SARAH CANNON
Development Innovations

PRO 10

A Phase II Study to Evaluate the Activity of Commercially Available Molecularly Matched Targeted Therapies in Selected Tumor Types Based on Genomic Alterations

SARAH CANNON DEVELOPMENT INNOVATIONS STUDY NUMBER:	PRO 10
STUDY DRUG(S):	Regorafenib, Afatinib, Cabozantinib
SPONSOR:	Sarah Cannon Development Innovations, LLC (SCDI) 1100 Charlotte Ave, Suite 800 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
STUDY CHAIR:	Howard A. Burris, III, MD. Sarah Cannon Research Institute 1100 Charlotte Avenue , Suite 800 Nashville, TN 37203 1-877-MY-1-SCRI
DATE FINAL:	6 May 2016
AMENDMENT NUMBER 1	20 May 2016
AMENDMENT NUMBER 2	23 January 2018

SARAH CANNON
Development Innovations

Clinical Study Statement of Compliance

A Phase II Study to Evaluate the Activity of Commercially Available Molecularly Matched Targeted Therapies in Selected Tumor Types Based on Genomic Alterations

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**

Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

Clinical Study Signature Approval Page

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Study Chair Chief Medical Officer Sarah Cannon Research Institute	**Study Chair Signature**	**Date**
Sarah Cannon Development Innovations , LLC	**Sarah Cannon Development Innovations , LLC** **Representative Signature**	**Date**

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Clinical Study Principal Investigator Signature Form

A Phase II Study to Evaluate the Activity of Commercially Available Molecularly Matched Targeted Therapies in Selected Tumor Types Based on Genomic Alterations

SARAH CANNON DEVELOPMENT INNOVATIONS STUDY NUMBER:	PRO 10
DATE FINAL:	6 May 2016
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By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

_____	_____	_____
Principal Investigator Name (Please Print)	**Principal Investigator Signature**	**Date**

Please retain a copy of this page for your study files and return the original signed and dated form to:

Sarah Cannon Development Innovations, LLC
1100 Charlotte Avenue, Suite 800
Atten: PRO 10 Study Team
Nashville, TN 37203

PRO 10 Protocol Summary of Changes

AMENDMENT NUMBER 2	AMENDMENT DATE 23 January 2018

Global changes

Cabozantinib has been added as a possible IP

Minor editorial and formatting changes are not detailed in this Summary of Changes

PRO 10 PROTOCOL SYNOPSIS

Title of Study:	A phase II study to evaluate the activity of commercially available molecularly matched targeted therapies in selected tumor types based on genomic alterations	
Sarah Cannon Development Innovations Study Number:	PRO 10; ONC-2014-138 (Bayer); PRO10/1200.262 (Boehringer Ingelheim)/Pro 10 Exelixis	
Sponsor:	Sarah Cannon Development Innovations, LLC – Nashville – TN	
Study Duration:	Enrollment will occur over approximately 18 months. The total duration of the study is planned to be approximately 27 months.	**Phase of Study:** II
Study Centers:	This study will be conducted at approximately 20 sites.	
Number of Patients:	Up to 160 patients are planned to be enrolled in this study.	
Objectives:	**Primary Objective** The primary objective of this study is to: • Determine the overall response rate (Complete Response [CR] + Partial Response [PR]) in each patient population receiving targeted therapy based on relevant genomic alterations. **Secondary Objectives** The secondary objectives of this study are to: • Evaluate the clinical benefit rate (CR + PR + stable disease [SD] ≥ 6 months) in each patient population receiving targeted therapy based on relevant genomic alterations. • Determine the time to treatment failure (measured from the first day of treatment until the patient is removed from study for toxicity, disease progression, patient choice, or death) in each patient population receiving targeted therapy based on relevant genomic alterations. • To determine the progression free survival (PFS) in each patient population receiving targeted therapy based on relevant genomic alterations.	
Study Design:	This four-arm pilot phase II study will evaluate the preliminary antitumor activity of selected commercially available molecularly matched targeted therapies in patients who have failed first line treatment for one of the following tumor types: (1) non-small cell lung cancer, (2) urothelial carcinoma, (3) non-colon gastrointestinal cancers, and (4) upper aerodigestive tract cancers. Patients will be profiled with next-generation sequencing technology results known prior to consideration for enrollment on this protocol. Patients with the specified tumor types demonstrating one of the genomic alterations described in Table 1 may be assessed for protocol eligibility and treatment. All eligible patients will receive one of the FDA-approved targeted agents at the recommended dose outlined in Table 2. Patients with a genomic alteration that is not described in Table 1 but is covered by a targeted agent in Table 2 will also be eligible. Dose modifications will be implemented based on criteria outlined in the product package insert for each individual agent. Patients will be re-evaluated for treatment response after receiving 8 weeks of oral therapy (with the exception of regorafenib which is dosed intermittently for 21 out of every 28 days). Response to therapy will be assigned using RECIST v1.1 (see Section E). Patients who have	

