ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A021202

PROSPECTIVE RANDOMIZED PHASE II TRIAL OF PAZOPANIB (NSC # 737754, IND 75648) VERSUS PLACEBO IN PATIENTS WITH PROGRESSIVE CARCINOID TUMORS

Pazopanib and matching placebo will be supplied by Novartis and distributed by CTEP.

[X]	**Update:**	[ ]	**Status Change:**
[ ]	Eligibility changes	[ ]	Activation
[ ]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Closure
[X]	Informed Consent changes	[ ]	Suspension / temporary closure
[ ]	Scientific / Statistical Considerations changes	[ ]	Reactivation
[ ]	Data Submission / Forms changes		
[X]	Editorial / Administrative changes		
[X]	Other: Updated CAEPR for Pazopanib		

The CAEPR and Risk List changes included in this update to A021202 have been made in response to the NCI Request for Amendment from Dr. Fernanda Arnaldez. A revised CAEPR for pazopanib with new risks has been added to the protocol. Therefore, the model consent form has been revised to incorporate these new risks, consistent with the NCI Model Consent Template instructions. There are no changes to the risk/benefit ratio.

Expedited review is allowed. IRB approval (or disapproval) is required within 90 days. Please follow your IRB of record guidelines.

UPDATES TO THE PROTOCOL:

Cover Page

Brandon Bright has replaced Luke Wilson as the Data Manager; all contact information has been updated.

Section 5.5 (Re-Registration [Step 2] at the Time of Progression)

A new second paragraph has been added for clarity. It reads: "Note: As of 03/14/2019, patients who were initially assigned to placebo were given the option to receive open-label pazopanib due to the release of study results.

Section 16.2 (Comprehensive Adverse Events and Potential Risks list [CAEPR] for Pazopanib [GW786034, NSC 737754])

This section has been revised to include the updated pazopanib CAEPR (Version 2.8, January 31, 2019) provided by CTEP. Changes from Version 2.7 to Version 2.8 include the following:

- Added New Risk:
  - Also Reported on Pazopanib Trials But With Insufficient Evidence for Attribution: Muscle cramp.
- Deleted Risk:
  - Also Reported on Pazopanib Trials But With Insufficient Evidence for Attribution: Acute coronary syndrome; Musculoskeletal and connective tissue disorder - Other (muscle spasms).
- Provided Further Clarification:
  - Eye disorders - Other (eye/retinal hemorrhage) (*CTCAE 4.0 language*) is now reported as Eye disorders - Other (eye hemorrhage, retinal hemorrhage).
  - Female genital tract fistula (*CTCAE 4.0 language*) is now reported as Reproductive system and breast disorders - Other (female genital tract fistula).
  - Skin and subcutaneous tissue disorders - Other (hair color change/hair depigmentation) (*CTCAE 4.0 language*) is now reported as Hair color changes.
  - Vascular disorders - Other (arterial thromboembolic event) (*CTCAE 4.0 language*) is now reported as Arterial thromboembolism.
  - Gastrointestinal disorders - Other (oropharyngeal pain), previously listed under the GASTROINTESTINAL DISORDERS SOC (*CTCAE 4.0 language*), is now reported as Oropharyngeal pain and is now listed under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.
  - Investigations - Other (blood lactate dehydrogenase increased) (*CTCAE 4.0 language*) is now reported as Blood lactate dehydrogenase increased.

UPDATES TO THE MODEL CONSENT:

What side effects or risks can I expect from being in the study?

Based on the updated CAEPR described above, the following changes have been made to the NCI condensed risk profile for pazopanib:

- Added New Risk:
  - Rare: Blood clot in artery which may cause swelling, pain, shortness of breath or change of color in extremity.
- Deleted Risk:
  - Rare: Bleeding of the eye which may cause blurred vision with a chance of blindness.
- Provided Further Clarification:
  - High blood pressure which may cause blurred vision (under Common) is now reported as High blood pressure which may cause headaches, dizziness, blurred vision (under Common).
  - Bleeding from multiple sites including the nose or vagina (under Occasional) is now reported as Bleeding from multiple sites including the nose or vagina which may cause blurred vision with a chance of blindness (under Occasional).

- Anemia, kidney problems which may require dialysis (under Rare) is now reported as Anemia, kidney problems which may cause tiredness, bruising, swellings, or may require dialysis (under Rare).
- Blood clot which may cause confusion, paralysis, swelling, pain, or shortness of breath (under Rare) is now reported as Blood clot which may cause confusion, paralysis, seizures and blindness, swelling pain, shortness of breath (under Rare).

Replacement protocol and informed consent documents have been issued.
This protocol remains permanently closed to new patient accrual.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A021202

PROSPECTIVE RANDOMIZED PHASE II TRIAL OF PAZOPANIB (NSC #737754, IND #75648) VERSUS PLACEBO IN PATIENTS WITH PROGRESSIVE CARCINOID TUMORS

ClinicalTrials.gov Identifier: NCT01841736

Pazopanib and matching placebo will be supplied by Novartis and distributed by CTEP.

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Expedited Adverse Event Reporting
https://eapps-ctep.nci.nih.gov/ctepaers

Medidata Rave® iMedidata Portal
https://login.imedidata.com

OPEN (Oncology Patient Enrollment Network)
https://open.ctsu.org

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Protocol-related questions may be directed as follows:

Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, or (where available) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol and model informed consent:	Protocol Coordinator
Questions related to IRB review:	Regulatory Affairs Manager *regulatory@alliancenctn.org*
Questions regarding CTEP-AERS reporting:	Pharmacovigilance Inbox *pharmacovigilance@alliancenctn.org*

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) see the 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 – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

PROSPECTIVE RANDOMIZED PHASE II TRIAL OF PAZOPANIB (NSC #737754, IND #75648) VERSUS PLACEBO IN PATIENTS WITH PROGRESSIVE CARCINOID TUMORS

Eligibility Criteria

Low- or intermediate-grade neuroendocrine carcinoma. (See §4.1.1)

Patients must have locally unresectable or metastatic carcinoid tumors arising in the foregut, midgut, hindgut, or other non-pancreatic site (See §4.1.2, 4.1.3)

Radiological evidence for progressive disease (measureable or non-measurable) within 12 months prior to randomization. (See §4.1.4)

No known endobronchial lesions and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage. (See §4.1.5)

Patients must have measurable disease

No prior treatment with an inhibitor of VEGF or VEGFR

Prior treatment must be completed at least 4 weeks prior to registration

Concurrent use of somatostatin analogs is allowed

Progression on octreotide required for patients with tumors arising in the midgut

Prior treatment with embolization or ablative therapies is allowed

No major surgeries < 4 weeks from registration

No concurrent condition resulting in immune compromise

No clinical evidence of brain metastases or carcinomatous meningitis

No history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to registration

No clinically significant GI abnormalities that may increase the risk for GI bleeding < 28 days prior to registration

No history of serious non-healing wound, ulcer, or bone fracture within 28 days prior to registration

Patients with a history of hypertension must have blood pressure that is adequately controlled (< 140/90 mmHg).

No symptomatic congestive heart failure, arterial thrombotic events including TIA, CVA, peripheral arterial thrombus, MI or unstable angina or angina requiring surgical or medical intervention within 6 months prior to registration

Patients on therapeutic anticoagulation with low molecular weight heparins are allowed

No ongoing cardiac dysrhythmias, atrial fibrillation, or prolongation of corrected QTc interval to > 480 msec.

No evidence of active bleeding, bleeding diathesis, or hemoptysis within 8 weeks prior to registration.

No currently unstable angina and/or uncontrolled cardiac arrhythmias

No symptomatic peripheral vascular disease

Ejection fraction on Echo or MUGA > 50%

No chronic concomitant treatment with strong inhibitors of CYP3A4. Any such treatment must be discontinued 14 days prior to start of study treatment (See §4.5)

Non-pregnant and non-nursing (See §4.6)

Age ≥ 18; ECOG Performance Status: 0 – 1

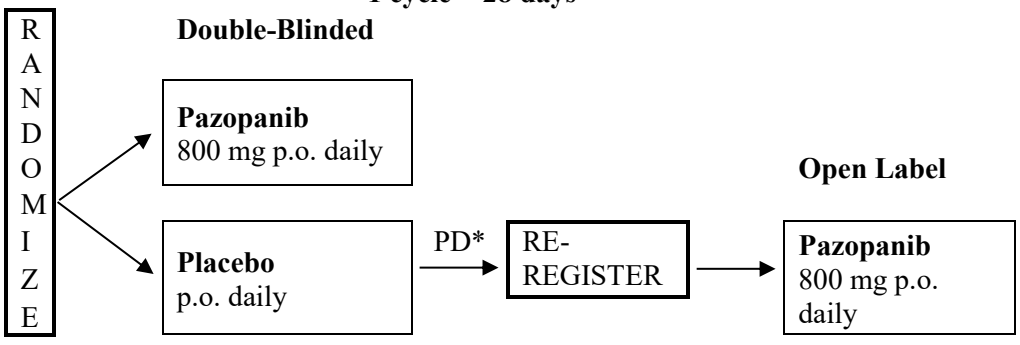
Required Initial Laboratory Values

Granulocytes	≥ 1,500/mcL
Platelets	≥ 100,000/mcL
INR*	≤ 1.2 x ULN
QTc	≤ 480 msecs
TSH	WNL
Bilirubin	≤ 1.5 x ULN
AST/ALT	≤ 2.5 x ULN
Serum Creatinine	≤ 1.5 x ULN
UPC	< 1
OR	
24-hour urine protein	< 1 g

* Only needed if patient is on anticoagulant therapy

Schema

1 cycle = 28 days



Treatment with pazopanib/placebo will continue until disease progression or unacceptable toxicity.

* Upon progression as determined by central review, patients may be unblinded and those who were receiving placebo may elect to crossover to treatment with pazopanib. Patients who opt to cross over to active drug must be re-registered to the study; see Section 5.5.

See Section 4.0 for eligibility criteria details and Section 8.0 for complete treatment information.

Table of Contents

1.0 INTRODUCTION

1.1 Rationale for Selected Approach and Study Design

Carcinoid tumors are relatively indolent, but treatment of advanced disease remains a challenge. Somatostatin analogs are routinely used to control hormone-mediated symptoms (carcinoid syndrome), but the identification of agents with anti-tumor efficacy has proven difficult.[1, 2] Aside from octreotide for small bowel carcinoid, no treatment has proven anti-tumor activity.[3] In the setting of liver-dominant disease, liver-directed treatment such as resection, ablation, and embolization are often employed. No standard chemotherapy exists, and the use of interferon is controversial. As such, additional therapeutic options are sorely needed. Advances in our understanding of the potential mechanisms underlying tumor progression have suggested several therapeutic targets (including the VEGF- and mTOR signaling pathways), but the precise role of targeted agents in carcinoid has not been established. (In contrast, everolimus and sunitinib are approved by the FDA for the treatment of patients with pancreatic NET). Progress in the field has been hampered by a number of factors, including the rarity of the disease, the heterogeneity that characterizes patients with the same diagnosis, and challenges related to interpreting the radiological response to treatment.

Neuroendocrine tumors (NETs) are highly vascular and express VEGF as well as the VEGF receptor.[4, 5] Yao et al. performed a randomized phase II study in which patients with advanced carcinoid received 18 weeks of bevacizumab or pegylated interferon alpha-2b. Up-front bevacizumab was associated with a higher response rate, reduction of tumor blood flow by functional CT, and improved progression-free survival at 18 wk compared to interferon.[6] The results prompted initiation of an ongoing phase III trial in patients with high- risk/poor prognosis carcinoid (SWOG-0518) (accrual completed, results pending).

Phase II studies with TKIs targeting the VEGF receptor, including sunitinib, sorafenib and pazopanib, have also suggested activity in NETs (pancreatic neuroendocrine tumors and carcinoid).[7-9] Phase III data are lacking, however, with the exception of sunitinib, which improves PFS in patients with progressive pancreatic NET (median PFS 11.4 mo vs. 5.5 mo; HR 0.42, $p<0.001$).[10] The activity of TKIs targeting the VEGFR in carcinoid is less convincing, perhaps because two studies evaluating these agents in metastatic carcinoid tumors have been terminated on interim analysis due to lack of objective radiographic response.[9] *In retrospect, while the likelihood of radiographic response is low with this class of agents in carcinoid, improved progression free survival appears very possible (based on 6 mo PFS data).*

Phase II trials with VEGFR TKIs: Carcinoid Population

	RR	6 mo PFS	Median PFS or TTP	
Sorafenib	10%	40%	11.9 mo	Hobday T et al. ASCO 2007
Sunitinib	2%	73%	10.2 mo	Kulke M et al. JCO 2008
Pazopanib	0%	68%	12.0 mo	Phan, et al. ASCO, 2010, Abstr#4001

Pazopanib is an oral multitargeted receptor tyrosine kinase inhibitor with activity against VEGFR-2, and -3, PDGFR-alpha and beta, and stem cell factor receptor (c-KIT).[11,12] It is a promising agent for treatment of metastatic carcinoid tumors because it's spectrum of kinase inhibition matches receptor expression in carcinoid and other NETs.[4,13,14] VEGF is upregulated in primary tumors, and in some studies expression correlates with angiogenesis and decreased progression-free survival.[15] Terris et al reported that levels of VEGF are higher in midgut carcinoids compared to PNET.[4] At least one group has shown that VEGF ligand/receptor

expression may be down-regulated in aggressive metastases.[16] However, other groups have shown stable VEGF expression in metastatic disease. [17]

Over 5000 patients (in the context of >40 studies) have been treated with pazopanib since clinical development of the drug began in 2002. It has a relatively long half-life and is not extensively metabolized: unchanged pazopanib is the major circulating species in human plasma. Pazopanib concentrations are affected by inducers and inhibitors of CYP3A4; renal clearance is minimal. Evidence for efficacy has been demonstrated in a phase III trial in renal cell carcinoma (VEGF10592, 435 pt, PFS 9.2 mo vs. 4.2 mo with placebo, HR 0.46, p<0.0000001). Pazopanib was generally well-tolerated. Most side effects were Gr 1/2, with the most common events (all grades) being diarrhea 52%, hypertension 40%, hair color changes 38%, nausea 26%, anorexia 22%, and vomiting 21%. Grade 3/4 events occurred in 40% (vs. 20% in placebo) of patients (33% grade 3, 7% grade 4), with the most common events being ALT increase (7%), AST increase (5%), hypertension (4%) and diarrhea (4%). Of note, additional rare, but potentially clinically significant events have occurred in pazopanib trials, including: proteinuria, hypothyroidism, bleeding, GI perforation/fistula, arterial thromboembolic events, QT prolongation and Torsade de Pointe.

Preliminary evidence for anti-tumor activity has been shown in several other solid tumors besides RCC.[18-20] While pazopanib is capable of inducing tumor regression (e.g. 49% RR in 39 patients with radioiodine-refractory metastatic differentiated thyroid cancers, 30% RR in the VEGF105192 randomized phase III trial in renal cell carcinoma), minor shrinkage is common, as is delayed tumor progression.[18,20] Single arm phase II data suggest that pazopanib may slow disease progression without causing overt tumor regression in carcinoid.[9] Recognizing that identification of agents that induce radiographic responses in carcinoid has proven exceedingly difficult, our hypothesis is that pazopanib will result in prolonged disease stability among patients with progressive advanced carcinoid tumors (and that this type of activity will be clinically meaningful). *Thus, in contrast to previous phase II studies with pazopanib and other VEGFR tyrosine kinase inhibitors, we will focus on* ***progression-free survival*** *as the primary trial endpoint (rather than response rate).* Importantly, PFS is considered a valid endpoint in well-differentiated NET and was the basis for FDA approval of everolimus, as well as sunitinib, in PNET.

Recent phase III data (see table below) from the RADIANT-2 study suggest a trend towards improved PFS in patients with progressive carcinoid treated with the mTOR pathway inhibitor, everolimus plus LAR.[21] Importantly, while the RADIANT-2 data provide useful estimates of baseline progression-free survival for the patient population under study in this proposal, the results did not achieve statistical significance (according to pre-specified statistical plan for primary endpoint), thus the agent is not FDA approved for this indication. Consequently, there remain no proven agents for treatment of metastatic carcinoid tumors beyond somatostatin analogs, and the relative benefits of VEGFR TKIs compared to mTOR inhibitors in this patient population are not known. New treatments are desperately needed for patients with progressive disease.

RADIANT-2 phase III study in progressive carcinoid[21]				
	Placebo	**Everolimus**	**HR**	**p-value**
Median PFS (central review) 1°Endpoint	11.3 mo	16.4 mo	0.77	0.026
Estimated 12 mo PFS (central review)	42%	54%		
Median PFS (investigator-reported)	8.6 mo	12 mo	0.78	0.018
Estimated 12 mo PFS (inv-reported)	38%	50%	0.72	

1.2 Trial Importance

As noted above, there are no FDA-approved agents for treatment of metastatic carcinoid tumors beyond somatostatin analogs for the treatment of mid-gut carcinoids. New treatments are desperately needed for patients with progressive disease. Of note, the relative benefits of VEGFR TKIs compared to mTOR inhibitors in this patient population are not known. If SWOG-0518 is negative, there will still be questions as to whether or not VEGF is a valid target for therapy, since bevacizumab is an antibody (not a small molecule) and the design (i.e. control arm interferon-treated) may confound the ability to see a true bevacizumab effect. If SWOG-0518 is positive, it will still be valuable to know if an oral, small molecule inhibitor of VEGFR has activity in this disease (and, if needed, our trial will be amended to stratify patients for prior exposure to bevacizumab). In short, whether or not SWOG-0518 is positive, evidence for activity in this study will provide strong support for a phase III study with pazopanib in carcinoid (e.g. bevacizumab vs. pazopanib, or pazopanib vs. placebo). If everolimus is used off-label for carcinoid, the optimal treatment of patients with everolimus-refractory disease will also be a valid question (and we can adjust for use of everolimus retrospectively). Thus the results of this study could lay the foundation for future trials in first line treatment of carcinoid.

