**

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.

- Do not drink or eat grapefruit/juice or Seville oranges.
    - Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.
    - Your study doctor's name is _____ and he or she can be contacted at _____.

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CLINCIAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: A021602

Study Drug(S): Cabozantinib/Placebo

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX IV PATIENT PHARMACOKINETICS FORM – A021602-PP1

Note: This form is required to be completed at <u>all</u> blood draw time points associated with the pharmacokinetic substudy (A021602-PP1).

On Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, and Cycle 3 Day 1, this form is to be administered by a nurse/CRP, completed by the patient, and entered into Rave by site staff.

Note: study medication should be taken *after* providing the blood sample.

Patient Initials: _____

Patient ID #: _____

Study #: _____

Cycle #: _____

Day #: _____

Date: _____

The following question refers to the day before yesterday (2 days ago):

What time did you take your study medication (*cabozantinib/placebo*)? __ __:__ __ AM / PM

The following question refers to yesterday (1 day ago):

What time did you take your study medication (*cabozantinib/placebo*)? __ __:__ __ AM / PM

The following question refers to today (THIS ONLY APPLIES IF YOU HAVE TAKEN YOUR STUDY MEDICATION BEFORE BEING SEEN IN THE CLINIC TODAY):

What time did you take your study medication (*cabozantinib/placebo*)? __ __:__ __ AM / PM

APPENDIX V DRUGS WITH RISK OF TORSADES DE POINTES/QTC PROLONGATION

The following table presents a list of drugs that have a known risk, possible risk, or conditional risk of causing Torsades de Pointes. Please note that this list is frequently updated; for the most current list of medications, sites should visit the following website: [redacted]

*Known Risk: Drugs that can prolong the QT interval **AND** are associated with a known risk of Torsades de Pointes, even when taken as recommended*	*Possible Risk: Drugs that can cause QT prolongation but currently lack evidence for a risk of Torsades de Pointes when taken as recommended*	*Conditional Risk: Drugs that are associated with Torsades de Pointes **BUT** only under certain conditions of their use (e.g. excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) **OR** by creating conditions that facilitate or induce Torsades de Pointes (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces Torsades de Pointes).*
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Amiodarone /Cordarone®	Alfuzosin /Uroxatral®	Amantadine /Symmetrel®
Amiodarone /Pacerone®	Aripiprazole / Abilify®	Amitriptyline /Elavil®
Arsenic trioxide /Trisenox®	Chloral hydrate /Noctec®	Atazanavir /Reyataz®
Astemizole /Hismanal®	Clozapine /Clozaril®	Clomipramine /Anafranil®
Azithromycin /Zithromax®	Dolasetron /Anzemet®	Desipramine /Pertofrane®
Bepridil /Vascor®	Dronedarone /Multaq®	Diphenhydramine /Benadryl®
Chloroquine /Aralen®	Efavirenz / Sustiva®	Diphenhydramine /Nytol®
Chlorpromazine /Thorazine®	Famotidine / Pepcid®	Doxepin /Sinequan®
Cisapride /Propulsid®	Felbamate /Felbatrol®	Esomeprazole / Nexium®
Cilostazol / Pletal®	Flecainide /Tambocor®	Fluconazole /Diflucan®
Ciprofloxacin / Cipro®	Foscarnet /Foscavir®	Fluoxetine /Sarafem®
Citalopram / Celexa®	Fosphenytoin /Cerebyx®	Fluoxetine /Prozac®
Clarithromycin /Biaxin®	Gatifloxacin /Tequin®	Galantamine /Reminyl®
Disopyramide /Norpace®	Gemifloxacin /Factive®	Imipramine /Norfranil®
Dofetilide /Tikosyn®	Granisetron /Kytril®	Itraconazole /Sporanox®
Domperidone /Motilium®	Hydroxyzine / Atarax®	Ketoconazole /Nizoral®
Donepezil / Aricept®	Lithium /Lithobid®	Loperamide / Imodium®
Droperidol /Inapsine®	Lithium /Eskalith®	Paroxetine /Paxil®
Erythromycin /Erythrocin®	Moexipril/HCTZ /Uniretic®	Protriptyline /Vivactil®
Erythromycin /E.E.S.®	Moxifloxacin /Avelox®	Quetiapine /Seroquel®
Escitalopram / Cipralex®	Nicardipine /Cardene®	Ranolazine /Ranexa®
Fluconazole / Diflucan®	Nilotinib /Tasigna®	Sertraline /Zoloft®

*<u>Known Risk</u>: Drugs that can prolong the QT interval **AND** are associated with a known risk of Torsades de Pointes, even when taken as recommended*	*<u>Possible Risk</u>: Drugs that can cause QT prolongation but currently lack evidence for a risk of Torsades de Pointes when taken as recommended*	*<u>Conditional Risk</u>: Drugs that are associated with Torsades de Pointes **BUT** only under certain conditions of their use (e.g. excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) **OR** by creating conditions that facilitate or induce Torsades de Pointes (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces Torsades de Pointes).*
Gatifloxacin / Tequin®	Nortriptyline /Pamelor®	Solifenacin /VESIcare®
Grepafloxacin / Raxar®	Ofloxacin /Floxin®	Torsemide / Demadex®
Halofantrine /Halfan®	Oxytocin /Pitocin®	Trazodone / Desyrel®
Haloperidol /Haldol®	Paliperidone /Invega®	Trimipramine /Surmontil®
Ibutilide /Corvert®	Risperidone /Risperdal®	Voriconazole /VFend®
Levofloxacin / Levaquin®	Sertindole /Serlect®	
Levomethadyl /Orlaam®	Sertindole /Serdolect®	
Mesoridazine /Serentil®	Sunitinib /Sutent®	
Methadone /Dolophine®	Tacrolimus /Prograf®	
Methadone /Methadose®	Tamoxifen /Nolvadex®	
Moxifloxacin / Avelox®	Telithromycin /Ketek®	
Ondansetron / Zofran®	Tizanidine /Zanaflex®	
Pentamidine /Pentam®	Vardenafil /Levitra®	
Pentamidine /NebuPent®	Venlafaxine /Effexor®	
Pimozide /Orap®		
Probucol /Lorelco®		
Procainamide /Pronestyl®		
Procainamide /Procan®		
Quinidine /Cardioquin®		
Quinidine /Quinaglute®		
Roxithromycin / Rulide®		
Sotalol /Betapace®		
Sparfloxacin /Zagam®		
Terfenadine /Seldane®		
Thioridazine /Mellaril®		

Note: the above list is not all-inclusive.

Reference: [redacted] accessed on March 24, 2017.

APPENDIX VI COLLABORATIVE AGREEMENTS LANGUAGE

NCI/DCTD Collaborative Agreements Language

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" [redacted] 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 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: [redacted]
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other 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 NCI, 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 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 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 [redacted] 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: [redacted]

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