	objective response (OR) or stable disease (SD) will continue treatment with re-evaluations every 8 weeks, until the time of tumor progression or intolerable treatment-related side effects. If a patient was not profiled with Foundation One® prior to study enrolment, Sarah Cannon Development Innovations shall use reasonable efforts to collect and send to Foundation Medicine adequate tumor tissue meeting the tissue specimen requirements for Foundation One® for retrospective profiling that will be completed and compared to the profiling report provided at study entry. A total of 160 patients are planned to be enrolled on the trial (40 patients per study arm).
Study Drugs, Doses, and Modes of Administration:	The study drugs are outlined in Table 2 and will be provided to the sites. The initial dosing regimen for each agent is outlined in Section 8.1. All drugs are to be administered orally according to the dosing guidelines in the product package insert. Copies of the product package inserts are included in Appendices G and H.
Inclusion Criteria:	1. Patients with a histologically or cytologically confirmed diagnosis of one of the following tumor types whose disease has progressed following one line of standard therapy and/or for which no standard treatment is available that has been shown to prolong survival: a. Non-small cell lung cancer b. Urothelial carcinoma c. Non-colon gastrointestinal cancers (including hepatobiliary, pancreatic, and gastroesophageal tumors) d. upper aerodigestive tract cancers (including lip, tongue, salivary gland, gum, oral cavity, mouth, tonsils, oropharynx, nasopharynx, nasal cavity, sinus, and larynx tumors) 2. Patients must have a predefined genomic alteration included in Table 1 that can be targeted with one of the FDA-approved targeted agents listed in Table 2. Patients with a genomic alteration that is not described in Table 1 but is covered by a targeted agent in Table 2 will also be eligible. 3. Patients must have measurable disease as measured by Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 (Appendix E). 4. Patients must have an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A). 5. Age greater than or equal to 18 years. 6. Adequate hematologic function defined as: - Absolute neutrophil count (ANC) ≥1500/μL - Platelets ≥75,000/μL 7. Adequate liver function defined as: - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x the upper limit of normal (ULN) or ≤ 5.0 X ULN if liver metastases present - Total bilirubin ≤1.5 x ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin)