Table 1: Progression Free Survival Times in Selected Carcinoid Tumor Trials

	N	**Octreotide requirement**	**Radiographic PD at entry?**	**PFS (TTP)**	**Reference**
Pazopanib					
Pazopanib + LAR	20	Stable dose x 2 mo required	NO, but 85% had PD	12.0 mo	Phan et al. Proc ASCO, 2010, abstr#4001
Everolimus					
Ph II RAD001 (Everolimus) +Octreotide LAR	30	63% (+) prior LAR	NO	14 mos.	Yao JC, J Clin Oncol 2008; 26: 4311-4318
Ph III RAD+LAR vs. placebo +LAR (RADIANT-2) in patients with h/o carcinoid syndrome	429	80% prior SSTa; 100% concurrent LAR	YES (w/i 12 mo)	11.3 mo VS 16.4 mo (HR 0.77, p=0.0026) central rev (1°EP) 8.6 mo VS 12 mo (HR 0.78, p=0.018); inv-reported	J, Yao, et al. *Journal of Clinical Oncology.* 2011;29 (Suppl 4; abstr 159).
Other VEGF pathway inhibitors					
Sorafenib	42	No	No	11.9 mos.	Hobday T, Proc ASCO 2007; A4504 (and personal commun.)
Phase II Interferon/LAR VS Bevacizumab/LAR	44	Stable dose of LAR	NO	14 mo (63 wk)	Yao, et al JCO, 2008
Sunitinib (Phase II)	41	50% on Oct at entry	NO	10.2 mos. (TTP)	Kulke et al. JCO 2008

Chemotherapy					
Phase II/III Strept/5-FU vs. Strept/DOX	249	?	No	5.3 mo vs. 4.5 mo	Sun, et al. J Clin Oncol, 2005
Streptozocin/5-FU vs. Interferon	64	?	Yes	5.5 mos. vs. 14.1 mos.	Dahan, et al. Endocr Relat Cancer, 2009
Octreotide					
Phase III Octreotide vs. Placebo (PROMID)	85	Per protocol (OK if started <4 wk)	No	14.3 mo vs. 6.0 mo (by WHO)	Rinke, et al. 2009. J Clin Onc
Octreotide vs. Octreotide plus interferon (PNET plus carc)	109	Required on study	YES (required for rand)	(27% had SD at 6 mo in both groups)	Arnold, et al. Clin Gast Hep, 2005
OTHER AGENTS					
Bortezomib (carc>PNET)	?	?	NO	3 mo	Shah et al. Clin Can Res, 2004 (CT q 12 wk)
Endostatin	22	Allowed	NO	7.6 mo	Kulke et al JCO, 2008
Imatinib	27	?	?	5.9 mo	Yao, et al Clin Cancer Res, 2007
Other pending carcinoid studies					
SWOG-0518 : BEV/OCT VS IFN/OCT	283 (↑to 400)	Prior OK; 20 mg q 21d on study	High risk (includes PD)	Data 2012	PFS 1°EP (central review)
Radiant-4 RAD001 + BSC vs. PLACEBO+BSC	279	Not Allowed	YES (w/13mo) Non-functional NET of lung/GI origin	OPEN 3/2012	PFS 1°EP
Other potentially relevant studies (in PNET)					
Phase III in PNET: Sunitinib VS Placebo (concurrent SSTa allowed—25% in both groups)	171	?	Yes (w/i 12 mo)	11.4 mo vs. 5.5 mo; HR 0.42 (CI: 0.26-0.66) (p<0.001) RR=9.3% sunit VS 0% placebo 6 mo PFS: 71.3% VS 43.2%	Raymond et al. NEJM, 2011;364: 501-513. (1°EP-inv-reported PFS by RECIST)
Phase III in PNET; RAD001/LAR VS Placebo/LAR (RADIANT-3) (about 50% prior SSta in both groups; concurrent SSta in about 40%)	410	Allowed w/i last 12 mo IF prior PD on it	YES (w/i 12 mo)	11.0 mo 4.6 mo (HR 0.35, CI=0.27-0.45, p<0.001); PFS at 18 mo: 34% VS 9%; RR 5% with rad, 2% placebo; 11.4 vs. 5.4 mo, HR 0.34 by central adjudicated review	Yao et al. NEJM, 2011;364: 514-23 (1°EP inv-reported PFS by RECIST; excellent concordance with central and adjudicated central review)

1.3 Registration Quality of Life (QOL) Measurements

QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and

Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates. [22]

1.4 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of pazopanib treatment in subsets defined by race, gender, or ethnicity, and there is no reason to expect that such differences exist.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	1	+	4	=	5
Not Hispanic or Latino	73	+	87	=	160
Ethnic Category: Total of all subjects	74	+	91	=	165
Racial Category					
American Indian or Alaskan Native	1	+	0	=	1
Asian	0	+	7	=	7
Black or African American	6	+	8	=	14
Native Hawaiian or other Pacific Islander	0	+	1	=	1
White	67	+	75	=	142
Racial Category: Total of all subjects	74	+	91	=	165

2.0 OBJECTIVES

2.1 Primary Objective

For patients with progressive carcinoid tumors, progression-free survival (PFS defined by central review according to RECIST 1.1) will be compared between patients randomized to treatment with pazopanib versus placebo.

2.2 Secondary Objectives

2.2.1 Overall Survival (OS) will be compared between treatment arms.

2.2.2 Objective Response Rate duration of response, and time to treatment failure will be compared between treatment arms.

2.2.3 Progression Free Survival (PFS) as assessed by central radiology review and local radiology review will be compared overall and within treatment arms.

2.2.4 Safety and Tolerability of treatment with pazopanib/placebo will be evaluated within each treatment arm.

2.2.5 PFS and other indicators of efficacy will be estimated in patients who crossover to pazopanib from placebo.

2.2.6 To determine the turn-around time for timely adjudicated central review.

2.2.7 To characterize the nature of discordance between local and central radiology review in assessment of progression.

2.2.8 To characterize the type and rate of progression in carcinoid (at study entry, on-study, and at progression).

2.2.9 To develop new methods for modeling carcinoid growth and detecting treatment effects, and to perform simulations that advance new clinical trial designs to apply to future trials of carcinoid therapeutics.

2.2.10 To assess for differences in QOL-related domains between the two treatment groups (pazopanib versus placebo)

2.2.11 To determine if the more brief measures of QOL-related domains provide comparable information to that which is provided by the longer assessments (EORTC, NET21)

2.2.12 To provide validation data for the EORTC NET21 module in terms of responsiveness over time and differences across arms.

2.2.13 To determine whether components of the plasma Angiome panel that have been shown to be predictive previously (IL-6 and VEGF-D) are predictive of a therapeutic advantage for pazopanib treatment in baseline samples from the patients treated on A021202.

2.2.14 To determine whether other components of the plasma Angiome panel tested (not IL-6 and VEGF-D) are predictive of a therapeutic advantage for pazopanib treatment in baseline samples from the patients treated on A021202.

2.2.15 To evaluate the changes in the plasma Angiome markers after treatment with or without pazopanib over time.

2.3 Exploratory Objectives

2.3.1 PFS at 6 months will be estimated within each treatment arm.

2.3.2 Biochemical response (for chromogranin A, defined as a decrease of 50% or more in chromogranin A levels from baseline, and for 5-HIAA, defined as a decrease of 50% or more in urinary 5-HIAA levels from baseline) will be compared between treatment arms among patients with elevated baseline levels of CGA and 5-HIAA.

3.0 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. Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness that impairs patient's ability to give informed consent or comply with study procedures.
- Medical condition such as uncontrolled infection (including HIV/AIDS/chronic hepatitis), or uncontrolled diabetes mellitus which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient and/or interfere with subject's safety, provision of informed consent, or compliance to study procedures.

- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed any necessary therapy and are considered by their physician to be at less than 30% risk of relapse.
- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study 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).
- Inability to swallow solid medications
- Because pazopanib is metabolized by CYP3A4, inducers of CYP3A4 can decrease pazopanib exposure. The clinical significance of this, to date, is unknown.
- Drugs that prolong the QTc interval should be avoided if possible. Pazopanib can prolong the QTc interval. Drugs that are generally accepted to have a risk of causing Torsades de Pointes (See Appendix II) 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 II) should be monitored closely.
- For patients on anti-hypertensive medication at baseline: Concomitant use of pazopanib can alter exposure (increase or decrease) to anti-hypertensive medications. As such, investigators should consider replacing one medication with another in the same pharmacologic class that is less likely to interact with pazopanib. If such a medication is discontinued and replaced, the transition period should occur no less than 7 days prior to the first dose of pazopanib.

4.0 ELIGIBILITY CRITERIA

All questions regarding eligibility criteria should be directed to the Alliance Study Chair. Please note that the Study Chair cannot grant waivers to eligibility requirements.

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 four weeks later would be considered Day 28.

4.1 Documentation of Disease

4.1.1 Histologic Documentation: Low- or intermediate-grade neuroendocrine carcinoma, including the following subtypes: carcinoid tumor, low- to intermediate-grade or well- to moderately-differentiated neuroendocrine carcinoma or tumor, atypical carcinoid tumor. Documentation from a primary tumor or metastatic site is sufficient.

Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid tumor, or goblet cell carcinoid tumor are not eligible.

4.1.2 Stage: Locally unresectable or metastatic carcinoid tumors.

4.1.3 Tumor Site: Patients must have histologic documentation or clinical evidence of a carcinoid tumor of primary site (including foregut, midgut, hindgut or other non-pancreatic site). Tumors of unknown primary site are eligible provided the treating physician does not suspect medullary thyroid cancer, pancreatic neuroendocrine tumor, paraganglioma, or pheochromocytoma.

Unknown primary tumors will be classified as small bowel tumors for the purpose of stratification.

Functional (associated with a clinical syndrome) or nonfunctional tumors are allowed.

Target lesions must have shown disease progression if therapy included peptide receptor radiotherapy (PRRT) and PRRT must be completed at least 8 weeks prior to registration.

4.1.4 Radiological Evidence: Radiological evidence for progressive disease (measureable or non-measurable) within 12 months prior to registration. Patients who have received anti-tumor therapy during the past 12 months (including octreotide analogs) must have had radiological documentation of progression of disease while on or after receiving therapy.

Baseline CT or MRI scan must meet imaging criteria in Section 6.2.2.

4.1.5 No known endobronchial lesions and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage. Patients with lesions infiltrating major pulmonary vessels (contiguous tumor and vessels) are excluded; however, the presence of a tumor that is touching, but not infiltrating (abutting) the vessels is acceptable (CT with contrast is strongly recommended to evaluate such lesions).

Patients with large protruding endobronchial lesions in the main or lobar bronchi are excluded; however, endobronchial lesions in the segmented bronchi are allowed.

4.2 Measurable Disease

Patients must have measurable Disease per RECIST 1.1 by computer tomography (CT) scan or MRI. 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). Index lesions for the purpose of RECIST 1.1 measurements will not be selected from within the radiation therapy treatment field. However, if there is evidence of disease progression within the radiation treatment field, measurement of the progressing lesions will be documented.

4.3 Prior Treatment

4.3.1 No prior treatment with an inhibitor of VEGF or VEGFR.

4.3.2 Prior treatment (somatostatin analogs excepted) must be completed **at least 2 weeks prior to registration.** In addition, prior treatment (somatostatin analogs excepted) must be completed **at least 4 weeks prior to initiation of study drug.** Treatment-related toxicities must have improved to ≤ grade 1 prior to registration, with the exception of alopecia.

4.3.3 Concurrent use of somatostatin analogs (SSTa) is allowed, provided that the patient is on a stable dose for at least two months and progressive disease on somatostatin analog has been documented.

Progression on octreotide is required for patients with tumors arising in the midgut.

4.3.4 Prior treatment with 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 there is documented disease progression in a treated site. There is no limit on the prior number of procedures; prior liver-directed or other ablative treatment must be completed at least 8 weeks prior to registration. Index lesions for the purpose of RECIST 1.1 measurements will not be selected from within the radiation therapy treatment field. However, if there is evidence of disease progression within the radiation treatment field, measurement of the progressing lesions will be documented.

4.3.5 Patients should have completed any major surgery ≥ 4 weeks prior to registration and must have completed any minor surgery ≥ 2 weeks prior to registration. Patients must have fully recovered from the procedure.

- The following are examples of procedures considered to be minor: port placement, laparoscopy, thoracoscopy, bronchoscopy, mediastinoscopy, skin biopsies, incisional

biopsies, imaging-guided biopsy for diagnostic purposes, and dental extraction procedures.

- Insertion of vascular access device, thoracentesis, paracentesis, and endoscopic ultrasonographic procedures are not considered to be major or minor surgeries.

4.4 Patient History

4.4.1 No concurrent condition resulting in immune compromise, including chronic treatment with corticosteroids or other immunosuppressive agents.

4.4.2 No clinical evidence of central nervous system (CNS) metastases (including carcinomatous meningitis) at baseline, with the exception of those patients who have previously-treated CNS metastases (surgery ± radiotherapy, radiosurgery, or gamma knife) and who meet both of the following criteria: a) are asymptomatic and b) had no requirement for steroids or enzyme-inducing anticonvulsants within 6 months prior to registration.

4.4.3 No history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to registration.

4.4.4 No clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding within 28 days prior to registration including, but not limited to:

- Active peptic ulcer
- Known endoluminal metastatic lesion(s) with history of bleeding.
- Inflammatory bowel disease (e.g. ulcerative colitis, Crohn's Disease), or other gastrointestinal conditions with increased risk of perforation.

4.4.5 No history of serious (i.e., requiring active medical therapy with medication or medical device under the supervision of a physician) non-healing wound, ulcer, trauma, or bone fracture within 28 days prior to study entry.

4.4.6 Patients with a history of hypertension must have blood pressure that is adequately controlled on antihypertensives. (< 140/90 mmHg).

4.4.7 No symptomatic congestive heart failure (New York Heart Association Class II, III, or IV) within 6 months prior to registration.

4.4.8 No arterial thrombotic events within 6 months of registration, including transient ischemic attack (TIA), cerebrovascular accident (CVA), peripheral arterial thrombus, myocardial infarction (MI), or unstable angina or angina requiring surgical or medical intervention in 6 months prior to registration. Patients with clinically significant peripheral artery disease (i.e., claudication on less than one block) are ineligible.

Patients who have experienced a deep venous thrombosis or pulmonary embolus within 6 months prior to registration must be on stable therapeutic anticoagulation for at least 6 weeks prior to enrollment of this study.

4.4.9 Patients on therapeutic anticoagulation with low molecular weight heparins, fondaparinux, rivaroxaban or warfarin are eligible, provided that they are on a stable dose of anticoagulants.

Patients who are currently receiving antiplatelet therapy of prasugrel or clopidogrel or antiaggregation agents (e.g., eptifibatide, epoprostenol, dipyridamole) or low doses of acetylsalicylic acid (up to 100 mg daily) are also eligible

4.4.10 No ongoing cardiac dysrhythmias, atrial fibrillation, or prolongation of corrected QTc interval to > 480 msec.

4.4.11 No evidence of active bleeding, bleeding diathesis, or hemoptysis (≥ ½ teaspoon of red blood) within 8 weeks prior to registration.

4.4.12 No currently unstable angina and/or uncontrolled cardiac arrhythmias.

4.4.13 Patients with symptomatic peripheral vascular disease are ineligible.

4.4.14 Ejection fraction on Echo or MUGA > 50%.

4.5 Concomitant Treatment

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this trial. Patients on strong CYP3A4 inhibitors must discontinue the drug 14 days prior to the start of study treatment. See Section 12.9 for more information.

4.6 Pregnancy/Nursing Status

Women must not be pregnant or nursing. Women of child bearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to registration.

Women of child-bearing potential include any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL].

4.7 Age and Performance Status

4.7.1 Age ≥ 18 years of age

4.7.2 ECOG Performance Status 0 – 1

4.8 Required Initial Laboratory Values:

Granulocytes	≥ 1,500/mcL
Platelets	≥ 100,000/mcL
International normalized ratio (INR)*	≤ 1.2 X ULN
QTc	≤ 480 msecs
TSH****	WNL
Bilirubin	≤ 1.5 x ULN
AST (SGOT) & ALT (SGPT)	≤ 2.5 x ULN **
Serum Creatinine	≤ 1.5 x ULN

Urine Protein to Creatinine Ratio < 1, or, 24-hour urine protein < 1g***

* Only required for patients receiving anticoagulant therapy. Patients are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation

** Concomitant elevations in bilirubin and AST/ALT above 1.0 X ULN are NOT permitted. Also, if liver metastases are present, AST & ALT ≤ 5 x ULN is allowed

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

**** Medications for thyroid dysfunction are allowed as long as TSH is normal at registration. In patients with abnormal TSH, if the Free Thyroxine (Free T4) and Free Thyroxine Index (FTI) are normal and patient is clinically euthyroid, patient is eligible.

5.0 PATIENT REGISTRATION

5.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e. clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/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 CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

5.2 CTSU Registration Procedures

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

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

5.2.1 Downloading Site Registration Documents

Site registration forms may be downloaded from the A021202 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the NCTN - Alliance link to expand, then select trial protocol #A021202
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided

5.2.2 Requirements for A021202 Site Registration

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

5.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office

1818 Market Street, Suite 3000

Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

5.2.4 Checking Your Site's Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

5.2.5 Credentialing

See Section 6.2.1 for Institutional credentialing requirements for imaging.

5.3 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.
- **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 A021202 website) and faxing the form to the CTSU data operations center at 1-888-691-8039. Samples of the booklets are found in Appendix V, which are to be used for reference and IRB submission only. They are not to be used for patient completion.

5.4 Patient Registration/Randomization (Step 1) Procedures

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data, and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

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

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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

Once the patient has been registered and randomized, the initial shipment of blinded pazopanib/placebo will arrive within 7-10 days.

5.5 Re-Registration (Step 2) at the Time of Progression

Upon confirmation of progression by the Imaging Core Lab, patients may elect to be unblinded to their treatment assignment; see Section 11.2.5. Patients who were initially assigned to placebo will have the option to receive open-label pazopanib.

Note: As of 03/14/2019, patients who were initially assigned to placebo were given the option to receive open-label pazopanib due to the release of study results.

Re-registration should occur within 14 days of the CT or MRI scan documenting progression.

- **Women of child-bearing potential must have a negative pregnancy test within 72 hours prior to re-registration.**

Re-registration Procedures:

OPEN may be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU website at https://www.ctsu.org.

To enroll a patient within OPEN, institution staff must have:

1. A valid and active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam>). This is the same user ID and password used for CTSU's website (for more information see https://www.ctsu.org/public/CTEP-IAM_Factsheet.pdf).
2. Enrollment of patients on Alliance coordinated protocols requires a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type. Assignment of the 'Registrar' role for Alliance member sites is managed

through the Alliance Central Office via submission of a roster update form signed by the Principal Investigator of the member network.

The OPEN system will provide the registering site with a printable confirmation of re-registration. Please print the confirmation for your records. Further instructional information is provided on the CTSU members' website OPEN tab, or within the OPEN URL. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923, or ctsucontact@westat.com.

Once the patient has been re-registered and crossed over to the open-label portion of the study, the initial shipment of pazopanib will arrive within 7-10 days.

5.6 Registration to Correlative and Companion Studies

5.6.1 Registration to Substudies Described in Section 10.0

There is one substudy within Alliance A021202. This study must be offered to all patients enrolled on Alliance A021202 (although patients may opt not to participate). This substudy does not require separate IRB approval. The substudy included within Alliance A021202 is:

- A021202-HO1: "Quality of Life Studies in Alliance A021202"

If a patient answers "yes" to "I choose to take part in the Quality of Life Study. I agree to fill out the Quality of Life Questionnaires," (Question #1) in the Model Consent, s/he has consented to participate in the quality of life study described in Section 10.2. The patient should be registered to Alliance A021202-HO1 at the same time that s/he is registered to the treatment trial (A021202) Questionnaires should be submitted per Section 6.3.

When ordering the booklets, the type of Patient Questionnaire must be specified:

- Patient Questionnaire-Baseline, Prior to Cycle 4, and 12 months

  or

- Patient Questionnaire-Cycle 1 (Weeks 1, 2, 3, and 4).

5.7 Stratification Factors

5.7.1 Site of Primary

a) Small Bowel (defined as tumors arising in the small bowel, cecum, appendix, or unknown primary site)

b) Other

5.7.2 Concurrent Somatostatin Analog

a) Yes

b) No

6.0 DATA SUBMISSION, SPECIMEN SUBMISSION AND IMAGING

6.1 Data Submission

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or the participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a

minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold Read-Only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

6.1.1 Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. Section 16.0 provides information about expedited reporting.

Common Terminology Criteria for Adverse Events: This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for toxicity and adverse event reporting. However, CTCAE version 5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018; see Section 16.0.

6.1.2 Routine Adverse Event Reporting

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.

- Alanine aminotransferase increased
- Aspartate aminotransferase increased
- Blood bilirubin increased
- Diarrhea
- Fatigue
- Hair color change/hair depigmentation
- Hypertension
- Nausea
- Neutrophil count decreased

6.2 Imaging Submission

6.2.1 Institutional Credentialing Procedures for Imaging

Prior to the enrollment of the first patient, the Alliance Imaging Core Laboratory (ICL) at the Ohio State University Medical Center must approve institutions to participate in the trial. For this purpose, participating sites need to submit the baseline CT (and/or MRI) imaging

data of the first subject to be enrolled to the ICL for a quality check. The ICL will provide a brief A021202 protocol refresher if needed, and if necessary followed with a virtual site visit, to the site to complete the protocol specific site credentialing process. Once sites are credentialed by the ICL, the first patient and future patients can be enrolled into this trial. The ICL does perform a quality review of the images, identifies any non-compliant exams that have protocol deviations and notifies sites of the results within 72 hours upon data receipt.