	8. Adequate renal function defined as serum creatinine ≤1.5 x the upper limit of normal OR measured or calculated creatinine clearance ≥50 mL/min for patients with creatinine levels greater than or equal to 1.5 x the upper limit of normal. 9. Patients who are therapeutically treated with an agent such as warfarin or heparin will be allowed to receive either regorafenib or afatinib, provided that their medication dose and INR/PTT are stable. Close monitoring is mandatory if the patient is receiving anticoagulants. If values are above the therapeutic range the anticoagulant doses should be modified and assessments should be repeated until stable. (See Exclusion Criteria 15 for anticoagulant therapy information for patients receiving cabozantinib). 10. Male patients with female partners of childbearing potential and women patients of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the study and for 90 days following last dose of study drug(s). Male patients must also refrain from donating sperm during their participation in the study and for 90 days after the last dose of study drug (Appendix C). 11. Willingness and ability to comply with study and follow-up procedures. 12. Ability to understand the nature of this study and give written informed consent.
Exclusion Criteria:	1. Two or more prior chemotherapy regimens in the metastatic setting. 2. Most recent chemotherapy ≤ 3 weeks and > Grade 1 chemotherapy-related side effects, with the exception of neuropathy (> grade 2 excluded) and alopecia. 3. Use of a study drug or targeted therapy ≤21 days or 5 half-lives (whichever is shorter) prior to the first dose of study treatment. For study drugs for which 5 half-lives is ≤21 days, a minimum of 10 days between termination of the study drug and administration of study treatment is required. 4. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy. 5. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement. 6. Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 2 weeks prior to study entry and there is no evidence of central nervous system disease progression, mild neurologic symptoms, and no requirement for chronic corticosteroid therapy. Enzyme- inducing anticonvulsants are contraindicated. 7. Pregnant or lactating 8. Acute or chronic liver, renal, or pancreas disease. 9. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea Grade ≥2, and malabsorption syndrome). 10. Any of the following cardiac diseases currently or within the last 6 months: • Unstable angina pectoris

	• Congestive heart failure (New York Heart Association (NYHA) ≥ Grade 2 [Appendix B]) • Acute myocardial infarction • Conduction abnormality not controlled with pacemaker or medication • Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible) • Valvular disease with significant compromise in cardiac function 11. Inadequately controlled hypertension (i.e., systolic blood pressure [SBP] >180 mmHg or diastolic blood pressure (DBP) >100 mmHg) (patients with values above these levels must have their blood pressure (BP) controlled with medication prior to starting treatment). 12. Thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks) deep vein thrombosis or pulmonary embolism within 6 months of start of treatment. 13. Evidence or history of bleeding diathesis or coagulopathy; any haemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 4 weeks prior to start of treatment. 14. **For patients receiving cabozantinib only**: Do not administer cabozantinib to patients that have high risk or at high risk for severe haemorrhage. Examples include: a. The patient has radiographic evidence of cavitating pulmonary lesion(s). b. The patient has tumor invading or encasing any major blood vessels. c. The patient has had hemoptysis of ≥ 0.5 teaspoon (2.5ml) of red blood within 3 months before the first dose of study treatment. d. The patient has experienced clinically significant GI bleeding within 6 months of the first dose of study treatment. e. The patient has experienced any other signs indicative of pulmonary hemorrhage within 3 months of the first dose of study treatment. 15. **For patients receiving cabozantinib only**: Do not administer cabozantinib to patients that have high risk or at high risk of perforation or fistula: a. The patient has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction. b. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose. Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose. c. The patient has pre-existing fistula of head and neck area. Note: Treatment areas should be healed with no sequelae from prior radiation therapy that would predispose to fistula formation.

	d. The patient has pre-existing osteonecrosis of the jaw. 16. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel). **[Patients receiving cabozantinib only]** Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (< 1 mg/day), and low dose, low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects without radiographic evidence of brain metastasis, who are on a stable dose of LMWH for at least 12 weeks before randomization, and who have had no complications from a thromboembolic event or the anticoagulation regimen. 17. Presence of a non-healing wound, non-healing ulcer, or bone fracture. 18. Patients with phaeochromocytoma. 19. Serious active infection at the time of treatment, or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment. 20. Known diagnosis of human immunodeficiency virus, hepatitis B, or hepatitis C. 21. Presence of other active cancers unless indolent and not requiring therapy. Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer. 22. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.
Correlative Testing:	Patients will be profiled with next-generation sequencing technology outside of this protocol and will be enrolled based on the results of this profiling. If a patient was not profiled with Foundation One® prior to study enrolment, Sarah Cannon Development Innovations shall use reasonable efforts to collect and send to Foundation Medicine adequate tumor tissue meeting the tissue specimen requirements for Foundation One® for retrospective profiling that will be completed and compared to the profiling report provided at study entry.
Statistical Methodology	The design of this trial uses an exact single-stage design for each of the four arms. (A'Hern 2001) For this investigation, it has been determined that an ORR (CR + PR) of 10% or worse has low activity in line with standard of care. An ORR of 25% (or better) is considered to indicate interesting activity. Using a one-sided alpha of 5% and power of 80%, 40 evaluable patients will be required in each arm. A minimum of 8 responders in a particular arm would indicate that the corresponding tumor type would be worthy of further investigations.