6.2.2 Requirements for Participation

CT Scan Requirements

Optimal Technique: The requirements listed below are to be used 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 contraindicated by allergy.
- Reconstruction: Contiguous or overlapping sections; no gaps
- Consistency: Same technique to be used between baseline and follow-up scans

Minimum CT requirements are listed below. Note that a CT scan made as part of a PET-CT is acceptable if it meets these requirements. Any CT scan that does not meet these minimal requirements must 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 to be used between baseline and follow-up scans

Note: For both optimal and minimum CT requirements, if contrast used at baseline scans but contraindicated at a restaging time point while on protocol therapy, scans obtained at all future restaging time points should be obtained with both contrast and non-contrast to maintain consistency.

MRI Scan Requirements

MRI may be performed instead of CT. It is of utmost importance that the same imaging modality be used at baseline and all subsequent follow up visits if clinically able.

MRI should be performed with routine slice thickness generally not to exceed 5 mm. T1-weighted, T2-weighted as well as pre- and post-dynamic 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. Optimally, MRI should be performed of the abdomen and pelvis and if the chest needs to be scanned this should be done with non-contrast CT.

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.

6.2.3 Imaging Sub-study Data Submission

The primary endpoint of progression-free survival will be based on the timely central review of local imaging. Sites will be asked to transfer imaging data sets, as well as the results of "local radiologic review" to the Alliance Imaging Core Lab (ICL) **within 3 business days** (See Imaging Correlative Study Section 10.1 below). Central review of these scans will be performed as described in Section 6.2.6 and adjudication will occur in the event that there is discordance between the central review and the local review. The adjudicated central review will be available to the treating physician within one week of submission to the ICL. The central review interpretation will determine whether or not progression has occurred. (In the case of discordance, patients will be treated on study until progression by adjudicated central review). Refer to Section 6.2.6 for specifics on real-time central review of submitted images.

Adjudicated central review will be available to the treating site in RAVE within one week of submission.

Average time to submission of scans to the ICL and average ICL "turn-around" times will be determined. Baseline scans will be submitted for timely review to confirm adequate quality (refer to Section 6.2.5); inadequate baseline scans (e.g. non-contrast CT scan) will require a repeat scan prior to enrollment.

Scans that are deemed by the local interpretation to show stable disease, partial response or complete response may be batch shipped to the ICL, as these scans will not be read in real time. Batch shipment of these non-progression scans and their reports are to be submitted to the ICL within 6 months of their image acquisition.

6.2.4 Images to be Submitted

The following images will be collected digitally for centralized, real-time re-review:

- **Baseline** (28 days prior to patient registration)
- Time of **Restaging** (every 3 cycles after Cycle 1 Day 1)

In addition, submission of scans taken **within 12 months prior to study enrollment** will be collected for central review (not necessarily in real time) to assess the type and rate of progression at study entry. These scans should be submitted within 60 days after registration of the patient.

Patients that are crossed over to open label treatment should continue to submit restaging images to the ICL, with the same time frames for submission as blinded treatment patients (within 3 business days for a progression scan documenting progression or within 6 months for a non-progression scan).

6.2.5 CT/MR Scan Submission Instructions

All CT/MRI images will be collected digitally for archival purposes.

The complete re-staging CT/MRI scans in digital **DICOM** format will be submitted to Alliance Imaging Core Laboratory within **3 business** days once the image acquisition is completed at site. BMP files, JPG files, or hard copies (films) are not acceptable. The raw

data of the entire study should be saved until the scan is accepted by the Imaging Core Laboratory. The Imaging Core Lab will notify site and Alliance A021202 imaging committee within **2 business days** of the data receipt as well as within **3 business days** of the quality check report upon data receipt.

Sites need 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., A021202), respectively.

For baseline staging and pre-surgical restaging CT/MR scans, imaging data must be submitted to the Imaging Core Lab **electronically** via either Web-based data transfer or FTP data transfer approaches for timely central review purposes. For CT and/or MR scans at other time points, CD/DVD Shipment is acceptable.

Web-based Data Transfer:

Any PCs with Internet access can be used to upload images to the Imaging Core Lab via this approach. The standard Web access information will be provided separately through the specific trial e-mail Alliance021202@imagingcorelab.com, per the request by participating sites before their first data submission.

FTP Transfer:

Any FTP software can be used to upload images to the secure FTP Server of the Imaging Core Laboratory. The standard FTP access information will be provided separately through the specific trial e-mail Alliance021202@imagingcorelab.com, per the request by participating sites before their first data submission.

Shipment/Mail Transfer:

If the electronic data transfer approaches cannot be achieved at sites, the de-identified digital images in DICOM format can be burned to CDs, labeled with Alliance A021202 patient ID (e.g., 112136), date of study and study period (e.g., baseline, D22-28), and mailed to the Imaging Core Lab at:

Alliance Imaging Core Lab
Attn: Alliance A021202
Wright Center of Innovation
The Ohio State University
Rm#414, 395 W. 12th Ave
Columbus, Ohio, 43210
Direct: (614) 293-2929 Office: (614) 293-2788
Fax: (614) 293-9275

Send an e-mail notification to inform the Imaging Core Lab at Alliance021202@imagingcorelab.com of the imaging data submission once the data transfer is completed. Any questions or problems about the data transfer to the Imaging Core Lab, call the Core Lab IT group at 614-293-2630 or 614-366-4932 for help.

6.2.6 Real-time Imaging Central Review

A real-time imaging central review will be performed by the A021202 imaging central review panel, if either one of the following events happen:

1. **Site determines the patient based upon local completion of the imaging endpoint CRF to be PD.**

   Participating site needs to notify the ICL of local radiology assessment at the time of site determination of **PD,** 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.**

2. **Local site PI and/or local radiologist has questions about the appropriate interpretation of the scan.**

The Imaging Core Laboratory will contact the A021202 central review panel, **within 24 hours (except weekends and holidays) after images being received**, for scheduling a real-time remote review. The ICL notifies both the participating site and Alliance of the central review results **within 24 hours after receiving the results from the 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)**.

Central review results will be reported back to the site PI for further evaluation and determination of patient status. Under whichever events above, i**f participating site disagrees with the central review results**, an adjudicator organized through the Imaging Core Lab will be involved, blindly review images, and determine with which interpretation (local or central) they agree. This process may take **additional 24-72 hours** turn-around time, and the adjudicator's decision will be used as the **final central review decision** from the Imaging Committee through the Imaging Core Laboratory for the interpretation and response determinations.

The final treatment decision is determined by the central review. If progressive disease is the final determination by the central review adjudication of the results, blinded treatment will be discontinued and the patient will be unblinded. If patient is found to be on placebo, patient will be offered to crossover to open-label pazopanib.

Scans for patients on open-label pazopanib should be submitted to the ICL with the same submission schedule as with blinded therapy. If patient on open-label pazopanib is deemed to have progressive disease, the scan should be submitted to the ICL for real time central review of the scan. The process will follow the same procedure as described above for the double blinded portion of the study, including the adjudication process. Sites should also indicate to the ICL that the patient is on the open-label pazopanib treatment arm.

For any such related questions, participating sites may directly contact the ICL instead of the central reviewer(s), via either the trial email at Alliance021202@ImagingCoreLab.com or call at (614) 293-2929.

6.3 Submission of Quality of Life Questionnaires

	Prior to treatment	Weekly during cycle 1	Prior to cycle 4	At 1 year
EORTC-QLQ	X	X	X	X
NET21	X	X	X	X
LASA	X	X	X	X

6.4 Specimen Submission for Banking

All participating institutions must ask patients for their consent to participate in the banking of their specimens for future correlative studies, although patient participation is optional. Potential uses for these samples are outlined in Sections 10.3 and 10.4

		During Blinded Therapy		During Open Label Therapy			
	Prior to Treatment	**Prior to Day 1 of Cycle 2**	**At Progression***	**Prior to Day 1 of Cycle 2**	**At Progression***	**At the End of Protocol Therapy***	**Ship to:**
EDTA Plasma[1] (lavender top)	1 x 10 mL	1 x 10 mL	1 x 10 mL	1 x 10 mL	1 x 10 mL	1 x 10 mL	OSU
Citrate Plasma[1] (light blue top)	3 x 2.7 mL or 2 x 4.5 mL	3 x 2.7 mL or 2 x 4.5 mL	3 x 2.7 mL or 2 x 4.5 mL	3 x 2.7 mL or 2 x 4.5 mL	3 x 2.7 mL or 2 x 4.5 mL	3 x 2.7 mL or 2 x 4.5 mL	OSU
Whole Blood[1,2] (lavender top)	1 x 10mL						OSU

* Patients for whom the end of treatment occurs within 28 days of documented progression do not need to have samples submitted twice at this time point.

1 To be banked for potential correlative science studies as noted in Sections 10.3 and 10.4.

2 Sample may be drawn at any time, although baseline (prior to treatment) is preferred

6.4.1 Specimen Registration and Tracking

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: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, or for assistance in using the application, or questions or problems related to specific specimen logging, please contact: 855-55BIOMS.

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. Instructions for the collection of samples are included below.

6.4.2 Plasma Collection Procedures

For EDTA plasma, collect 10 mL of peripheral venous blood in one lavender top tube (K2EDTA anti-coagulant) at baseline, after one cycle of treatment, and at the end of protocol therapy. Draw 1 x 10 mL of blood into lavender top vacutainer. Invert several times and centrifuge for 15 minutes at 2500 x g. Remove plasma and transfer to clean 10 mL tube. Repeat centrifuge at 2500 x g for 15 minutes. Aliquot 0.5 mL plasma into each cryovial.

Label and freeze cryovials at –80°C. (If –80°C is not available, temporary storage at -20°C prior to shipment is acceptable.) Ship on dry ice to the Alliance Biorepository at Ohio State University (OSU) per Section 6.4.3.

For citrate plasma, collect 10 mL of peripheral venous blood in 3 x 2.7 mL or 2 x 4.5 mL light blue top tubes (3.2% sodium citrate anti-coagulant) at baseline, after one cycle of treatment, and at the end of protocol therapy. Draw 3 x 2.7 mL or 2 x 4.5 mL of blood into

light blue top vacutainer. Invert several times and centrifuge for 15 minutes at 2500 x g. Remove plasma and transfer to clean 10 mL tube. Repeat centrifuge at 2500 x g for 15 minutes. Aliquot 0.5 mL plasma into each cryovial.

Label and freeze cryovials at –80°C. (If –80°C is not available, temporary storage at –20°C prior to shipment is acceptable.) Ship on dry ice to the Alliance Biorepository at Ohio State University (OSU).

Label samples with the following identification:

1) Procurement date

2) Alliance patient number

3) Alliance study number (i.e. A021202)

4) EDTA plasma, citrated plasma or urine (as applicable).

6.4.3 Whole Blood Collection Procedures

For patients who consent to participate (on the addendum to the consent added with Update #05 to the protocol), whole blood samples will be used for future pharmacogenomic studies as noted in Section 10.4.

Collect 10 mL of peripheral venous blood into EDTA (lavender) tube. The tubes should be inverted several times to mix the EDTA and refrigerated until shipped on cool pack by overnight mail to the Alliance PCO. The samples should be shipped the same day that the blood is drawn.

6.4.4 Plasma and Whole Blood Labeling and Shipping Procedures

Many of the biomarker assays are time-sensitive. Please process the samples as **quickly** as possible. For each plasma sample processed, please log the following information in the Specimen Tracking System: time sample was obtained (i.e. 9:04 am), time sample was frozen (i.e. 9:45 am).

Plasma tubes and whole blood-containing tubes are to be labeled with the following information:

1. Protocol number
2. Alliance Patient ID
3. Patient initials
4. Sample Collection Date
5. Sample Type (i.e. EDTA plasma, citrate plasma, whole blood)

Plasma samples are to be delivered on dry ice by overnight delivery Monday through Thursday to the Alliance Biorepository at Ohio State University (see address below). The whole blood sample should be shipped to OSU the same day that it is drawn.

Do not ship specimens on Friday or Saturday. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary. All samples should be sent to the following address:

Alliance Biorepository at Ohio State University
The Ohio State University
Innovation Centre
2001 Polaris Parkway
Columbus, OH 43240
Tel: 614-293-7073
Fax: 614-293-7967

7.0 REQUIRED DATA

Pre-Study Testing Intervals

To be completed within 16 DAYS before registration: history and physical and all blood work, urine tests, ECG, and MUGA (with the exception of pregnancy testing, which is to be completed within 72 hours prior to protocol treatment).
To be completed within 28 DAYS before registration: any X-ray, scan of any type, or ultrasound that is utilized for tumor measurements

NOTE: Requirements for tests, observations, labs, and staging are the same during either the blinded or unblinded portions of the study.

	Prior to Registration	Day 1 of Cycle 1*	Day 1 every cycle after Cycle 1*	Post Treatment Follow up**
Tests & Observations				
Physical Examination (MD, PA or NP visit)	X	X[A]	X	X
Pulse, Blood pressure	X	X[A]	X	
Performance status	X	X[A]	X	X
12-lead ECG	B		B	
Echo or MUGA	X			
Medication Diary		X	X	
Fatigue/Uniscale Assessment	G			
Drug Toxicity Assessment		X[A]	X	
Laboratory Studies				
CBC, Differential, Platelets	X	X	X	
Creatinine, Mg, Phos	X		X	
Albumin, alk. phos. ALT, AST, bili, total protein	X	H	H	
TSH	X		D	
UPC	X	X	D	
Pregnancy test (Urine HCG)	C			
PT/INR	E	E		
Chromogranin A^	X		F	
24 hour urine 5HIAA (and additional tumor markers***)	X		F	X
Staging †				
CT abd/pelvis (with and w/o contrast) or MRI abdomen with contrast	X		F	X
CXR or CT chest	X		F	X
Correlative Studies‡				
QOL measures	*See Section 6.3*			
Citrate and EDTA Plasma, Whole Blood	*See Section 6.4*			

* C1D1 of blinded and unblinded treatment. Pre-registration labs may be used for Day 1 of Cycle 1 tests if obtained within 7 days prior to Day 1 of Cycle 1. For subsequent cycles, Day 1 required tests, observations and laboratory studies may be obtained within 72 hours prior to day of treatment.

** For patients who discontinue study treatment prior to tumor progression, physical examination, performance status, and radiologic imaging studies should be performed every 12 weeks until tumor progression; radiologic imaging may be obtained +/- 10 days of the scheduled assessment date. After disease progression regardless of whether or not the patient is on open-label pazopanib, patients should be followed every 6 months for survival until 5 years after registration.

*** Additional tumor markers are optional. If elevated at baseline, repeat at each disease reevaluation

^ Plasma or serum chromogranin may be collected. Sample type must be maintained consistent throughout study

† Multiphase CT scan (chest/abdomen/pelvis) is the preferred modality for imaging. Equivalent modalities (e.g. CXR and MRI scan of abdomen) may be used at the discretion of the investigator. Octreotide scan cannot be used for tumor measurements. See Section 6.2 for imaging requirements, including the requirement for submission of all disease assessment scans (i.e. PD and non-PD scans) to the ICL. Scan modalities must be kept consistent throughout study.

‡ For those patients who have consented to these studies.

A Also to be completed on Day 15 of the first cycle of blinded treatment as well as Day 15 of open label treatment.

B Prior to initiation of protocol treatment then every 8 weeks.

C For women of childbearing potential. To be completed within 72 hours prior to the initiation of protocol therapy. NOTE: Pregnancy test must be repeated prior to re-registration.

D Every other cycle (C3, C5, C7, etc.).

E Required only for patients on warfarin: PT/INR is required at baseline, then as clinically indicated.

F Every 12 weeks +/- 10 days from the initiation of treatment regardless of treatment interruptions or holds. 24 hour urine 5HIAA (and additional tumor markers) do not need to be repeated prior to initiation of unblinded treatment.

G Within 21 days prior to registration.

H Also to be completed on Day 15 of Cycle 1 and 2 of blinded and open label treatment

8.0 TREATMENT PLAN

This is a randomized, double-blind trial. Blinded, patient-specific clinical supplies of pazopanib/placebo will be requested by the Alliance Statistical Center at the time of randomization and should arrive at the clinical site within 7 to 10 days of randomization (see Section 11.2). Protocol treatment is to begin within 14 days of registration. Questions regarding treatment should be directed to the Alliance Study Chair.

8.1 Pazopanib/Placebo

Patients will be instructed to take pazopanib/placebo 800 mg orally every day until disease progression or unacceptable toxicity.

Pazopanib/placebo should be taken orally without food at least two hours after or one hour before a meal. The tablets should be swallowed whole and must not be crushed or broken. The time of day the tablets are taken should be relatively constant.

CYP3A4 inducers may decrease plasma pazopanib concentrations. Please refer to the drug section for more information.

For patients receiving concurrent somatostatin analog, the somatostatin analog should be continued at the current dose and schedule according to institutional practice.

For patients receiving a medically necessary H2-receptor antagonist, pazopanib should be taken without food at least 2 hours before or at least 10 hours after a dose of the H2-receptor antagonist. Pazopanib should be administered at least 1 hour before or 2 hours after administration of short-acting antacids.

Central review of scans: After every staging scan, patients should continue protocol therapy until the results of the adjudicated central review are available. The results of the adjudicated review must be used by the treating physician if the patient is to remain on protocol treatment (see Section 10.1).

8.2 Disease Progression/Crossover to Open Label Treatment

At the time of documented radiographic progression as determined by central review, patients may be unblinded (see Section 11.2). Patients who were receiving placebo may elect to crossover to treatment with pazopanib 800 mg orally every day. Patients must be re-registered to the crossover portion of the study per Section 5.5.

Once the patient has been re-registered and crossed over to the open-label portion of the study, the initial shipment of pazopanib will arrive within 7-10 days. Patients should initiate open-label treatment within 28 days of the most recent CT or MRI scan documenting progression. Dose modifications for open-label therapy will proceed according to Section 9.0.

Patients who discontinue protocol treatment for reasons other than progressive disease by central review (e.g. toxicity or progression by local read only) will not be eligible for crossover.

Required tests should be collected per Section 7.0. Abnormal labs found on Cycle 1 Day 1 of open-label treatment are to be managed according to the dose modifications found in Section 9.0.

Central Review of Scans: Scans should continue to be submitted to the ICL as outlined in Section 6.2. Determination of progression will be done in real-time using the same procedures as the double-blinded portion of the study. After every staging scan, patients should continue protocol therapy until the results of the adjudicated central review are available. Once the patient has deemed to have progressive disease by the central review, protocol treatment will be discontinued and further treatment is at the discretion of the treating physician. See Section 6.2.6 for further details.

9.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

General rules for dose modifications:

- Pazopanib/placebo will not be re-escalated once reduced.
- If dose reduction below 400 mg/day is required or pazopanib/placebo is held > 3 weeks, pazopanib/placebo will be discontinued.
- If more than one of these apply, use the most stringent (i.e. the greatest dose reduction).

Dose level table for pazopanib

Dose level	Pazopanib/placebo
0	800 mg daily
-1	600 mg daily
-2	400 mg daily

9.1 Hematologic Toxicity

For grade 3 ANC on Day 1 of a cycle: Delay pazopanib/placebo until toxicity resolves to ≤ grade 2, then resume pazopanib/placebo at the previous dose level.

For grade 4 ANC on Day 1 of a cycle: Delay pazopanib/placebo until toxicity resolves to ≤ grade 2, then resume pazopanib/placebo with one dose level reduction.

For grade 3 or 4 ANC decreased during a cycle interrupt pazopanib/placebo until ANC improves to ≤ grade 2, then resume pazopanib/placebo with one dose level reduction.

Febrile neutropenia: Delay pazopanib/placebo until toxicity resolves and ANC ≤ grade 2, then resume pazopanib/placebo with one dose level reduction.

For grade 3 or 4 thrombocytopenia: Delay pazopanib/placebo until platelets ≥ 100,000, then resume pazopanib/placebo with one dose level reduction.

For grade 3 or 4 anemia: Delay pazopanib/placebo until toxicity resolves to ≤ grade 2, then resume pazopanib/placebo at the previous dose level.

9.2 Hepatic Toxicity

For grade 2 ALT, AST, or bilirubin, continue pazopanib/placebo, but monitor weekly until ALT, AST, and bilirubin return to ≤ grade 1.

For grade 3 or 4 ALT or AST or Bilirubin, delay pazopanib/placebo. Restart treatment with one dose level reduction of pazopanib/placebo when AST, ALT and bilirubin improve to ≤ grade 1.

For grade ≥ 2 ALT/AST AND concurrent grade ≥ 2 bilirubin, discontinue protocol therapy.

For ≥ grade 3 hepatic failure, discontinue protocol therapy.

For any AST/ALT elevation occurring in a patient receiving simvastatin, discontinue simvastatin and follow the appropriate dose modification for pazopanib.

9.3 Proteinuria

For UPC Ratio < 2.0 or urine protein < 2 g/24 hours, continue same dose of pazopanib/placebo.

For UPC Ratio ≥ 2.0 and < 3.0 or urine protein ≥ 2.0 g/24 hours and < 3.0, hold pazopanib/placebo until proteinuria resolves to UPC < 2.0 or urine protein < 2.0 g/24 hours. Once resolved, continue treatment at current dose level.

For UPC Ratio ≥ 3.0 and < 4.0 or urine protein ≥ 3.0 g/24 hours and < 4.0, hold pazopanib/placebo until proteinuria resolves to UPC < 2.0 or urine protein <2.0 g/24 hours. Once resolved, resume treatment with one dose level reduction.

For UPC Ratio ≥ 4.0 or Nephrotic Syndrome: Discontinue pazopanib/placebo.

9.4 Nephrotoxicity

For grade 2 creatinine increased, delay pazopanib/placebo until toxicity resolves to ≤ grade 1, then resume pazopanib/placebo with one dose level reduction.

For grade 3 or 4 creatinine increased, discontinue pazopanib/placebo.

9.5 Cardiac Toxicity

For QTc interval > 500 msecs, check calcium, potassium, and magnesium levels and correct any abnormalities interrupt pazopanib and if possible, stop any medications that may prolong the QTc interval. Once QTc returns to ≤ 500 msecs, electrolyte abnormalities have been corrected, and any symptoms have resolved, resume pazopanib/placebo with one dose level reduction for all subsequent cycles. Remove patient from study if repeat ECG shows QTc interval >500 msec.

9.6 Thrombosis

For grade 2 or 3 venous thrombosis requiring anticoagulation, interrupt pazopanib/placebo. If the planned duration of full dose anticoagulation is ≤ 2 weeks, omit pazopanib/placebo until anticoagulation is completed. If the planned duration of full dose anticoagulation is > 2 weeks, pazopanib/placebo may be restarted during anticoagulation if all of the following are met:

- The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or be on a stable dose of LMWH prior to restarting pazopanib/placebo.
- 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 resumption of pazopanib/placebo, discontinue pazopanib/placebo.

For grade 4 venous thromboembolic events, discontinue pazopanib/placebo.

For arterial thromboembolic events (any grade) including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia, discontinue pazopanib/placebo.

9.7 Hypertension

- If patients require a delay of greater than 3 weeks for management of hypertension, discontinue protocol therapy.
- 24 to 48 hours should elapse between modifications of anti-hypertensive therapy.
- Treating physicians should avoid adding antihypertensive medications that are strong inducers or inhibitors of CYP3A4.

9.7.1 Persistent Grade 2 Hypertension (Systolic 140-159, Diastolic 90-99)

Recommend maximal medical management as described in Section 12.8. If BP is still not controlled after maximal medical management (see guidelines under Section 12.8), proceed with 1 dose level reduction.

NOTE: Stopping or reducing the dose of pazopanib/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.

9.7.2 Persistent Grade 3 Hypertension (Systolic ≥ 160 Diastolic ≥ 100)

Hold pazopanib/placebo until systolic BP ≤ 159 and diastolic BP ≤ 99. Once BP is controlled to this level, resume pazopanib/placebo at1 dose level reduction. HOWEVER, if the patient requires hospitalization for management of symptomatic systolic BP > 180 or diastolic BP > 110**, permanently discontinue pazopanib/placebo.**

NOTE: Stopping or reducing the dose of pazopanib/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

9.7.3 Grade 4 Hypertension (Life-threatening Consequences of Hypertension)

Permanently discontinue pazopanib/placebo. Recommend optimal management with intensive IV support in ICU

NOTE: Stopping or reducing the dose of pazopanib/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

9.8 Reversible Posterior Leukoencephalopathy Syndrome (RPLS) (see CTCAE v.4: Nervous System Disorders)

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

- If RPLS is ruled out via MRI, the decision to resume pazopanib/placebo should be based on the signs and symptoms: for grade 2 to 4 RPLS considered at least possibly related to pazopanib/placebo, discontinue pazopanib/placebo.

9.9 Hemorrhage

For grade 2 CNS or pulmonary hemorrhage, discontinue pazopanib/placebo. **For other grade 2 bleeding**, hold pazopanib/placebo until resolved to ≤ grade 1; reduce dose to next lower dose level, and continue treatment. If grade 2 or greater hemorrhage/bleeding recurs following dose reduction, discontinue pazopanib/placebo.

For any grade 3 or 4 hemorrhage, discontinue pazopanib/placebo.

9.10 Fistula, Perforations, Bowel Obstruction or Wound Dehiscence

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

For any grade bowel obstruction requiring medical intervention, interrupt pazopanib/placebo until obstruction resolves completely, then resume pazopanib/placebo at the previous dose. For obstruction requiring surgery interrupt pazopanib/placebo until full recovery from surgery, then resume pazopanib/placebo at the previous dose. If pazopanib/placebo is interrupted for > 21 days for bowel obstruction, discontinue pazopanib/placebo.

For wound dehiscence requiring medical or surgical intervention discontinue pazopanib/placebo.

9.11 Thyroid Dysfunction

For grade 3 or 4 hyper-or hypothyroidism, discontinue pazopanib/placebo.

9.12 Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura (See CTCAE Blood and Lymphatic System Disorders)

For any grade of hemolytic uremic syndrome (thrombotic microangiopathy) or thrombotic thrombocytopenic purpura, discontinue pazopanib/placebo.

9.13 Pneumonitis

For grade 2 or 3 pneumonitis, interrupt pazopanib/placebo until ≤ grade 1. Resume pazopanib/placebo at one dose level reduction.

For grade 4 pneumonitis, discontinue pazopanib/placebo.

9.14 Other Non-Hematologic Grade 3 or 4 Toxicity

For other grade 3 or 4 non-hematologic toxicity not described above, (excluding nausea, vomiting, and diarrhea; unless refractory to anti-emetics and/or anti-diarrheals) and considered at least possibly related to treatment, interrupt pazopanib/placebo treatment until toxicity improves to ≤ grade 1, then resume treatment with one dose level reduction.

For recurrent other non-hematologic grade 3 or 4 toxicity regardless of attribution, discontinue pazopanib/placebo.

10.0 COMPANION STUDIES

There is one mandatory substudy and one optional companion study for Alliance A021202. The mandatory substudy is comprised of the imaging study and is described in Section 10.1. Section 10.2 describes the optional Quality of Life companion study (A021202-HO1). Section 10.3 and Section 10.4 describe the potential uses of the optional banked biospecimens.

10.1 Imaging

10.1.1 Study Design

Turn-around Time for Central Review

Radiographic studies will be performed 7-10 days before the next cycle of therapy begins and will be electronically transmitted to the Alliance ICL for expert, timely central review (PD images should be submitted within 3 business days, and, as of 03/15/2015 [i.e. the issuance of Update #05], at which time 112 patients had been accrued, non-PD images should be submitted in batches within 6 months; see Section 6.2.3). Dr. Nathan Hall will coordinate this effort given the ICL's experience with timely central review (the logistics are already in place). Baseline scans will be submitted for timely review to confirm adequate quality. The type of follow-up scan required will be specified in the imaging submission section of the protocol (see Section 6.2). The central review interpretation will determine whether or not progression has occurred. Results of the central radiology review (after adjudication, if necessary) will be provided to the local investigators. The central radiology review will determine progression and is the basis of the primary analysis. Average times to submission (and variability) of scans to the ICL and average ICL "turn-around" times will be determined.

Assessment of Discordance between Local and Central Radiology Determination of Progression

Discordance between the local radiology and central radiology reviews (PD; no PD) will be assessed at the time of the final analysis for the primary endpoint. Discordance will be

assessed at the time the first progression is determined by either local or central radiology review. Patients will continue to be followed on study until progression has been determined by (if necessary, adjudicated) central review. Once progression is determined by adjudicated central review, changes in therapy (including crossover from placebo to pazopanib) will be made at the discretion of the treating physician.

Rate and Quality of Progression

The definition of rate of progression is fully articulated in Section 10.1.5, and effectively it is the slope of the sum of the longest dimensions of RECIST target lesions over time. Scans up to 12 months prior to enrollment will also be reviewed centrally (not necessarily in real-time) to assess type of progression at entry (RECIST or not), time period over which the progression occurred (< 3 mo, 3-6 mo, 6-9 mo, 9-12 mo, 12 mo or greater) and rate of progression at study entry. In addition, the nature of the progression will also be tracked (existing lesions vs. new lesions, single site vs. multiple sites, liver-only vs. extrahepatic). Analyses will be descriptive.

10.1.2 Specific Hypothesis

A) Timely expert central review can be performed within seven days in an Alliance-sponsored clinical trial.

B) Discordance between the local and central review interpretations is likely in a subgroup of carcinoid patients enrolled on this study.

Carcinoid tumors are historically difficult to image radiographically.[23] This characteristic, coupled with an inherent insensitivity to treatment, and the indolent nature of the disease profoundly limits our ability to develop new treatments for carcinoid. While targeted therapies hold much promise, recent data suggest that our inability to reliably assess response may limit our capacity to identify active agents (particularly those which are cytostatic in nature). RADIANT-2 was a randomized phase III trial of everolimus vs. placebo in carcinoid. [21] The primary endpoint of the study was PFS by central review, which was not performed in real time. Crossover at the time of progression was allowed in patients initially assigned to placebo. Discordance between investigator-reported response and that of the central review occurred in approximately 30% of cases. Adjudication was performed by an expert panel in the setting of discordance, however, the study design ultimately required the censoring of many patients in whom progression was declared prematurely by the investigator (relative to central review). This led to a loss of power for the primary endpoint (PFS by central review). In the end, the study just missed meeting its primary endpoint and everolimus was not approved for the treatment of carcinoid. Several additional observations are worth noting: 1) consistent with the refractory nature of carcinoid, everolimus is less active in carcinoid than in PNET (HR 0.77 vs. HR 0.4 respectively), 2) discordance between investigator-reported response and central review may be a much bigger problem in the carcinoid than the PNET (discordance was minimal in the everolimus and sunitinib phase III studies in PNET).[10, 24] In short, historically, carcinoid tumors have proven to be relatively refractory to chemotherapy, as well as targeted agents. As such, stability is a much more likely indicator of efficacy than shrinkage. Our ability to identify active agents, however, is limited by our ability to reliable assess these tumor radiographically, a problem which seems to be more of an issue in carcinoid, than in PNET. To date, no one has undertaken a careful analysis of the radiographic features of carcinoid, explored the causes underlying our inability to reliably image the disease, or made a serious attempt to identify potentially superior radiographic endpoints for assessing treatment activity. We plan to examine cases in which discordance occurs between central and

investigator-reported response in an effort to define the areas of disagreement (i.e., new sites of disease versus extent of progression at existing sites) and inform future trial design.

C) The rate of progression is not constant in carcinoid.

We anticipate that rate or type of progression may be a valuable endpoint in carcinoid. We also hypothesize that the type/rate of progression may vary between patients at the time of enrollment and that this may have an impact on response to therapy. As a result, we plan to characterize the type of progression at baseline (by RECIST or not, new sites of metastases and/or growth of existing lesions, progression in liver metastases vs. other sites). In addition, the rate of progression at baseline will be calculated; scans up to 12 months prior to enrollment will be reviewed centrally in order to assess the time period over which the progression occurred (< 3 mo, 3-6 mo, 6-9 mo, 9-12 mo, 12 mo or greater). This information will inform future trial design/eligibility criteria. Given the presence of preclinical data suggesting that VEGF inhibitors may change the biology of well-differentiated neuroendocrine tumors in the setting of evasive resistance, the type and rate of progression will also be assessed in pazopanib-treated patients and compared to controls.[25, 26] Changes in rate of progression over time will be explored as a potentially novel endpoint (at study entry, after 3 months on study, and at study termination). The type of progression (growth of existing lesions vs. new lesions, liver vs. other sites) will also be characterized, and then treatment arms will be compared adjusting for the type of progression. Interestingly, similar issues have been identified in glioblastoma, in which the exact nature of bevacizumab effects has proven extremely difficult to define radiographically.[27] In short, a critical review of the radiological effects of pazopanib in carcinoid is warranted. Note that the proposed imaging endpoints complement the correlative studies focused on pharmacogenetics and angiome profiling (both of which have the potential to lend insight into primary, as well as, evasive resistance).

D) Novel metrics based on technical advancements in image analysis (tumor burden change and radiomic feature analysis at baseline and change analysis) and computational modeling of disease should improve evaluation of therapeutics for carcinoid.

To categorize a continuous outcome (quantitative change in tumor burden) discards useful quantitative information and reduces statistical power to detect true differences in treatment effects.[28, 29] One limitation on improving clinical trials with all solid tumors, but especially in carcinoid, is reliance on RECIST-based categorical assessment (CR, PR, PD, and SD). The use of continuous tumor measurements (CRF-captured RECIST) collected at multiple time points from each subject by means of quantitative disease-drug-trial modeling framework would be an efficient way to assess treatment effects in this indolent form of cancer.[30] This placebo-controlled trial provides a unique opportunity to enhance the understanding of carcinoid growth trajectory with placebo and with pazopanib. We expect that pooling all available continuous tumor measurements from different subjects and using a quantitative modeling framework will help to develop a new biomarker that predicts overall survival and effect of treatment on overall survival accounting for subject-specific prognostic factors in a basic disease progression model. The biomarker-overall survival model, thus established, could be used to evaluate and inform efficient trial designs in the future for carcinoid by clinical trial simulations. Recently, there has been several published reports of continuous tumor progression modeling in non-small cell lung cancer, colorectal cancer, and renal cell carcinoma with demonstrated benefit of quantitative modeling for early decision making in drug development.[31-33]

Tumor volume measurements have been especially informative of treatment effects in slower growing tumors such as tuberous sclerosis.[34, 35] Alliance member investigators have been instrumental in developing new image analysis technology for semi-automated volume

measurement of liver lesions.[36, 37] This provides an opportunity to fully investigate the potential for these quantitative measurements to augment detection of treatment effects in a slower progressing disease like carcinoid.[38] To date, there are no reports of quantitative modeling of tumor volume measurements to assess disease progression and treatment effects specifically in carcinoid. In addition to quantitative modeling of CRF-captured RECIST tumor measurements, we also plan to develop a quantitative disease-drug framework for tumor volume measurements which could potentially lead to capturing slow progressive cancer in a more efficient manner with far-reaching implications for future carcinoid trial designs.

10.1.3 Objectives

10.1.3.1 To determine the turn-around time for timely adjudicated central review

10.1.3.2 To characterize the nature of discordance between local and central radiology review in assessment of progression

10.1.3.3 To characterize the type and rate of progression in carcinoid (at study entry, on-study, and at progression)

10.1.3.4 To develop new methods for modeling carcinoid growth and detecting treatment effects, and to perform simulations that advance new clinical trial designs to apply to future trials of carcinoid therapeutics.

10.1.4 Methods

Radiographic studies (CT scans or MRIs) will be transmitted to the ICL in real-time (within 3 business days of scan acquisition) via FTP (electronic) transfer. Pretreatment images should be available on up to 165 patients (Minimum 150 pt). There are two types of characterizations which are described as follows:

1) Progression associated with study treatment: Although the study was originally designed to perform central reviews of disease status using RECIST v1.1 and in real time for all enrolled patients, it was later amended in Update #04 to focus the real-time review on only those suspected of having progression by local determination. Regardless, the remainder of the images (e.g. non-PD cases) will be reviewed throughout the course of the trial. Statistical analyses will take into account this trial modification. Progression associated with study treatment will be characterized in detail by the Expert Readers coordinated through the ICL and entered into the Rave database. Patients having PD based on deterioration of global health status (see Section 13.4) will be described separately, as clinical PD in the absence of radiographic PD cannot be assessed by the central reviewers.
2) Rate of progression for up to 12 months prior to enrollment: The central reviewers will determine if the baseline scan is adequate and will characterize the type and rate of progression at baseline (reviewing scans up to 12 months prior to enrollment). The type of scans allowed for follow-up are defined in the protocol, as are the definition of progression (according to RECIST v1.1 for radiographic measures and new lesions). Submitted scans that indicate progressive disease will be reviewed centrally at the time of submission and the results of the central review will be documented. Progression at the time of enrollment will be characterized in detail by the Expert Readers coordinated through the ICL (rate and type of progression).

The images received at the ICL have been coded with subject identifiers, but with all PHI removed, per the process described above in #1. They will then be transferred via secure FTP to Dr. Lawrence Schwartz, the Alliance Imaging Committee Chair, and designated

research radiologists at the Columbia University Image Analysis Lab. Designated research radiologists will identify target lesions and perform the semi-automated volumetric measures of carcinoid by a well standardized procedure.[36] Measurements for each lesion for each subject ID on each CT/MRI study will be entered by ICL staff directly into the Medidata Rave® database. The Alliance Statistics and Data Center (SDC) A021202 Statistician will prepare analysis datasets in conjunction with clinical/outcome data. The A021202 Statistician will then coordinate the analyses of the images specified in Section 10.1 with the Alliance ICL and the A021202 Population Pharmacology and Pharmacogenomics Co-Chair, Dr. Michael Maitland, and designated computational analysis teams at the Inova Schar Cancer Institute and the University of Maryland. Analyses will be conducted using the analysis datasets used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g. data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

10.1.5 Statistical Considerations

Turn-around Time for Central Review (Assessments Required for Registration and Treatment)

Assessment of timely central review of scans for confirmation of progressive disease associated with study treatment (including the baseline scan taken within the 28 days prior to enrollment) will be based on the scan submission times and ICL turn-around times for results. The unit of analysis will be the scan. Average times from date of a scan to submission of the scan to the ICL (expected to be < 3 business days) and average time in the ICL ("turn-around" times; date of scan receipt at ICL to date scan results are returned; expected to be 7 days) will be computed. Average submission and turn-around times will be estimated among patients for whom scans indicating progression are submitted. Analyses will take into account the timing of the protocol modification requiring real-time reviews on patients having reported progression by the local site and subsequently not in real time (e.g. covariate for pre- versus post-Update #04 changing expectations of which reads were real-time versus not real-time). One hundred fourteen (n=114) patients with progression are expected at the time of the final analysis. With 114 scans a difference between mean turn-around times of 7 days (null hypothesis) and 9 days (alternative hypothesis) can be detected with 85% power (1-sided test of single exponential parameter, α=0.05). Differences in average turn-around times among the first group of 38 scans, second group of 38 scans, and third group of 38 scans will be explored.

Discordance

At the time of the final analysis, the proportion of images reporting progression by the local radiology and not confirmed by the central radiology review as PD will be estimated among all patients with progression based on the local radiology review. In each case, discordance will be assessed at the time the first progression is determined. One hundred fourteen patients (d=114) are expected to have progressed at the time of the final analysis. The 95% CI estimate will be computed for the discordant proportion. With progression data on 114 patients the discordant proportion can be estimated to within at most +/- 0.092 with 95% confidence.