ASSESSMENTS	PRE-TREATMENT	STUDY TREATMENT (*Cycles repeated every 28 days*			FOLLOW-UP
	Baseline[a]	Cycle 1 Day 1[a]	Cycle 1 Day 15	Cycles 2+[h]	End of Study Evaluation[i]
Tests and Observations					
Informed consent	X				
Medical history	X	X			X
Physical exam (including vital signs)[b]	X	X	X[j]	X	X
ECOG PS	X	X		X	X
Concomitant medication review	X	X	X	X	X
Adverse event evaluation			X	X	X
Study Drug Compliance Review[c]			X	X	X
Laboratory Observations					
CBC, 3-part differential, and platelets[d]	X	X	X	X	X
CMP plus magnesium[d]	X	X	X	X	X
PT/INR/PTT	X				
Serum or urine pregnancy test[e]	X	X		X	
Disease Assessment					
Tumor marker (if applicable)	X			X	
CT Scan chest/abdomen/pelvis[f]	X			X	
MRI or CT Scan of Brain[g]	X				

a Baseline procedures including medical history, physical examination, 12-lead ECG, ECOG PS, and laboratory tests should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated.

b Physical examination will include measurements of height (pretreatment visit only), weight, and vital signs.

c On day 15 of cycle 1 and at the beginning of each subsequent treatment cycle, study drug compliance should be reviewed with the patient and a sufficient supply of drug should be dispensed to the patient to take at home. A final drug compliance assessment should be done at the End of Treatment visit (if applicable) and any remaining drug should be retrieved from the patient.

d May be done up to 72 hours prior to day 1 of each treatment cycle.

e Serum or urine pregnancy test required on day 1 of each treatment cycle in women of child-bearing potential only.

f CT scan s of the chest/abdomen/pelvis required at baseline. Scans will be repeated every 2 cycles. Only abnormal scans need to be repeated after baseline.

g Head CT or MRI scan required at baseline for patients with a history of treated brain metastases only.

h There is a +/- 7 day window on day 1 of all subsequent cycles to accommodate scheduling issues.

i Patients must be followed for AEs for 30 calendar days after the last dose of study drug. Patients who have not progressed at the time of study discontinuation will be followed for disease assessment only every 3 months (± 1 month) until disease progression.

j. On CD15, vital signs only. No physical exam is required on this visit.

PRO 10 CONTACT INFORMATION

Sarah Cannon Development Innovations Contact Information:	Sarah Cannon Development Innovations 1100 Charlotte Avenue, Suite 600 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
Study Chair:	Howard A. Burris, III, MD Sarah Cannon Development Innovations 1100 Charlotte Avenue, Suite 800 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
Safety Dept. Fax #: **Safety Dept. Email:**	1-866-807-4325 CANN.SAE@SCRI-Innovations.com
Regulatory Phone # **Regulatory Email:**	1-877-MY-1-SCRI SCRIRegulatory@SCRI-Innovations.com

LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Adverse reaction
AST (SGOT)	Aspartate aminotransferase
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CMP	Comprehensive metabolic profile
CR	Complete response/remission
CRF	Case Report Form
CT	Computerized tomography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
MRI	Magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OR	Objective response
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PHI	Protected health information
PIS	Patient Information Sheet
PFS	Progression-free survival
PR	Partial response/remission
QA	Quality assurance
SAE	Serious adverse event
SAR	Suspected adverse reaction
SD	Stable disease
UAE	Unexpected Adverse Event
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal

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Post Text Supplement

1. INTRODUCTION

1.1 Background and Rationale

Advances in next generation sequencing technologies in combination with decreasing costs of testing has allowed broader implementation of genomic profiling in the clinical practice of medical oncology and clinical research. (Thomas et al. 2014; Johnson et al. 2014; Gray et al. 2014; Schwaederle et al. 2014) The identification of genomic alterations that drive the development and progression of specific tumors has resulted in the discovery of targeted agents that may produce tumor regressions in tumors that possess the alteration. More than 30 targeted small molecules and monoclonal antibodies have been approved by the FDA for the treatment of a variety of cancers.

Johnson et al. recently published a retrospective evaluation of the use of a targeted next-generation sequencing platform (FoundationOne) in advanced cancer patients. (Johnson et al. 2014) The assay identified potentially actionable genomic alterations in 83% of tumors with a median of two actionable mutations per patient. Fifty-seven percent of patients were identified by NGS testing as potential candidates for clinical trials in which the tumor-targeted treatment had demonstrated early clinical activity or preclinical rationale for use. Twenty-six percent of patients had alterations that predicted sensitivity to targeted agents that were already approved for the cancer type assessed and an additional 17% demonstrated alterations that could be targeted by an FDA-approved agent for another tumor type.

Researchers at MD Anderson Cancer Center have also reported on the ability to select therapy in a phase I clinical trials program based on tumor alterations detected with an institutionally developed CLIA-certified sequencing panel. (Tsimberidou et al, 2012) Approximately 40% of the patients tested had 1 or more alteration. Patients whose tumors had an alteration were treated with matched targeted therapy when available and compared to a group without matched targeted therapy. Patients receiving matched therapy had a higher overall response rate (27% vs 5%), longer time to treatment failure (5.2 vs 2.2 months) and longer survival (13.4 vs 9 months) compared to the non-matched group. In a separate manuscript, patients with PIK3CA mutations were treated, whenever feasible, with agents targeting the PI3K/AKT/mTOR pathway and compared to patients with wild-type PIK3CA treated on the same protocols. (Janku et al. 2012) Patients with PIK3CA mutations who were treated with targeted therapies demonstrated a higher response rate than patients without mutations (30% vs 10%).

Similar data have been reported by Von Hoff et al. In this pilot study, patients from nine different centers were molecularly profiled in a CLIA-certified lab. (Von Hoff et al 2010) A molecular target was detected in 98% of patients and 66 patients were treated with the regimen recommended by the profiling. Patients in the study served as their own control as progression-free survival following the treatment regimen selected by molecular profiling was compared with the progression-fee survival for the most recent regimen on which the patient experienced progression. The molecular-profiling approach to treatment selection resulted in a longer

progression-free survival in 27% of patients compared to the progression-free survival obtained with their most recent therapy.

The University of California San Diego Moores Cancer Center recently reported their initial experience with a molecular tumor board created to review molecular test results. (Schwaederle et al. 2014) There was a median of 4 molecular alterations per patient found by next-generation sequencing. Among the 11 evaluable patients whose treatment was determined by molecular diagnostics, 3 achieved partial responses. The most common reasons for not acting on the molecular diagnostics results were that patients were ineligible for or could not travel to an appropriately targeted clinical trial and/or that insurance would not cover the recommended agent.