Rate of Tumor Progression (Prior to Registration)

The sum of the longest diameters of the target lesions (and new lesions, if observed) will be computed for each patient at each radiologic assessment (central radiology review). Rate of tumor progression will be measured by the slopes associated with the recorded tumor measurements at three time points: pre-study (prior to study enrollment based on scans from

the 12 month prior to study entry), on-study (baseline to 3 months after enrollment), time of progression (measurements at the time of progression and nearest prior). Pre-study scans up to 12 months prior to enrollment will be obtained and reviewed centrally to determine the pre-study rate. Differences in the average rates of tumor progression between two treatment groups and across three time points will be explored using a two-way, fixed effects analysis of variance. No preliminary data are available for this study. The test of 'no interaction' between time point and treatment will be considered. Let the effect size for interaction be denoted by $f=\sigma_x/\sigma$, where σ denotes the common, within-population standard deviation and σ_x denotes the square root of the mean of the squared interaction effect values ($x_{ij}=m_{ij}-m_{i.}-m_{.j}+m$, where i=2, j=3 and m_{ij}, $m_{i.}$, m_j, and m denote the cell mean, the main effect means and the total population mean, respectively) for the 2 x 3 cells. We expect at least 40 patients with data in each treatment group at all three time points (approximately 70% of 114 patients with progression at the final analysis). With this sample size at least 80% power is achieved to detect an effect size of f=0.20 (α=0.05). Equal sample sizes within cells and independence across cells are assumed. Power will be greater due to repeated measures on the same patient at each time point. If no significant interaction is detected differences in mean tumor progression rates will be compared across the three time points and between the two treatment groups, respectively. Let the main effect size be denoted by $f=\sigma_m/\sigma$, where σ denotes the common, within-population standard deviation and σ_m denotes the standard deviation of the population means. Assuming that no interaction is observed, with data on at least 40 patients in each treatment group at all three time points: for the comparison across time points (k=3), an effect size of f=0.20 can be detected with at least 80% power (α=0.05) and for the comparison between treatment arms (k=2), an effect size of f=0.20 can be detected with at least 88% power (α=0.05). Assuming maximum variability in the means, these effect sizes translate to ranges of standardized means of d=0.42 and d=0.53, respectively, considered to be "medium" effect sizes. The range of standardized means is defined as $d=mmax-mmin/\sigma$. Assuming maximum variability $f=0.471d$.[39]

Tests of binomial proportions will be used to characterize the types of progression by treatment arm (e.g. existing lesions vs. new lesions, single site vs. multiple sites, liver-only vs. extrahepatic). With data on approximately 80 patients, 40 patients per treatment arm, differences in the proportions of patients with a given characteristic of 0.35 and 0.65, for treatment with and without pazopanib, can be detected with 0.86 power (2-sided α=0.1). Since only large differences are detectable these analyses will be considered exploratory.

Disease-drug Modeling in Carcinoid

The disease-drug modeling in carcinoid will be performed in two steps: 1) development and evaluation of the tumor measurement model, and 2) tumor – overall survival model development and evaluation.

Tumor Model: The sum of the longest diameter of the target lesions obtained from CRF-captured RECIST measurements and the tumor volume measurements available at pre-study, on-study and time of progression for all subjects will be utilized to develop the tumor (size/volume) progression model. Disease-drug models will be developed separately for longitudinal tumor size or tumor volume measurements as dependent variables. The longitudinal tumor measurements will be analyzed by the non-linear mixed effects modeling technique using Phoenix NLME 1.3 software (Certara USA, Inc., Princeton, NJ, USA). Extensive graphical analysis and descriptive statistics of the tumor (size/volume) measurements will be used as a guide for the quantitative model building exercise and will be performed using R (R Foundation for Statistical Computing, Vienna, Austria) running under the R Studio interface (Free Software Foundation, Inc., Boston, MA, USA). Different reported structural models, but not limited to, describing the tumor progression and tumor

shrinkage pertinent to carcinoid will be evaluated.[40] The tumor shrinkage/drug effect parameter will reflect the effect of the treatment (placebo/pazopanib). Since multiple tumor measurements will be available from each subject, both random between subject variability in tumor shrinkage and progression parameters and residual variability in tumor measurements will be estimated. The structural model describing the tumor progression will be chosen based on the standard goodness of fit plots (observed vs. predicted, conditional weighted residual vs. time and conditional weighted residual vs. predicted) and difference in Akaike information criteria (AIC). Subject-specific prognostic factors (covariates) that may influence the tumor (size/volume) model parameters will be investigated and the significance of prognostic factors will be determined by comparison of the AIC values. The independently developed final tumor (size/volume) model will be assessed by a set of diagnostics such as goodness of fit plots (described above), shrinkage in the parameter estimates, the precision of the parameter estimates and by comparing the precision of the estimates obtained by non-parametric bootstrap with the model based estimates.

Since, to our knowledge, there has not been a quantitative analysis of the tumor size or volume in carcinoid, it is expected that the tumor measurement progression model might offer new insights in to the understanding of the disease progression in carcinoid. Additional thorough explorations of relationship between tumor size and tumor volume in carcinoid will be performed as needed.

Overall Survival Model: To determine the relationship between the tumor measurement (size/volume) and the time of death, the individual tumor model will be used to predict tumor measurements at relevant time points considered mechanistically plausible to be a predictor for overall survival in carcinoid. A parametric survival model (accelerated failure time model) will be considered to establish a quantitative link between different metrics of the tumor measurements (for ex: change from baseline at a given time [t], percent change from baseline at a given time [t]) and overall survival. Several widely used survival functions such as exponential, weibull, log-normal, etc. will be considered and model selection will be based on AIC differences and diagnostic plots. The tumor-overall survival model will be adjusted for subject specific covariates. The final tumor-survival model will be thoroughly evaluated by means of simulations and comparing the simulated data with observed overall survival data.

Finally, we will utilize the developed and evaluated tumor (size/volume) model and tumor-overall survival model to explore scenarios pertaining to different treatment effects and trial design considerations that can be applied to inform future trials of carcinoid therapeutics.

10.2 Quality of Life (A021202-HO1)

10.2.1 Study Design

The aim of the correlative study is to assess the effects of pazopanib 800 mg p.o. daily on quality of life, sexual function, bowel function and recovery parameters. Measures of quality of life are relevant here because patients with carcinoid/neuroendocrine tumours are relatively young, making family, social and financial issues important, including sexual function.[41] Much attention has been paid to the flushing and diarrhea symptom expression among NET patients, but data on the impact of the disease, these symptoms, and the treatment on overall QOL and other specific aspects is lacking. While some work has been done in this area[42] (Froid, 2007), there are challenges remaining with the assessment of QOL in this patient population (carcinoid tumors).

There is not a measure to assess QOL-related domains specifically for carcinoid tumors: The recent literature reviews indicate that the most common approach has been to use generic measures such as the EORTC-QLQ-C30, with some supplementation for specific

domains. The evidence to date indicates that while QOL issues in this population are considerable[42], the assessment of these disease-specific issues has suffered by a lack of specificity among the measures.[43] In a 2010 presentation at ASCO, Beaumont indicated that NET patients did express deficits in various QOL domains that could be detected by general measures but was in need of supplementary specific domain assessment.[44] A further example of this lack of sensitivity to NET-specific issues was evident in a study of sunitinib[45] wherein a generic multi-item measure of fatigue (the FACIT-fatigue scale) failed to detect any change in fatigue despite differences in adverse event reporting. This is consistent with our own previous work within the NCCTG that demonstrated how a multi-item measure was less sensitive in detecting fatigue than a single item measure, which we now use in all Alliance trials due to its prognostic implications for survival. In choosing measures for this study then, we have taken particular care to combine measures validated in previous work that can be used alongside developing measures specific for the key issues relevant to patients with carcinoid tumors.

In particular, while extensively validated, the EORTC-QLQ-C30 does not contain issues specific to carcinoid disease. This has led the EORTC to develop a neuro-endocrine-specific QOL module. The EORTC has followed its usual careful and methodic approach to the development of the NET 21 over a period of close to a decade. The measure remains to be fully validated however and so we believe that the platform of this modest study is perfectly suited to provide key validation data to inform the design of future studies. We have been in contact with the EORTC (personal correspondence with Andrew Bottomley and Neil Aaronson) and they wholeheartedly support the application of their NET measure for this trial. Quality of life in this study hence will be evaluated using the EORTC-QLQ-C30 and NET12 questionnaires, the Linear Analog Self-Assessment items for general QOL and protocol-specific issues.

The impact of the disease on patient function and quality of life (QOL) will be evaluated at registration. These data will serve as our baseline data. Subsequent assessments will be collected weekly for the first month, and thereafter at the three month and one year visits. This schedule of assessments is consistent with the sunitinib trial, although measures were collected weekly through the first four cycles of treatment, which we believe is excessive. These assessment time-points have been chosen to gather information on short and long-term QOL-related deficits so that future interventions may be planned. The weekly assessments in the first month will capture acute QOL deficits, which may point us to interventions that could be incorporated into future procedures. The 3-month and 12-month time points are included to gain information about long term impact on QOL. Not only will we be able to compare these different impacts on QOL between these two treatments, we will be able to gain knowledge about potential interventions to improve QOL for patients in this population.

A cross-comparison of instruments will be conducted, specifically to compare the single-item indicators to the more lengthy and detailed multi-item instrumentation (the EORTC-QLQ C30, NET21 and the LASA single-items). This is a core line of research that will allow the Alliance to plan efficient QOL assessments for future Alliance trials. Dr. Sloan has done considerable research in this area; demonstrating that in general cancer patient populations, there is merit to the use of simple, single-item assessments. Limited work has been done, however, in NET trials and assessment of quality of life is thought to be critical when using agents like pazopanib, which are considered to be cytostatic/palliative in nature.

Regardless of whether the study is positive, in terms of observing impacts on QOL by the disease/treatment processes involved, valuable information will be obtained just as is the case for biologic endpoints, which are often little more than exploratory investigations. The

QOL science here, however, is based on a long and substantiated line of research within the NCCTG and now the Alliance cooperative group. If the study is positive, we expect the individual items in the EORTC measures to indicate differences over time and across treatment. We will not only be using the overall scale measures produced, we will also look at individual items. We expect that we will observe a subset of items that will be most useful to detecting the specific QOL-related impacts of treatment and disease, instead of an overall aggregated score as was used in the sunitinib study. Were the study to be negative, we would still be able to obtain comparative data on the relative amount of information that is to be gained from the general EORTC QLQ-C30, versus the NET21, versus the simple LASA items. Irrespective of the results, the study will provide vital validation data for the EORTC NET21 measure, as expressed by the EORTC leadership (personal communication: Andrew Bottomley).

NOTE: QOL may be completed at any time during the day in the clinic, or they may be taken home by the patient for completion and then returned.

10.2.2 Measures

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.[46] 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.[47] These instruments are available in other languages upon request.

The 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 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.

The Linear Analogue Self-Assessment (LASA) consists of 6 single-item numeric analogue scales. One item measures overall QOL while the five remaining items address the major domains of QOL (mental, physical, emotional, social, and spiritual well-being) on a scale of 0-10. LASA items such as these have been validated as general measures of global QOL dimensional constructs in numerous settings.[48-52] The six items have been validated at the Mayo Clinic for use in cancer patients and have been successfully used in numerous clinical trials.[53] Normative data for the LASA have recently been published so that the results of this trial can be compared relative to other patient populations.[54, 55]

This instrument is available in English only. It may be administered to non-English speaking patients via an interpreter.

10.2.3 Hypotheses

A. There will be differences in QOL-related domains between the two treatment groups (pazopanib 800 mg p.o. daily versus placebo) in terms of the patients' overall experience during the trial.

B. The more brief measures of QOL-related domains will provide comparable information to what is provided by the longer assessments.

C. The NET21 module will demonstrate sensitivity across treatment arms for NET-specific domains

10.2.4 Objectives

10.2.4.1 To assess for differences in QOL-related domains between the two treatment groups (pazopanib versus placebo)

10.2.4.2 To determine if the more brief measures of QOL-related domains provide comparable information to that which is provided by the longer assessments (EORTC, NET21)

10.2.4.3 To provide validation data for the EORTC NET21 module in terms of responsiveness over time and differences across arms.

10.2.5 Statistical Considerations

For Objective 10.2.4.1 and 10.2.4.3, the AUC summary statistic will be calculated for each patient using the baseline and weeks 1-4 and at three months, and first year (12 month) data. AUC will be applied to all QOL endpoints. If a patient only provides baseline data, they will be excluded from the analysis. All QOL endpoints will be translated where appropriate onto a 0 – 100 point scale for comparability and ease of interpretability in the analysis phase.[56-59] Parametric procedures (e.g. *t*-tests) will be used unless there is evidence of non-normality via Shapiro Wilk testing 65, in which case non-parametric procedures (e.g. Wilcoxon tests) will be applied.

Analysis of the AUC scores for the QOL endpoints will compare the average AUC for the Pazopanib 800 mg p.o. daily arm to the average AUC for the placebo arm using a single two-sample independent samples *t*-test. Confidence intervals will be constructed for mean reduction in total AUC score for the two arms. With the minimum expected sample size of 150 (75 per treatment arm), this study will provide 86% power to detect a difference in the two groups in QOL endpoints of 0.5 standard deviations, a moderate effect size, using two-sided test at level 0.05.

For Objective 10.2.4.2, the EORTC-QLQ C30 and the LASA single-items will be compared via Bland-Altman procedures, which have been established as the preferred methodology to compare assessments intended to measure the same concept.[60] Dr. Sloan's QOL team has experience in applying these procedures in cancer clinical trials.[61]

Supplementary analysis of QOL scores will involve *t*-tests and Wilcoxon procedures at each time point as well as a repeated measures analysis of variance (ANOVA) and general estimating equations (GEE) modeling using data from all time points.[62] Models will include covariates of patient characteristics as well as treatment arm to perform a conditional analysis of treatment comparison in the presence of potentially confounding variables.

Further analysis will involve an examination of the clinical significance for changes over time by calculating the percentage of patients on each arm that report an improvement of more than 10 points on the 0-100 point scale for any QOL endpoint. These percentages will be compared via chi-square testing.

Correlative analyses will be done on QOL endpoints to determine the relationships between various QOL endpoints. Such correlations will be done at single data points such as baseline or months 3, 12, or 24. The extent of missing data will be explored for non-random influences.[63] Sensitivity analysis will be performed using various simple imputation techniques for which Dr. Sloan's QOL team has developed specific computer algorithms, to ensure results are not unduly influenced by the presence of missing data.[64, 65] The impact of imputing will be examined using such methods as last-value-carried forward, nearest-neighbor imputation, zero-value imputation, minimum-value imputation, maximum-value

imputation on the result of the primary analysis. The degree of variability in the results will allow for a calibration of the impact of the best and worst case scenarios in terms of patterns in the missing data on the stability of the analytical results.

Analyses will be coordinated by the Alliance SDC A021202 Statistician using the analysis datasets used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g. data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

10.3 Banked Blood Plasma Specimens for Circulating Angiogenic and Inflammatory Markers ("Angiome")

10.3.1 Background

There is an urgent need to develop biomarkers that can guide the use of novel agents in patients and to better understand and overcome the mechanisms of resistance to these therapies. Previously, we developed a novel protein multiplex array ("Angiome") to assess tumor inflammation and angiogenesis (see Table 1 below). We identified several biomarkers that were shown to be prognostic and/or predictive of benefit from anti-VEGF therapies in patients with colorectal, pancreatic, ovarian, and renal cancers. Potential predictive markers for bevacizumab include IL-6, SDF-1, VEGF-D, ANG-2, and HGF.

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	sVERGFR1	TGFβ2	IL-6R
PDGF-BB	sVEGFR2	TGFβR3	IL-6ST (GP130)
PlGF	sVEGFR3	TIMP1	SDF-1
		TSP2	VCAM-1

Previous multiplex analyses have identified IL-6 as a potential predictive biomarker of benefit from bevacizumab. IL-6 has been identified by our group as a strong candidate predictive biomarker for bevacizumab in CALGB 90206, a phase III study of IFN +/- bevacizumab in advanced renal cell cancer.[66] Interestingly, high IL-6 was a negative prognostic factor but a strongly favorable predictive marker. Importantly, nearly identical prognostic and predictive effects for IL-6 were noted in the phase III study of pazopanib versus best supportive care in refractory renal cancer.[67] Interestingly, this group employed the same multiplex technology (Aushon Biosystems) that we employed in our analysis of CALGB 90206. The CALGB 90206 study also found a predictive role for HGF that was IL-6 dependent (i.e. a 3-way treatment interaction).[66] The role of the IL-6-Jak-Stat axis is particularly intriguing given its role in tumor associated inflammation and anti-tumor immunity.[68]

We recently presented new data supporting IL-6 as a candidate predictor for bevacizumab in patients enrolled on the GOG-218 study.[69] GOG-218 was a phase III, 3-arm, placebo-controlled, randomized clinical trial evaluating the efficacy of concurrent and maintenance bevacizumab in women with advanced ovarian cancer. Our results demonstrate that IL-6 levels are predictive for benefit from bevacizumab for both progression-free survival (PFS) and overall survival (OS) in ovarian cancer patients.[69] For PFS: Q1 hazard ratio (HR) 0.87 [95% CI 0.70-1.08]; Q2 HR 0.77 [95% CI 0.58–1.006]; Q3 HR 0.67 [95% CI 0.48–0.94]; and interaction p = 0.009. For OS: Q1 HR 1.07 [95% CI 0.84–1.37]; Q2 HR 0.92 [95% CI 0.67–1.26]; Q3 HR 0.79 [95% CI 0.54–1.16]; and interaction p = 0.005. Additionally, IL-6 was found to be highly prognostic for PFS ($p = 1.97^{-4}$) and OS ($p = 7.85^{-6}$). The data across all three studies are highly congruent and strongly suggest that IL-6 levels can predict for benefit or lack of benefit from bevacizumab in these patient populations.

Previous multiplex analyses have identified VEGF-D, and markers of inflammation, as potential predictive biomarkers of benefit from bevacizumab. In addition to these studies in which IL-6 has been identified as a potential predictive biomarker, we have analyzed two other phase III studies of bevacizumab. CALGB 80303 was a randomized, double-blind, placebo-controlled study of standard of care gemcitabine +/- bevacizumab in patients with advanced or metastatic pancreatic cancer.[70] Three statistically significant predictive markers were identified using Cox proportional hazards modeling: VEGF-D, ANG2, and SDF1.[71] With respect to VEGF-D levels, we observed benefit from bevacizumab in the patients with low VEGF-D, while lack of benefit was observed in patients with high VEGF-D. Relatedly, our initial analysis of VEGF-related biomarkers for CALGB 80405 was just presented at ASCO 2016.[72] Of the markers evaluated, we observed that low VEGF-D protein levels were predictive of PFS benefit. Patients with low baseline VEGF-D levels received greater benefit from bevacizumab (HR=1.70) than cetuximab (HR=0.92), uncorrected interaction p = 0.0097. This data in colon cancer is consistent with our biomarker analyses in pancreatic cancer (CALGB 80303). Finally, the ability of VEGF-D to predict for benefit from bevacizumab is supported by the independent findings of the Australian GI Cancer Trials Group, who analyzed tissue VEGF-D by immunohistochemistry using archived FFPE tumor samples from the MAX trial.[73] For many reasons, testing plasma VEGF-D by ELISA is likely to be far more convenient and reproducible than analysis of IHC in legacy FFPE samples, and analysis in blood also allows for serial monitoring during the course of treatment. Regardless, across all three trials, VEGF-D levels in the bottom quartile had the strongest predictive effect for benefit from bevacizumab. These consistent results support the role of VEGF-D as an alternate ligand for VEGFR2, a finding well described in preclinical systems.[74, 75] Taken together, these data serve as proof of principle for the ability of multiplex protein arrays in general, and the Nixon Lab in particular, to identify profiles that can reliably select patients for targeted therapies.

10.3.2 Objectives

10.3.2.1 To determine whether components of the plasma Angiome panel that have been shown to be predictive previously (IL-6 and VEGF-D) are predictive of a therapeutic advantage for pazopanib treatment in baseline samples from the patients treated on A021202.

10.3.2.2 To determine whether other components of the plasma Angiome panel tested (not IL-6 and VEGF-D) are predictive of a therapeutic advantage for pazopanib treatment in baseline samples from the patients treated on A021202.

10.3.2.3 To evaluate the changes in the plasma Angiome markers after treatment with or without pazopanib over time.

10.3.3 Methods

Our laboratory serves as the Molecular Reference Laboratory for multiplex ELISAs within the NCTN cooperative group system. The laboratory is an SOP-driven, HIPAA-compliant laboratory, and it has quality control procedures in place for all aspects of sample handling, inventory management, assay conduct, and data storage. We also have extensive experience working with cooperative group sample repositories and statistical centers, having conducted similar analyses on several large, randomized phase III studies. All assays, whether custom ordered from a commercial vendor or developed internally, are quality assured for issues related to performance in cancer patient plasma, type of sample (EDTA plasma, citrate plasma, serum), and interference from related soluble receptors or ligands or any relevant antibody therapeutics.

Blood samples (1 x 10 mL = 10 mL) will be obtained at various time points coinciding with patient visits for clinical assessments (both study arms: baseline, on-treatment, end of treatment, progression, withdrawal, or removal from study) from all patients enrolled in the clinical trial who consent for participation in correlative analyses. One 10 mL sample will be used for the analysis of plasma inflammatory factors.

Plasma Protein Analyses: Double-spun platelet-poor plasma will be isolated from 10 mL of blood collected into lavender-topped (K2EDTA) tubes (BD Vacutainer, Catalog no. 366643). Within one hour of the time the blood is drawn each sample will be spun at 2500 x g for 15 min at 4°C, and the resulting plasma layer will be removed to a fresh polypropylene tube and respun in the same manner. The final double-spun plasma will be aliquoted into 1 mL volumes in screw-capped cryotubes, frozen, and stored at -80°C. Prior to analysis, all samples will be shipped frozen to the Phase I Biomarker Laboratory at Duke University, an Alliance Molecular Reference Laboratory directed by Andrew Nixon, PhD. The laboratory has quality control procedures in place to address many of the issues involved in clinical trials research including sample quantity, sample integrity, and sample heterogeneity and expertise in the utilizing ELISA technologies with clinical trials samples. Samples will be analyzed using multiplex ELISAs for the plasma angiome.

10.3.4 Statistical Analyses

The data collected from the samples, as described above, will be sent using encrypted secure spreadsheets to the Alliance SDC A021202 Statistician to prepare analysis datasets in conjunction with the clinical/outcome data. The A021202 Statistician will then coordinate the analyses with the A021202 Correlative Science Co-Chair, Dr. Andrew Nixon. Analyses will be conducted using the analysis dataset used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g. data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

Predictive and Prognostic Biomarker Analysis (See Section 10.3.2.1): Baseline protein levels of candidate biomarkers will be correlated with OS and PFS using multiplicative Cox proportional hazards models to test for interaction between marker expression level and treatment.[76] Expression levels will be log-transformed and analyzed as continuous measures, ensuring normal distribution of the covariates used in the modeling. Model assumptions will be verified to assess the validity of the models and statistical tests.

Prediction of Treatment Benefit: The two biomarkers of interest are IL-6 and VEGF-D, for the analysis of the interaction between each marker and treatment. We will assume that

approximately 150 of 171 (57% pazopanib, 43% pazopanib) cases will have viable samples and test results for this analysis. We will test the hypothesis of no interaction with treatment and for one marker, using a multivariate Cox Proportional Hazards model including covariates of treatment, marker level (dichotomous), and an interaction term. We may adjust each model further to account for other known prognostic factors. The significance level of each of these two statistical tests for the significance of a single marker (IL-6, VEGF-D) by treatment interaction will be adjusted using appropriate multiple testing methods. Interaction terms will be visualized using forest plots. As an additional visual tool, optimal cut points for expression levels will be determined and used to generate Kaplan-Meier plots for the dichotomized expression levels.[77] We will conduct sensitivity analyses to assess the potential effects of outliers and influential data points on the results.

The following tables represent the estimated power of each test of interaction between treatment and each marker (Table 1 IL-6 or Table 2 VEGF-D), individually, and assuming that we observe the targeted clinical hypotheses of observing a 14 month median PFS with pazopanib and 9 month median PFS in the placebo treated patients. Low versus High IL-6 will be classified based on the median value observed IL-6 result from our sample. Similarly, Low versus High VEGF-D will be classified based on the VEGF-D value associated with the 1st quartile of our sample and the remaining 75% of patients will be classified as having high VEGF-D.

As of March 31, 2018, we have observed a minimum follow-up of 75.5 months on all enrolled patients and assume that any of the estimated 150 patients having viable samples were possibly enrolled in the last few months of enrollment (i.e. we could observe 75.5 months of follow-up). We further assumed 57% of 150 cases were enrolled to pazopanib, 43% of 150 cases were enrolled to placebo, 50% of patients will have Low IL-6 (vs. High) and which is associated with improved PFS compared to patients having High IL-6, and that 25% of patients will have Low VEGF-D (vs. High) and which is associated with improved PFS compared to High (75% of patients).

Table 1. Estimated Power[a] of a Statistical Test for Interaction (IL-6 & Treatment)

Lack of benefit, within HIGH IL-6		Benefit, within LOW IL-6		Estimated Power (%), when alpha =					
Median PFS Pazopanib	Median PFS Placebo	Median PFS Pazopanib	Median PFS Placebo	0.05[c]	0.10	0.15	0.20	0.25	0.30
9[b]	5	19	13	9	16	21	26	30	34
9	4.5	19	13.5	18	28	35	41	46	51
9	4	19	14	33	46	54	60	65	69
9	3.5	19	14.5	53	66	73	78	82	84
9	3	19	15	70	80	85	89	91	93
8	4	20	14	17	27	34	40	45	49
9	4	19	14	33	45	54	60	65	69
10	4	18	14	52	64	72	77	81	84
11	4	17	14	70	80	85	88	91	93

a) Using application located at https://stattools.crab.org/Calculators/interactionSurvivalColored.html

b) In months, assuming no interaction (i.e. pazopanib median PFS=14 months, placebo median PFS=9 months)

c) 2-sided test

Table 2. Estimated Power [a] of a Statistical Test for Interaction (VEGF-D & Treatment)

Lack of benefit, within HIGH VEGF-D		Benefit, within LOW VEGF-D		Estimated Power (%), when alpha =					
Median PFS Pazopanib	Median PFS Placebo	Median PFS Pazopanib	Median PFS Placebo	0.05[c]	0.10	0.15	0.20	0.25	0.30
9[b]	5	29	21	10	17	23	28	33	37
9	4	29	24	37	49	57	64	68	72
9	3.5	29	25.5	57	69	76	80	84	86
9	3	29	27	77	85	89	92	94	95
10	8	26	12	30	42	50	56	61	66
9	8	29	12	52	64	71	76	80	83
8	8	32	12	73	82	87	90	92	94
7	8	35	12	96	98	99	99	99	100
6	8	38	12	99	100	100	100	100	100

a) Using application located at https://stattools.crab.org/Calculators/interactionSurvivalColored.html

b) In months, assuming no interaction (i.e. pazopanib median PFS=14 months, placebo median PFS=9 months)

c) 2-sided test

Biomarker Predictive (Not IL-6 & VEGF-D) (See Section 10.3.2.2): We will repeat the analysis described above for Objective 10.3.2.1 for the remaining biomarkers.

Analysis of Changes in Markers Over Time (See Section 10.3.2.3): The characteristics of blood analytes will be investigated using a variety of measures. Baseline and on-treatment samples will be assessed. Coefficients of variation will be used to assess the dispersion of each marker. Pair-wise correlations among the analytes will be estimated using Kendall's Tau. For additional visualization of these analytes, plots of dendrograms and/or heat maps with clustering relationships among the analytes will be presented. Descriptive statistics will also be presented. Summary statistics, including mean, standard deviation, and %CV, will be calculated for each marker for each time point. Linear mixed effect models will be used to examine inter- and intra-patient variability and trends.[78] We will conduct sensitivity analyses to assess the potential effects of outliers and influential data points on the results. Box plots will be used to illustrate the variability of the markers over time.

10.4 Banked Whole Blood Sample

Due to insufficient sample collection, the potential pharmacogenomic studies described below will not be performed as of Update #11. The whole blood samples collected for potential correlative science studies will remain in the Alliance Biorepository at The Ohio State University until a separate correlative science protocol has been reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

The current trial offers an excellent opportunity for pharmacogenetic research. The presence of a placebo arm ensures that the toxicity profile and overall efficacy is likely to be different in the individual arms. All patients enrolled in the accompanying randomized phase II study will be given the option to provide written informed consent for germline DNA analysis. A single blood sample (10 ml in a lavender top) will be collected at baseline (or any follow-up visit) for pharmacogenetic analysis. Germline DNA will be extracted using standard techniques and genetic testing appropriate to specific study questions will be performed. The concentration and quality of DNA will be quantified by ultraviolet spectroscopy.

All DNA samples and unprocessed blood will be frozen and will be banked at the Alliance Biorepository at Ohio State University until they are distributed to the appropriate laboratory for analysis. The typical yield of DNA from a 10ml blood sample is 100 ug (range of 80-150 ug).

For the potential studies described below we will need up to 5 ug for both the candidate gene analysis as well as the whole genome analysis, leaving the majority of the sample stored at the Alliance Biorepository at Ohio State University and available for additional future genotyping projects. In addition, plasma samples will be collected at baseline (prior to starting therapy), and after one cycle of treatment (cycle 2 day 1) according to standard protocol.

All samples are being banked for future use. Below are description of potential studies using the banked specimens and the possible hypotheses, objectives and statistical considerations that would be involved in future studies. Once more information is available from the parent study, a separate and full pharmacogenomics study proposal providing more details of the background scientific hypothesis, research plan, assay methods for use of the biospecimens, and a complete statistical section will be submitted for review by the Correlative Science Committee at CTEP in accordance with the NCI policies for banked tissue specimens.

10.4.1 Potential Hypothesis

A. Germline variants in angiogenesis/tumor microenvironment- related genes may predict response to pazopanib in carcinoid patients

Response to pazopanib monotherapy varies between patients, and up-front or secondary resistance is the rule. In carcinoid, the treatment effect is expected to be cytostatic rather than cytotoxic. Thus, radiographic responses are likely to be rare, with transient disease stabilization the more likely indicator of "response". To date, no predictive biomarkers have been validated. A recent limited scope candidate functional polymorphism analysis identified several polymorphisms nominally associated with pazopanib treatment outcomes in a cohort of 397 patients with renal cell carcinoma.[79] The SNP with the strongest association was rs1126647, encoding an A/T change in the 3'UTR of the gene encoding Interleukin-8, IL8.[79] The same authors also reported an inferior PFS for the homozygous carriers of the minor allele TT (median PFS 27 weeks) compared with the homozygous carriers of the common allele AA (median PFS, 48 weeks, P = 0.009). Notably, a proximal region of the 3'UTR has been demonstrated to regulate IL-8 expression via the micro RNA mir17/20. The down-regulation of IL-8 expression in stromal cells via this mechanism is associated with reduced breast cancer cell migration and invasiveness.[80] That this SNP has a putative functional mechanism by which the germline variant could affect response to therapy and that this SNP had the strongest association with PFS among many candidate SNPs and genes supports further study.

B. Genotype/endophenotype associations are relevant to pazopanib therapy

A challenge for use of genetic markers in predicting treatment outcomes in oncology is the myriad environmental, patient-specific, and tumor-specific factors that modify the genotype/ultimate clinical phenotype relationship. In other fields of complex medical genetics, notably the heritability of schizophrenia-spectrum diseases, the concept of endophenotyping has been adopted to advance investigation and understanding of the complex relationships.[81, 82] For developing predictors of tumor response to kinase inhibitors, the circulating protein sVEGFR2 has features consistent with an endophenotype worth intensive study. Among cancer patients, those with greater declines in sVEGFR2 with exposure to the VEGFR2 inhibitor motesanib in thyroid cancer and pazopanib in non-small cell lung cancer were more likely to have tumor response to therapy.[83, 84] The PET Committee Co-Chair for the study (in collaboration with the Genetics team from Glaxo SmithKline and collaborators within the Pharmacogenomics Research Network), Dr.

Maitland, has completed an investigation of the circulating protein, sVEGFR2 as an endophenotype for genome-wide study in non-cancer patient populations. Those studies identified the missense polymorphism rs34231037 within the gene for VEGFR2, KDR, as a functional polymorphism affecting circulating concentrations of this marker. Further study has revealed that carriers of the uncommon allele have greater declines with pazopanib exposure than non-carriers. We expect to replicate this finding in this carcinoid study in the future proposal. Similarly, we plan to determine the association between the IL-8 polymorphism associated with PFS in renal cell carcinoma patients with the pre-treatment and end-of-cycle-1 measurements of IL-8 in the carcinoid patients.

C. Genome-wide association studies

As a randomized trial with uniform assessment and follow-up especially for an uncommon disease like carcinoid this represents an important opportunity to better understand the relationships among germline genetic variation, disease, and treatment-response phenotypes. In unusual and useful fashion, the therapeutic intervention in this trial is under evaluation in renal cell carcinoma patients with an accompanying genome-wide association study. A similar evaluation in this trial will provide the opportunity to detect disease-independent effects of germline genetic variants of modest effect size through meta-analysis strategies on both disease response and adverse effect phenotypes. At this time, the Population Pharmacology and Pharmacogenomics Committee of Alliance is conducting genome-wide analyses of previously completed CALGB trials using The Illumina 1M platform in collaboration with the RIKEN Center for Genomic Medicine. More than 1,000,000 SNPs are simultaneously genotyped. In addition, there are 4,300 SNPs in regions of copy number variations (CNVs), thus allowing for the detection of CNVs as well. In addition, the Pharmacogenomics Research Network of NIGMS has begun to conduct genome-wide meta-analyses.

10.4.2 Potential Objectives

10.4.2.1 To determine whether biomarker associations discovered in other diseases treated with pazopanib have a consistent effect in carcinoid

10.4.2.2 To investigate the association between the genotypes of rs1126647 and baseline IL-8 levels

10.4.2.3 To investigate the association between the IL-8 SNP (rs1126647) and progression-free survival (PFS)

10.4.2.4 To investigate the potential for a SNP by drug, and SNP by IL8 level interactions with respect to PFS

10.4.2.5 To identify specific SNPs and/or copy number variations that are associated with the response to and toxicity associated with pazopanib therapy

10.4.3 Potential Statistical Considerations

Germline DNA will be extracted from peripheral blood using standard techniques. The primary objective for the proposed pharmacogenomic companion is to investigate the association between the genotypes of rs1126647 and baseline IL-8 levels. The primary analyses will be restricted to the European population. Evidence from a series of GWAS completed by the CALGB suggests that using a combination of self-reported race (white) and ethnicity (non-Hispanic) serves as a reasonable surrogate filter to identify a genetic European population. The patient population selection can of course be refined using genome-wide SNP data.

This companion will be designed under the assumption that 150 patients will be randomized to the two arms of the clinical study. It is expected that 85% of the patients will provide usable DNA along with consent to the pharmacogenomic analyses and that 85% will self-report as non-Hispanic whites. Thus, the expected sample size for the pharmacogenomic analyses will be n=108 (54 patients from each arm).

The Jonkheere Terpstra test, at the two-sided, will be employed to the test the baseline IL-8 level and genotype association. The analysis will be powered for an additive trend with T as the risk allele. The reported relative allele frequency by Xu et al (JCO 2011) for this SNP is 0.43. The relative genotypic frequencies are assumed to follow Hardy-Weinberg based on this relative minor allele frequency. The estimated mean and standard deviation of baseline IL-8 plasma levels in 10 patients provided data set by Maitland et al are 46 and 23 pg/ul respectively. We will assume that the mean level in the population is 46 pg/ul and is expressible as a mixture of normally distributed components with means m0, m0*R and m0*R^2 respectively. The mixture probabilities are 0.57^2, 2*0.43*0.57 and 0.43^2 respectively. The standard deviation for each component is assumed to be 23 pg/ul. Under these assumptions, the minimum effect size detectable with a power of 0.8, at the two-sided 0.05 level, is R=1.25

As secondary objectives we will investigate the association between this SNP and progression-free survival (PFS), to validate the results reported by Xu et al (JCO 2011), and the association between baseline IL-8 level and PFS. The Cox score test will be employed to test the PFS by SNP association while the association between PFS and IL8 levels will be investigated using the Cox rank score test. We will also investigate if the change in IL-8 levels from baseline is associated with this.

As an exploratory objective, we will investigate the potential for a SNP by drug, and SNP by IL8 level interactions with respect to PFS within the framework of two-way multiplicative Cox models.

In addition, we may use the DNA collected to consider other candidate SNPs or to conduct a GWAS to validate other or identify novel candidates, or, as next generation sequencing platforms become more cost effective, consider exome or whole-genome sequencing.

All SNPs will be evaluated for deviation from Hardy-Weinberg. In the absence of a hypothesized effect, the association analyses will be powered for allele dosing (i.e., additive) effects. To this end, the Cochran-Armitage test (for binary endpoints), Jonkheere-Terpstra test (for quantitative traits including biomarker or gene expressions in serum or tumor RNA) and the Cox score test (for censored time-to-event outcomes) will be used to quantify marginal associations. Multivariable models, with molecular, clinical and demographic variables, will be constructed using conditional inference trees and random forests.

As stated above, when sufficient information is available from this treatment study, a separate pharmacogenomics study proposal providing more details of the scientific hypothesis, research plan, assay methods for use of the biospecimens, and a complete statistical section will be submitted and reviewed by CTEP in accordance with the NCI policies for banked tissue specimens.

11.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

11.1 Qualified Personnel

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

11.2 Pazopanib (GW786034) (NSC 737754)

For more information, please refer to the Investigational Brochure for pazopanib.

11.2.1 Availability

Pazopanib (NSC 737754) and matching placebo will be provided free of charge by Novartis and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Pazopanib monohydrochloride (GW786034) (NSC 737754) and placebo will be supplied in induction-sealed bottles made of high-density polyethylene, have a white, plastic child-resistant closures, and contain 34 tablets. Each tablet has an aqueous film-coating and contains either 200 mg or 0 mg of the pazopanib free base or placebo for pazopanib. The tablets are oval-shaped and white in color. Refer to the pazopanib IB for information regarding the physical and chemical properties of pazopanib. Tablet excipients include microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate. The film-coat consists of titanium dioxide, hypromellose, macrogol/polyethylene glycol 400, and polysorbate 80.

Pazopanib open-label supplies will be provided in commercially labeled bottles. The commercial tablets are gray and debossed with “GS JT” on one side. In addition to the excipients listed above, the film-coat for commercially-labeled 200 mg tablets contains iron oxide black.

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

- Protocol Number (i.e., A021202)
- Bottle Number (i.e., “Bottle 1 of 2”, “Bottle 2 of 2”, etc.)
- Number of Tablets (i.e., “34 tablets” or “120 tablets”)
- Patient ID Number (e.g., "999999")
- Patient Initials (i.e., **L**ast initial, **F**irst initial, **M**iddle initial [e.g., “L, FM”])
- Agent Identification (i.e., “Pazopanib 200 mg or Placebo” or “Pazopanib 200 mg”)
- A blank line for the pharmacist to enter the patient’s name
- Administration Instructions (i.e., “Take __ tablets every day for 28 days.”)
- Storage Instructions (i.e., “Store at Controlled Room Temperature between 20° and 25° C.”)
- Emergency Contact Instructions
- Julian Date

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., 2009 = 09, 2010 = 10) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2009 would have a Julian date of ‘09001’ and a bottle labeled and shipped on December 31, 2010 would have a Julian date of ‘10365’. The Julian Date – Order Number (e.g., 2014352-0003)

from the patient-specific label must be used as the "Lot No." field on the NCI Agent Accountability Form (DARF), as it 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 pazopanib and placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30AM and 4:30PM Eastern Time or by emailing PMBAfterHours@mail.nih.gov anytime.