Targeting specific molecular alterations with next-generation sequencing and other genomic technologies could transform oncology. In order to facilitate the incorporation of molecular profiling into routine clinical practice, the French National Cancer Institute and French Ministry of Health have established a process to profile patients free of charge nationwide across the health-care system. (Nowak et al. 2012) Decreasing technology costs and increased insurance coverage of sequencing tests will allow for increased availability in other regions. Additional challenges that may limit widespread use of molecular profiling include information processing, genomic medical education and interpretation, cost, and reimbursement. (Thomas et al. 2014) Perhaps the biggest challenge for physicians utilizing molecular profiling is being unable to act on a known alteration because a targeted drug is not available commercially for that indication or in the clinical trial setting. (Munoz et al. 2013) Both the clinical trial system and the system of financial coverage for approved drugs are inadequate, as they were designed for individual drugs being utilized in unselected patient populations. Preliminary profiling results suggest that an individual patient's tumor possesses a unique set of molecular alterations that may require a customized treatment regimen based on the targeted alterations rather than the histologic tumor type. Initial trials have demonstrated improved clinical outcomes in patients receiving treatment regimens matched to known molecular alterations. However, additional trials in this setting are warranted to further identify patient subgroups that may benefit from targeted therapies.

This phase II study will evaluate the preliminary antitumor activity of selected commercially available molecularly matched targeted therapies in patients whose tumors have progressed while receiving or following first line treatment for one of the following four tumor types: (1) non-small cell lung cancer, (2) urothelial carcinoma, (3) non-colon gastrointestinal cancers (including hepatobiliary, pancreatic, and gastroesophageal tumors), and (4) upper aerodigestive tract cancers (including lip, tongue, salivary glands, gum, oral cavity, mouth, tonsils, oropharynx, nasopharynx, nasal cavity, sinus, and larynx tumors). The most common genomic alterations associated with these tumors are summarized in Table 1.

Table 1**: Common Genomic Alterations by Tumor Type**

NSCLC	Urothelial	Non-Colon GI	Upper Aerodigestive

	Carcinoma	Cancers	Tract
AKT1	EGFR	ALK	EGFR
ALK	FGFR1,3	BRAF	FGFR3
BRAF	HER2	EGFR	HER2
DDR2	mTOR	FGFR fusions	HRAS
EGFR	PIK3CA	HER2	KIT
FGFR1	RAS	KRAS	KRAS
HER2	TSC1,2	NRAS	MET
KRAS	VEGF	PDGFRα	PDGFRα
MEK1		PDGFRβ	PI3K
MET		PIK3CA	PTEN
NRAS		PTEN	
PIK3CA		TSC1,2	
PTEN			
RET			
ROS1			

Sourced from My Cancer Genome Website and COSMIC database

Patients will be profiled with next-generation sequencing technology outside of this protocol and will be enrolled based on the results of this profiling. This testing can be tissue or blood. If a patient was not profiled with Foundation One® prior to study enrolment, Sarah Cannon Development Innovations shall use reasonable efforts to collect and send to Foundation Medicine adequate tumor tissue meeting the tissue specimen requirements for Foundation One® for retrospective profiling that will be completed and compared to the profiling report provided at study entry. Patients with the specified tumor types that demonstrate one of the above genomic alterations may be assessed for protocol eligibility and treatment. Patients with a genomic alteration that is not described in Table 1 but is covered by a targeted agent in Table 2

will also be eligible. Non-small cell lung cancer patients with ALK or EGFR mutations should receive targeted treatment as part of standard of care and will not be eligible for this protocol. RAS and BRAF mutations are in the MAPK/ERK pathway and may be targeted with BRAF inhibitors as appropriate.

1.2 Targeted Treatment for Known Genomic Alterations

Table 2 lists the FDA-approved targeted agents that will be utilized in this study as matched therapies for the genomic alterations.

Table 2: FDA-Approved Targeted Agents

Approved Drug	**Targets Listed in Package Insert**	**Manufacturer**	**Recommended Dose**
Regorafenib (Stivarga)	RET, VEGF1-3, KIT, PDGFR-α and β, FGFR1-2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, SAPK2, PTK5, Abl	Bayer	160 mg once daily for the first 21 days of each 28 day cycle
Afatinib (Gilotrif™)	EGFR, HER2, HER4	Boehringer Ingelheim	40 mg once daily
Cabozantinib (Cabometyx™)	MET, VEGFR1-3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, TIE2	Exelixis, Inc	60 mg once daily

All drugs will be administered according to the recommended package insert dose. Dosing will be continuous daily for all drugs except regorafenib, which is dosed for 21 days out of every 28 days. For the purposes of the study, a treatment cycle will be defined as 28 days. Recommended dose modifications for treatment-related toxicities are outlined in the package insert prescribing information. Patients will return to clinic on day 1 of every treatment cycle for evaluation and scans will be performed every 2 cycles for disease assessment. The product package inserts for the individual drugs are included in Appendices G and H.