11.2.2 Drug Orders, Transfers, Returns, and Accountability

Drug Orders:

BLINDED PHASE

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 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 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 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; shipments to Canada will be sent by FedEx (generally one to two day delivery). 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 Center at the time the patient is randomized.

The initial request will be for 8 bottles - 34 tablets per bottle - [a 2 cycle (8 week) supply at a dose of 4 tablets given once daily] of pazopanib 200 mg or matching placebo. After 6 weeks (two weeks before needed), sites may reorder an additional 8 bottles- 34 tablets per bottle - [a 2 cycle (8 week) supply at a dose of 4 tablets given once daily] of pazopanib 200 mg or matching placebo using the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/), and the maintenance of an "active" account status and a "current" password. 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.

UNBLINDED CROSSOVER PHASE (OPEN-LABEL)

NOTE: Patients will not be able to obtain unblinded supplies until the patient has been unblinded (at progression) by following the unblinding procedures in Section 11.2.5 AND a clinical drug request has been transmitted to the PMB. The patient ID number will NOT change for the crossover portion of the study.

No open-label starter supplies will be available for this study. Open-label, 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. This re-registration will be performed by the Alliance Statistics and Data Center. Once a patient has been re-registered, the Alliance Statistics and Data 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 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 will be sent by FedEx (generally one to two day delivery). 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 Center at the time the patient is re-registered.

The initial request will be for 2 bottles – 120 tablets per bottle - [a 2 cycle (8 week) supply at a dose of 4 tablets given once daily] of pazopanib 200 mg. After 6 weeks (two weeks before needed), sites may reorder an additional 2 bottles – 120 tablets per bottle - [a 2 cycle (8 week) supply at a dose of 4 tablets given once daily] of pazopanib 200 mg using the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/), and the maintenance of an "active" account status and a "current" password. 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.

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 (fax number 240-276-7893) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. 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. "A021202").

Drug Returns: When it is necessary to return undispensed study drug (e.g., sealed 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 (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., "99999") and the patient initials (e.g., "L, FM") should be entered in the "Lot Number" field.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Oral Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "99999") and each Phase (Blinded and Unblinded Crossover) on this protocol. Please note that a new Oral Agent Accountability Record must be started when patients transition from the 34 count bottle of blinded supplies to the 120 count bottle. The Julian Date – Order Number (e.g., 2014352-0003) from the patient-specific label must be used as the Lot number on the NCI DARF.

Investigator Brochure Availability: The current versions of the IBs for the agents will be accessible to site investigators and research staff 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 and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

Useful Links and Contacts:

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eappsctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eappsctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: 240-276-6575 Monday through Friday between 8:30AM and 4:30PM Eastern Time
- IB Coordinator: IBCoordinator@mail.nih.gov

11.2.3 Storage and Stability

Store tablets at USP controlled room temperature (20° to 25° C or 68° to 77° F).

Stability studies are ongoing. An opened original container of tablets is stable for 3 months. If exact quantity must be dispensed, then extra tablets must be removed, documented and destroyed immediately. Alternatively, if exact quantity is dispensed in a pharmacy bottle, the supply should be assigned a 30-day expiration. **If tablets of a patient-specific/blinded supply are dispensed in a pharmacy bottle, all of the information on the CTEP applied label (including the Julian Date) MUST be on the bottle dispensed to the patient.**

11.2.4 Administration

Oral pazopanib/placebo should be taken on an empty stomach either 1 hour before or 2 hours after meals. The tablets should be swallowed whole and cannot be crushed or broken.

Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold increase in area under the plasma drug concentration curve (AUC) and maximum observed plasma drug concentration (C_{max}).

If a dose is missed, the patient should take the dose as soon as possible, but only if there are 12 or more hours remaining before the next dose is due. If the next dose is due in less than 12 hours, the patient should skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking pazopanib/placebo, the patient should not take a replacement dose on that day. The patient should resume taking pazopanib/placebo at the next scheduled dose on the following day. If vomiting persists, the patient should be instructed to notify the investigator.

11.2.5 Unblinding Procedures

Emergency unblinding will be available 24 hours a day, every day, according to the criteria below.

Unblinding can be done in the event of an emergency or at progression. Please note that, if treatment is unblinded due to an emergency, the patient must permanently discontinue all protocol therapy.

Emergency Unblinding Procedures:

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact the Alliance Executive Office on call by calling 773-702-6800, pressing 1 to speak with an operator, and then asking for pager ID 8625 to return the call.

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

- Alliance study ID (i.e., "A021202")
- 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.

Unblinding Procedures upon Progression:

Study participants can be unblinded upon progression. To receive patient treatment assignment, contact the Mayo Registration Office at 507-284-0661 during regular business hours and provide the e-mail confirmation from the Imaging Core Lab to random01@mayo.edu that the patient has progressed radiographically. If the patient was assigned to the placebo arm of the study, s/he has the option to receive open label pazopanib. See Section 5.5 for instructions regarding re-registration and Section 11.2.2 regarding drug ordering.

11.2.6 Toxicities and Potential Drug Interactions

In vitro data indicate that pazopanib is primarily metabolized by the human CYP3A4 isoenzyme. Potent CYP3A4 inhibitors are prohibited, and potent CYP3A4 inducers should be used with caution. Pazopanib is also a substrate for p-glycoprotein and breast cancer resistance protein (BCRP) transporters and concomitant administration of inhibitors such as lapatinib will result in increased plasma pazopanib concentrations.

Medications that strongly inhibit CYP3A4 include (but are not limited to):

- Antibiotics: clarithromycin, telithromycin, troleandomycin
- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)

- Antifungals: itraconazole, ketoconazole, voriconazole
- Antidepressants: nefazodone

Clinical studies indicate that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6. Drugs that have narrow therapeutic windows and are substrates for these enzymes should be administered with extreme caution. Because of pazopanib's long half-life, caution should continue to be exercised for at least 7 days and up to 15 days after the last dose of pazopanib when administering these medications.

Medications that are substrates for these enzymes and have narrow therapeutic windows medications include (but are not limited to):

- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential increased risk for developing ergot toxicity that includes severe vasospasm leading to peripheral as well as cerebral ischemia)
- Neuroleptics: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death)
- Antiarrhythmics: bepridil, flecainide, lidocaine, mexiletine, amiodarone, quinidine, propafenone (potential increased risk for QT interval prolongation and Torsade de Pointes)
- Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.

Co-administration of pazopanib with medicines that increase gastric pH should be avoided. If the concomitant use of a proton pump inhibitor (PPI) is medically necessary, pazopanib/placebo should be taken without food once daily in the evening with the PPI. If the concomitant administration of an H2-receptor antagonist is medically necessary, pazopanib/placebo should be taken without food at least 2 hours before or at least 10 hours after a dose of an H2-receptor antagonist. Administer pazopanib/placebo at least 1 hour before or 2 hours after administration of short-acting antacids. See also Section 8.1.

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

Pazopanib can prolong the QTc interval. Drugs that are generally accepted to have a risk of causing Torsades de Pointes (See Appendix 1) 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 1) should be monitored closely.

Pazopanib may increase bleeding. Patients receiving pazopanib and anticoagulation agents should be monitored for bleeding.

Pazopanib may cause decreased glucose. Patients receiving pazopanib and hypoglycemia agents should be monitored for hypoglycemia.

Thrombotic microangiopathy (hemolytic uremic syndrome) has been reported in clinical trials with pazopanib as monotherapy, in combination with bevacizumab, and in combination with topotecan. Reversal of the manifestations of thrombotic microangiopathy has been observed following discontinuation of pazopanib.

Avoid co-administration of pazopanib/placebo with simvastatin. Concomitant use of pazopanib and simvastatin increases the risk of ALT elevation. Data are not sufficient to assess the risk of concomitant administration of other statins and pazopanib.

Recent reports describe hepatotoxicity occurring in patients receiving pazopanib. Elevations in ALT and AST, including grade 3/4 elevation in approximately 9.4% and 6.9% of patients, respectively, have been reported. Less common are grade 3/4 elevations in bilirubin, and fatal hepatotoxicity has been reported to occur in < 1% of patients. Most elevations in liver function tests have been seen within the first two months of beginning pazopanib.

For patients who develop hepatic impairment, refer to the protocol document for appropriate dose modification or dose delay.

Pazopanib/placebo should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. Monitor ECGs and serum electrolytes (e.g., calcium, magnesium, potassium) at baseline and periodically and maintain within the normal range.

12.0 ANCILLARY THERAPY

12.1 Supportive Care

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate.

12.2 Treatment with Hormones or Other Chemotherapeutic Agents

Treatment with hormones (besides somatostatin analogs**)** or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone.

12.3 Somatostatin Analog

Patients already receiving a somatostatin analog (e.g. octreotide LAR) with or without subcutaneous octreotide for breakthrough at the time of study initiation may continue at their current dose level and schedule (according to institutional practice) throughout the course of study treatment.

12.4 Growth Factors

Treatment with filgrastim (G-CSF), pegfilgrastim, and sargramostim (GM-CSF) are not allowed on this protocol. The use of epoetin (EPO) is permitted at the discretion of the treating physician, but is discouraged.

12.5 Nausea/Vomiting

Every attempt should be made to control nausea and vomiting in patients who have emesis and are unable to retain pazopanib/placebo. Routine pre-medication for nausea is not necessary, but symptomatic patients should be treated with standard anti-nausea/anti-emetic therapy as necessary.

If a patient vomits after taking study medication, the patient should be instructed not to take a replacement dose on that same day. The patient should resume taking pazopanib/placebo at the next scheduled dose on the following day. If vomiting persists, then the patient should contact their physician.

To prevent or treat nausea and vomiting standard medications are recommended. Depending upon approved medications in your region, these may include: 5-HT3 receptor antagonist (granisetron, ondansetron, dolasetron mesylate); NK-1 receptor antagonists such as aprepitant, metoclopramide, phenothiazines (prochlorperazine); corticosteroids, (dexamethasones,

prednisone); and cannabinoids (dronabinol). If ondansetron is used, the dose should be no more than 16mg/day due to concerns related to possible prolongation of QTc interval.

12.6 Management of Diarrhea

Hydration: have patient drink 8 to 10 large glasses (approximately 2 liters) of clear non-caffeinated liquids a day (e.g., broth or electrolyte-containing sports drinks).
Dietary Modifications: have patient stop all lactose-containing products and eat frequent, small meals
Pharmacologic Intervention Using Loperamide: Begin loperamide at initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool. The recommended maximum daily dose of loperamide is 16 mg/day. Continuation of loperamide is suggested until diarrhea-free for 12 hours. If mild to moderate diarrhea persists for more than 24 hours, administer loperamide 2 mg every 2 hours and pursue evaluation for other treatable causes. If mild to moderate diarrhea persists after 48 hours total treatment with loperamide, discontinue study drug(s) and consider initiation of second-line agents (lomotil, octreotide).

12.7 Anticoagulants

Results from drug-drug interaction studies conducted in patients with cancer suggest that pazopanib has no effect on the metabolism of S-warfarin. Hemorrhagic events, however, have been reported in clinical studies with pazopanib; therefore, pazopanib should be used with caution in patients with increased risk of severe bleeding or who are receiving concomitant anticoagulant therapy (e.g. warfarin or its derivatives, low molecular weight heparin, unfractionated heparin). Patients taking concomitant anticoagulant therapy should be monitored regularly for changes in relevant coagulation parameters as clinically indicated, as well as for any clinical bleeding episodes.

12.8 Hypertension Guidelines

Antihypertensive Therapy:

Step 1) Consider initiating beta blocker treatment and 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.

Step 2) If BP still not controlled, consider adding another antihypertensive agent, a long acting dihydropyridine calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, alpha beta blocker; increase dose of this drug as described in Step 1.

Step 3) If BP is still not controlled, consider adding 3rd drug

For systolic BP >180 or diastolic BP > 110

If the patient is symptomatic: Recommend optimal management with intensive IV support in ICU; note that stopping pazopanib may result in a decrease in BP

If the patient is asymptomatic, consider adding 2 new anti-hypertensives given together from Step 1 (and dose escalated appropriately as in Step 1).

NOTE: Stopping or reducing the dose of pazopanib/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

12.9 CYP3A4 Inhibitors

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

- Indinavir
- Clarithromycin
- Ketoconazole

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 and/or IUPUI websites, or your local institution's pharmacist.

CYP3A4 inducers should also be used with caution.

12.10 Surgery

If a patient requires surgery while on study treatment, pazopanib/placebo may be held up to a maximum of 28 days. If study drug must be held greater than 28 days, patient must be taken off study. Patients should continue to follow the required test schedule per Section 7.0 of the protocol.

12.11 Management of Pneumonitis

The following are recommendations for toxicity management and are not required:

Grade 1: Recommend performing CT scans with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O2 saturation at rest. Repeat chest x-ray/CT scan every 2 Cycles until return to baseline.

Grade 2: Recommend CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Consider bronchoscopy. Consider corticosteroids for symptomatic disease

Grade 3 or 4: Recommend CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended. Treat with corticosteroids if infection is ruled out.

13.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

For the purposes of this study, patients should be reevaluated every 3 cycles (12 weeks). In addition to a baseline scan, confirmatory scans should also be obtained no less than 4 weeks following initial documentation of objective response.

13.1 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be chosen based on their suitability for accurate repetitive measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible repeated measurements in which case the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will

be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

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

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

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

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

13.2 Non-target Lesions

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

13.2.1 Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

13.2.2 Non-complete Response (non-CR)/Non-progression (non-PD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

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

13.2.4 FDG-PET: The use of FDG-PET in response assessments needs additional study. Alliance A021202 does not require or recommend FDG-PET for response assessment. If an FDG-PET is obtained at the discretion of the treating physician, the following algorithm may be used:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression

occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

13.3 Cytology and Histology

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

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

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

13.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

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

* Only for non-randomized trials with response as the primary endpoint.

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

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration" on the Off Treatment Form in Rave and are considered to have had "clinical progression." Every effort should be made to document the objective "radiographic" progression even after discontinuation of treatment.

For Patients with Non-measurable Disease (i.e. Non-target Disease)

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

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

13.5 Guidelines for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

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

13.5.3 Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. **If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).** CT and MRI scan requirements can be found in Section 6.2.2.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical

specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

13.5.4 PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data, which may bias an investigator if it is not routinely or serially performed.

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

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

13.5.7 Tumor Markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

13.6 Confirmation Measurement/Duration of Response

13.6.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of no less than 6 weeks.

13.6.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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

13.6.3 Duration of Stable Disease

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

14.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

14.1 Duration of Treatment

14.1.1 CR, PR, or SD (as determined by central radiology review)

Continue treatment at the highest tolerable dose until the appearance of disease progression or unacceptable toxicity per Section 9.0.

14.1.2 Disease Progression (as determined by central radiology review)

Patients who progress on blinded therapy, may be unblinded and if randomized to placebo, they will be allowed to cross over to open label pazopanib. After progression, follow the patient for survival and second malignancy every 6 months until death or 5 years after registration.

14.2 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:

- Notify the Study Chair.
- Document the reason(s) for discontinuation of therapy on the Off-Treatment Form.
- Follow the patient for protocol endpoints per the Required Data section.

15.0 STATISTICAL CONSIDERATIONS

15.1 Study Hypotheses

The primary endpoint for this trial is progression-free survival (PFS) based on central review. For determining the target HR we noted that everolimus (mTOR inhibitor) and sunitinib (VEGFR inhibitor like pazopanib) yielded similar HRs in the PNET population (0.35-0.42). The HR for everolimus in the RADIANT-2 study was around 0.78 in a patient population similar to the one proposed for this study (with the exception that concurrent octreotide *was* required and 20-25% patients had not received prior SSTa). We believe that targeting a larger difference, HR=0.64, is realistic in the proposed study with pazopanib for two main reasons: 1) concurrent octreotide will not be required and 2) previous progression on octreotide will be required in patients receiving concurrent octreotide. Both of these elements should reduce the potential for a confounding anti-tumor effect of octreotide in this study. Also, achieving a HR of 0.7 or lower is likely to reflect clinically meaningful drug activity. Since the primary endpoint of the study is PFS by central review, we believe a hypothesized median PFS of 9 months in the placebo group is reasonable based on the RADIANT-2 data.

15.2 Primary Endpoint

PFS will be measured from date of patient entry until documented progression of disease as determined by central review or death from any cause. If a patient does not have a documented date of progression or death, then PFS will be censored at the date of last adequate assessment. PFS will be estimated within treatment arm using the Kaplan-Meier method.

Patients will be randomized with equal probability to treatment with pazopanib or placebo. With 150 patients enrolled over 25 months (6 patients per month) and a follow-up period of 12 months, 85% power is achieved to detect the difference between a median PFS of 14 months with pazopanib and 9 months for placebo (logrank test, 1-sided α =0.1; hazard ratio 0.6429). One hundred and fourteen PFS events (d=114) are expected at the time of the final analysis. Accounting for 10% drop out, we estimate that we will need to enroll approximately 165 patients in order to meet the targeted sample size (N=150). This dropout rate includes patients who may withdraw from treatment due to lack of consensus between the local and central determination of progression.

The primary efficacy analysis will be conducted as intent-to-treat (ITT) and the ITT population will comprise all randomized patients by assigned treatment arm regardless of whether or not treatment was administered.

15.3 Secondary Endpoints

The objective response rate (ORR) will be defined as the percentage of patients with a confirmed CR or PR per RECIST 1.1 criteria. A patient with unknown or missing response will be omitted from the analysis. The exact binomial confidence interval will be used to estimate ORR.

Overall survival (OS) will be measured from randomization until death from any cause. A patient who is alive at the time of the statistical analysis will be considered censored at the last date of known contact. OS will be estimated by the Kaplan-Meier method within each treatment arm.

Duration of response (DR) will be defined, for the subset of patients with a confirmed CR or PR, as the time from first documented evidence of CR or PR until first documented disease progression or death from any cause. If sample size permits, DR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of patients with confirmed complete or partial tumor responses will be included in this analysis.

Time to treatment failure (TTF) will be measured from randomization until termination of protocol therapy for any reason including progression of disease, adverse events, and death. Patients will be censored at the last known follow-up date during therapy.

Patients who crossover from placebo to active therapy at the time of progression will be followed for a second progression unless they withdraw from treatment for other reasons; in that case they will be followed for toxicity and survival only. Any data analysis in this subset of patients will be considered exploratory.

15.4 Interim Analysis

Interim analyses for futility (PFS comparison between treatment arms) will be conducted when 38% and 75% of the expected number of events (d = 114) have been observed. The first interim analysis is expected to occur during the accrual period at approximately 18 months from trial activation (n=108 patients enrolled); the second interim analysis is expected during the follow-up period at approximately 28 months from activation. Study enrollment will not be suspended for interim analyses. The overall significance level of 0.10 will be maintained by employing the Lan-DeMets boundaries (O'Brien-Fleming analogue; one-sided α = 0.10). Futility will be assessed at these time points using a confidence interval approach. The adjusted 95% upper confidence bound (UCB) for the PFS log hazard ratio (placebo versus pazopanib) will be determined at each interim analysis. If the targeted log hazard ratio of log (1.55) = 0.4418 lies above the estimated 95% UCB, consideration will be given to declaring lack of efficacy for pazopanib.

15.5 Exploratory Objectives

Estimate PFS at 6 months within each arm. Kaplan-Meier methods will be used including calculations of 95% confidence intervals for 6 month PFS.

Biochemical response (for chromogranin A, defined as a decrease of 50% or more in chromogranin A levels from baseline, and for 5-HIAA, defined as a decrease of 50% or more in urinary 5-HIAA levels from baseline) will be compared between treatment arms among patients with elevated baseline levels of CGA and 5-HIAA.

15.6 Study Monitoring

15.6.1 CDUS

The Alliance Statistical Data Center will submit quarterly reports to CTEP by electronic means using the Clinical Data Update System (CDUS).

15.6.2 Data and Safety Monitoring

The principal investigator and the study statistician will review the study at least twice a year to identify accrual, adverse event/safety, and any endpoint problems that might be developing. The Alliance Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the study statistician.

16.0 EXPEDITED ADVERSE EVENT REPORTING

Investigators are required by Federal Regulations to report serious adverse events as defined below. Investigators are required to notify the Investigational Drug Branch, the Alliance Protocol Operations Office, the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. All such events must be reported in an expedited manner using the NCI CTEP Adverse Event Reporting System (CTEP-AERS). The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for expedited AE reporting beginning April 1, 2018. All treatment areas should have access to a copy of the CTCAE version 5.0. It can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

In the rare event when Internet connectivity is disrupted, a 24-hour notification should be made to the NCI by telephone at 301-897-7497. An electronic report must be submitted upon re-establishment of Internet connection.

The Alliance requires investigators to route all CTEP-AERS reports through the Alliance Protocol Operations Office for Alliance-coordinated studies

Be sure to read this entire section, as requirements are described in both the table and the bullet points following the table. Note that the table and the Additional Instructions or Exclusions may conflict. The Additional Instructions or Exclusions are protocol-specific, and in the case of a conflict, the Additional Instructions or Exclusions supersede the table. Most exclusions cover "expected" events that a sponsor would not be required to report to the FDA in an expedited manner.

16.1 Alliance A021202 Reporting Requirements

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

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

Expedited AE reporting timelines are defined as:

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

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs that are at least possibly related to treatment

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization, and that are at least possibly related to treatment
- Grade 3 adverse events that are at least possibly related to treatment

Effective Date: May 5, 2011

Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for A021202:

- Alliance A021202 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all treatment arms in this trial.
- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB, according to local IRB policies.
- Treatment expected adverse events include those listed in the package insert and in the CAEPR for pazopanib. Note that the ASAEL column of the CAEPR has been replaced with the Specific Protocol Exceptions to Expedited Reporting (SPEER) column. The SPEER includes "expected" severity grades in addition to event terms. Events listed in the SPEER only require expedited reporting if the severity grade is above the grade noted in SPEER.
- When evaluating hypertension, consider the description of severity (especially for grade 3) relative to the last AE reporting period/CTEP-AERS report. That is, for "more than one drug or more intensive therapy than previously used," "previously" should be considered the last reporting period. A regimen more intensive than that used in a previous reporting period need only prompt expedited reporting the first time that it us used. If blood pressure is stable on the more intensive regimen, do not continue to report the same grade hypertension 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 should be reported through CTEP-AERS independent of attribution to treatment. This includes solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), and in situ tumors. In CTCAE version 5.0, new malignancies (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, CTEP-AERS reports for new malignancies should include tumor pathology, history of 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 it was detected, molecular characterization or cytogenetics of the original and new malignancy (if available), and treatment and outcome of the new malignancy, if available. All new malignancies should also be reported on routine forms as required.
- All pregnancies and suspected pregnancies occurring in female patients during therapy or within 28 days after completion of treatment must be reported via CTEP-AERS.
    - CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities). In CTCAE v5.0, pregnancy loss is defined as "Death in utero," and any pregnancy loss should be reported

expeditiously as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A pregnancy 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.

- Neonatal death occurring within 28 days of birth that is considered at least possibly related to in utero exposure to treatment on A021202 should be reported via CTEP-AERS. A neonatal death should be reported expeditiously as Grade 4 "Death neonatal" under the General disorders and administration SOC.

- ≥ Grade 2 ALT and ≥ grade 2 bilirubin should be reported via CTEP-AERS within 10 calendar days.

16.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pazopanib (GW786034, NSC 737754)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2383 patients.* Below is the CAEPR for Pazopanib (GW786034).

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 2.8, January 31, 2019[1]

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Hemolytic uremic syndrome[2]	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Cardiac disorders - Other (Torsades de Pointes)	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Sinus bradycardia		
ENDOCRINE DISORDERS			
	Hypothyroidism		
EYE DISORDERS			

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Eye disorders - Other (eye hemorrhage, retinal hemorrhage)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
		Gastrointestinal fistula[3]	***Gastrointestinal fistula[3] (Gr 2)***
		Gastrointestinal hemorrhage[4]	
		Gastrointestinal perforation[5]	***Gastrointestinal perforation[5] (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
		Infection[6]	
INVESTIGATIONS			
	Activated partial thromboplastin time prolonged		
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 4)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 3)***
Blood bilirubin increased			***Blood bilirubin increased (Gr 3)***
	Creatinine increased		***Creatinine increased (Gr 2)***
		Ejection fraction decreased	
		Electrocardiogram QT corrected interval prolonged	
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Anorexia			***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 3)***
	Hypercalcemia		
Hyperglycemia			***Hyperglycemia (Gr 2)***
	Hyperkalemia		***Hyperkalemia (Gr 2)***
	Hypermagnesemia		
	Hypernatremia		
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		***Hypocalcemia (Gr 3)***
	Hypoglycemia		***Hypoglycemia (Gr 2)***
	Hypokalemia		
	Hypomagnesemia		
Hyponatremia			***Hyponatremia (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor pain		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
		Intracranial hemorrhage	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Hematuria	
	Proteinuria		***Proteinuria (Gr 2)***
		Urinary fistula	***Urinary fistula (Gr 2)***
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Reproductive system and breast disorders - Other (female genital tract fistula)	***Reproductive system and breast disorders - Other (female genital tract fistula) (Gr 2)***
		Uterine fistula	***Uterine fistula (Gr 2)***
		Vaginal fistula	***Vaginal fistula (Gr 2)***
		Vaginal hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
	Respiratory hemorrhage[7]		***Respiratory hemorrhage[7] (Gr 2)***

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease)[8]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
Hair color changes			***Hair color changes (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism[9]	
Hypertension			***Hypertension (Gr 3)***
		Thromboembolic event[9]	

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

[2]Thrombotic microangiopathy (TMA) which includes both Hemolytic uremic syndrome (HUS) and Thrombotic thrombocytopenic purpura (TTP) has been reported in clinical trials of GW786034.

[3]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Enterovesical fistula, Esophageal 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.

[4]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.

[5]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.

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

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

[8]Interstitial lung disease may include, Adult respiratory distress syndrome, Pneumonitis, Pulmonary fibrosis, Respiratory, thoracic and mediastinal disorders - Other (Acute respiratory distress syndrome), Respiratory, thoracic and mediastinal disorders - Other (Aveolitis), Respiratory, thoracic and mediastinal disorders - Other (Bronchiolitis obliterans), Respiratory, thoracic and mediastinal disorders - Other (Interstitial fibrosis), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonitis), Respiratory, thoracic and mediastinal disorders - Other (Organizing pneumonia),

Respiratory, thoracic and mediastinal disorders - Other (Pulmonary infiltrates), Respiratory, thoracic and mediastinal disorders - Other (Toxic pneumonitis).

[9]These events can result in life-threatening pulmonary, cardiac, cerebral, and other complications.

Adverse events reported on pazopanib (GW786034) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that pazopanib (GW786034) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (sinus arrest); Cardiac disorders - Other (supraventricular extrasystoles); Cardiac disorders - Other (Takotsubo [Broken Heart Syndrome]); Chest pain - cardiac; Pericardial effusion; Supraventricular tachycardia
ENDOCRINE DISORDERS - Adrenal insufficiency
EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (asthenopia); Eye disorders - Other (foreign body sensation in eyes); Eye pain; Floaters; Glaucoma; Photophobia; Retinal tear
GASTROINTESTINAL DISORDERS - Abdominal distension; Dry mouth; Duodenal obstruction; Dysphagia; Esophagitis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (hyperactive bowel); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal pain; Oral pain; Pancreatitis; Periodontal disease; Proctitis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Malaise; Non-cardiac chest pain; Pain
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Blood lactate dehydrogenase increased; Cardiac troponin T increased; Cholesterol high; GGT increased; INR increased; Investigations - Other (blood TSH increased); Lipase increased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Hypertriglyceridemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Generalized muscle weakness; Head soft tissue necrosis; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain
NERVOUS SYSTEM DISORDERS - Extrapyramidal disorder; Ischemia cerebrovascular; Memory impairment; Paresthesia; Peripheral sensory neuropathy; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Reproductive system and breast disorders - Other (vaginal necrosis); Vaginal discharge
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Laryngeal edema; Oropharyngeal pain; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumothorax; Postnasal drip; Sore throat; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Pruritus; Purpura; Skin hyperpigmentation; Skin ulceration
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Vasculitis

Note: Pazopanib (GW786034) 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.

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APPENDIX I: COLLABORATIVE AGREEMENT PROVISIONS

The pazopanib and placebo supplied by CTEP, DCTC, NCI used in this protocol are provided to the NCI under Collaborative Agreement (CRADA, CTA, CSA) between Novartis (hereinafter referred to as "Collaborator") 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 the Collaborator" (at http://ctep.cancer.gov/industrycollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the pazopanib/placebo in this study:

1. Pazopanib/placebo may not be used for any purpose outside the scope of this protocol, nor can it be transferred or licensed to any party not participating in the clinical study. Collaborator's data for agents are confidential and proprietary to Collaborator and shall be maintained as such by the investigators. The protocol documents for studies utilizing pazopanib/placebo contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol in which there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator and Provider shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator, the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order, as described in the IP Option to Collaborator (http://ctep.cancer.gove/industryCollaborations2/intellectual_propert.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for this 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 the 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 for advisory review and comment prior to submission for publication. Collaborator 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 intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   email: ncicteppubs@mail.nih.gov

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

APPENDIX II: DRUGS ASSOCIATED WITH QTC PROLONGATION

The following table presents a list of drugs that prolong, may prolong or are unlikely to prolong the QTc. Please note that this list is frequently updated. For the most current list of medications, users should be directed to the following website: *http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm.*

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	*Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes*	*Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in patients without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism)*
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Amiodarone /Cordarone®	Alfuzosin /Uroxatral®	Amitriptyline /Elavil®
Amiodarone /Pacerone®	Amantadine /Symmetrel®	Ciprofloxacin /Cipro®
Arsenic trioxide /Trisenox®	Atazanavir /Reyataz®	Citalopram /Celexa®
Astemizole /Hismanal®	Azithromycin /Zithromax®	Clomipramine /Anafranil®
Bepridil /Vascor®	Chloral hydrate /Noctec®	Desipramine /Pertofrane®
Chloroquine /Aralen®	Clozapine /Clozaril®	Diphenhydramine /Benadryl®
Chlorpromazine /Thorazine®	Dolasetron /Anzemet®	Diphenhydramine /Nytol®
Cisapride /Propulsid®	Dronedarone /Multaq®	Doxepin /Sinequan®
Clarithromycin /Biaxin®	Felbamate /Felbatrol®	Fluconazole /Diflucan®
Disopyramide /Norpace®	Flecainide /Tambocor®	Fluoxetine /Sarafem®
Dofetilide /Tikosyn®	Foscarnet /Foscavir®	Fluoxetine /Prozac®
Domperidone /Motilium®	Fosphenytoin /Cerebyx®	Galantamine /Reminyl®
Droperidol /Inapsine®	Gatifloxacin /Tequin®	Imipramine /Norfranil®
Erythromycin /Erythrocin®	Gemifloxacin /Factive®	Itraconazole /Sporanox®
Erythromycin /E.E.S.®	Granisetron /Kytril®	Ketoconazole /Nizoral®
Halofantrine /Halfan®	Indapamide /Lozol®	Mexiletine /Mexitil®
Haloperidol /Haldol®	Isradipine /Dynacirc®	Nortriptyline /Pamelor®
Ibutilide /Corvert®	Lapatinib /Tykerb®	Paroxetine /Paxil®
Levomethadyl /Orlaam®	Lapatinib /Tyverb®	Protriptyline /Vivactil®
Mesoridazine /Serentil®	Levofloxacin /Levaquin®	Sertraline /Zoloft®

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	*Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes*	*Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in patients without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism)*
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Methadone /Dolophine®	Lithium /Lithobid®	Solifenacin /VESIcare®
Methadone /Methadose®	Lithium /Eskalith®	Trimethoprim-Sulfa /Sulfa®
Pentamidine /Pentam®	Moexipril/HCTZ /Uniretic®	Trimethoprim-Sulfa /Bactrim®
Pentamidine /NebuPent®	Moxifloxacin /Avelox®	Trimipramine /Surmontil®
Pimozide /Orap®	Nicardipine /Cardene®	
Probucol /Lorelco®	Nilotinib /Tasigna®	
Procainamide /Pronestyl®	Octreotide /Sandostatin®	
Procainamide /Procan®	Ofloxacin /Floxin®	
Quinidine /Cardioquin®	Ondansetron /Zofran®	
Quinidine /Quinaglute®	Oxytocin /Pitocin®	
Sotalol /Betapace®	Paliperidone /Invega®	
Sparfloxacin /Zagam®	Perflutren lipid microspheres /Definity®	
Terfenadine /Seldane®	Quetiapine /Seroquel®	
Thioridazine /Mellaril®	Ranolazine /Ranexa®	
	Risperidone /Risperdal®	
	Roxithromycin* /Rulide®	
	Sertindole /Serlect®	
	Sertindole /Serdolect®	
	Sunitinib /Sutent®	
	Tacrolimus /Prograf®	
	Tamoxifen /Nolvadex®	
	Telithromycin /Ketek®	
	Tizanidine /Zanaflex®	
	Vardenafil /Levitra®	
	Venlafaxine /Effexor®	
	Voriconazole /VFend®	
	Ziprasidone /Geodon®	

* QTc prolongation associated with doses greater than 16 mg/day

APPENDIX III: MEDICATION LOGS

Pazopanib/Placebo Medication Log

Number of Pills Given:_____
Total Daily Dose:_____

Pill Bottle(s) returned: Circle Yes or No
Number of Pills returned:_____

(To be completed by RN)

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.

SPECIAL INSTRUCTIONS

1. Pazopanib/Placebo should be taken orally without food at least 1 hour before OR 2 hours after a meal.
2. The tablets should be swallowed whole and must not be crushed or broken.
3. If a dose is missed, please take the dose as soon as possible, but only if there are 12 or more hours remaining before the next dose
    a. If the dose is due in less than 12 hours, skip the missed dose and take the next dose as scheduled
4. If vomiting occurs after taking pazopanib/placebo, do not take a replacement dose on that day. Resume drug the next day.
    a. Even if you can see a whole tablet, do not take a replacement dose that day.
    b. If consistent vomiting occurs please notify the study doctor.
5. Pazopanib/placebo tablets should be stored at room temperature.

CYCLE #: _____ # of WEEKS_____

DAY	**Medication**	**DATE**	**TIME**		**Number of 200mg tablets taken**	**Comments**
Example	Pazopanib/placebo	*07/01/2012*	*9:00*	*AM*	*4 x 200*	
1	Pazopanib/placebo					
2	Pazopanib/placebo					
3	Pazopanib/placebo					
4	Pazopanib/placebo					
5	Pazopanib/placebo					
6	Pazopanib/placebo					
7	Pazopanib/placebo					
8	Pazopanib/placebo					
9	Pazopanib/placebo					
10	Pazopanib/placebo					
11	Pazopanib/placebo					
12	Pazopanib/placebo					
13	Pazopanib/placebo					
14	Pazopanib/placebo					
15	Pazopanib/placebo					
16	Pazopanib/placebo					
17	Pazopanib/placebo					
18	Pazopanib/placebo					
19	Pazopanib/placebo					
20	Pazopanib/placebo					
21	Pazopanib/placebo					
22	Pazopanib/placebo					
23	Pazopanib/placebo					
24	Pazopanib/placebo					
25	Pazopanib/placebo					
26	Pazopanib/placebo					
27	Pazopanib/placebo					
28	Pazopanib/placebo					

Patient Signature: _____Date:_____
Consenting Professional/Research RN Signature: _____Date:_____

Open Label Pazopanib Medication Log

Number of Pills Given:_____
Total Daily Dose:_____

Pill Bottle(s) returned: Circle Yes or No
Number of Pills returned:_____

(To be completed by RN)

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.

SPECIAL INSTRUCTIONS

1. Pazopanib should be taken orally without food at least 1 hour before OR 2 hours after a meal.
2. The tablets should be swallowed whole and must not be crushed or broken.
3. If a dose is missed, please take the dose as soon as possible, but only if there are 12 or more hours remaining before the next dose
    a. If the dose is due in less than 12 hours, skip the missed dose and take the next dose as scheduled
4. If vomiting occurs after taking pazopanib, do not take a replacement dose on that day. Resume drug the next day.
    a. Even if you can see a whole tablet, do not take a replacement dose that day.
    b. If consistent vomiting occurs please notify the study doctor.
5. Pazopanib tablets should be stored at room temperature.

CYCLE #: _____ # of WEEKS_____

DAY	**Medication**	**DATE**	**TIME**		**Number of 200mg tablets taken**	**Comments**
Example	Pazopanib	*07/01/2012*	*9:00*	*AM*	*4 x 200*	
1	Pazopanib					
2	Pazopanib					
3	Pazopanib					
4	Pazopanib					
5	Pazopanib					
6	Pazopanib					
7	Pazopanib					
8	Pazopanib					
9	Pazopanib					
10	Pazopanib					
11	Pazopanib					
12	Pazopanib					
13	Pazopanib					
14	Pazopanib					
15	Pazopanib					
16	Pazopanib					
17	Pazopanib					
18	Pazopanib					
19	Pazopanib					
20	Pazopanib					
21	Pazopanib					
22	Pazopanib					
23	Pazopanib					
24	Pazopanib					
25	Pazopanib					
26	Pazopanib					
27	Pazopanib					
28	Pazopanib					

Patient Signature: _____Date:_____
Consenting Professional/Research RN Signature: _____Date:_____

APPENDIX IV: REGISTRATION FATIGUE/UNISCALE ASSESSMENT

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and entered into RAVE.

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.

A translator may be used to administer the assessment. Additionally, a French version of the assessment has been provided on the following page.

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

Fatigue/Uniscale Évaluation

Instructions: S'il vous plaît, pour chaque article ci-dessous, encerclez le numéro (0-10) qui vous décrit le mieux.

Comment décririez-vous :

1. Votre niveau de fatigue moyen au cours de la dernière semaine, aujourd'hui inclus?

0	1	2	3	4	5	6	7	8	9	10
Aucune fatigue										La pire fatigue possible

2. Votre qualité de vie globale dans la semaine écoulée, y compris aujourd'hui?

0	1	2	3	4	5	6	7	8	9	10
Aussi mauvaise que possible										Aussi bonne que possible

APPENDIX V: QUALITY OF LIFE MEASURES

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.

Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

		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 on to the next page

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 on to the 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**	**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)*		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/	1	2	3	4

LINEAR ANALOGUE SELF ASSESSMENT

Patient Name: _____ Date: _____
Patient Number: _____

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.
How would you describe:

1. your overall Quality of Life?

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

2. your overall mental (intellectual) well being?

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

3. your overall physical well being?

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

4. your overall emotional well being?

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

5. your level of social activity?

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

6. your overall spiritual well being?

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

7. the frequency of your pain?

0	1	2	3	4	5	6	7	8	9	10
No pain										Constant pain

8. the severity of your pain, on the average?

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

9. your level of fatigue, on the average?

0	1	2	3	4	5	6	7	8	9	10
No fatigue										Constant tiredness

10. your level of support from friends and family?

0	1	2	3	4	5	6	7	8	9	10

No support — Highest level of support

11. your financial concerns?

0 1 2 3 4 5 6 7 8 9 10

Constant concerns — No concerns

12. your legal concerns (will, advanced directives, etc.)?

0 1 2 3 4 5 6 7 8 9 10

Constant concerns — No concerns