1.3 Rationale for the Study

With the increased availability of next-generation sequencing, oncologists are beginning to incorporate genomic profiling into the routine care of cancer patients. More than half of all patients will have an actionable genomic alteration in their tumor when profiled, which could help guide the choice of targeted therapy treatment. Multiple targeted agents are now available

for clinical use and numerous additional agents are currently in clinical trials. Several agents that target specific genomic mutations have been approved based on improved treatment outcomes in a population of patients enriched for the specific genomic alteration (eg. crizotinib, vemurafenib, dabrafenib, ceritinib). Preliminary studies also suggest that targeting treatment toward known tumor genomic characteristics improves the chances of disease response with targeted agents. This pilot study will evaluate the preliminary antitumor activity of selected commercially available molecularly matched targeted therapies in patients who have failed first line treatment for one of the following four tumor types: (1) non-small cell lung cancer, (2) urothelial carcinoma, (3) non-colon gastrointestinal cancers, and (4) upper aerodigestive tract cancers.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to:

- Determine the overall response rate (Complete Response [CR] + Partial Response [PR]) in each patient population receiving targeted therapy based on relevant genomic alterations.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the clinical benefit rate (CR + PR + stable disease [SD] ≥ 6 months) in each patient population receiving targeted therapy based on relevant genomic alterations.
- Determine the time to treatment failure (measured from the first day of treatment until the patient is removed from study for toxicity, disease progression, patient choice, or death) in each patient population receiving targeted therapy based on relevant genomic alterations.
- To determine the progression free survival (PFS) in each patient population receiving targeted therapy based on relevant genomic alterations.

3. STUDY PATIENT POPULATION

3.1 Inclusion Criteria

Patients must meet the following criteria in order to be included in the research study:

1. Patients with a histologically or cytologically confirmed diagnosis of one of the following tumor types whose disease has progressed following one line of standard therapy and/or for which no standard treatment is available that has been shown to prolong survival:
   a. Non-small cell lung cancer

b. Urothelial carcinoma
c. Non-colon gastrointestinal cancers (including hepatobiliary, pancreatic, and gastroesophageal tumors)
d. Upper aerodigestive tract cancers (including lip, tongue, salivary gland, gum, oral cavity, mouth, tonsils, oropharynx, nasopharynx, nasal cavity, sinus, and larynx tumors)

2. Patients must have a predefined genomic alteration included in Table 1 that can be targeted with one of the FDA-approved targeted agents listed in Table 2. Patients with a genomic alteration that is not described in Table 1 but is covered by a targeted agent in Table 2 will also be eligible.
3. Patients must have measurable disease as measured by Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 (Appendix E).
4. Patients must have an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A).
5. Age greater than or equal to 18 years.
6. Adequate hematologic function defined as:
   - Absolute neutrophil count (ANC) ≥1500/μL
   - Platelets ≥75,000/μL
7. Adequate liver function defined as:
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x the upper limit of normal (ULN) or ≤ 5.0 X ULN if liver metastases present
   - Total bilirubin ≤1.5 x ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin)
8. Adequate renal function defined as serum creatinine ≤1.5 x the upper limit of normal OR measured or calculated creatinine clearance ≥50 mL/min for patients with creatinine levels greater than or equal to 1.5 x the upper limit of normal.
9. Patients who are therapeutically treated with an agent such as warfarin or heparin will be allowed to receive either regorafenib or afatinib provided that their medication dose and INR/PTT are stable. Close monitoring is mandatory if the patient is receiving anticoagulants. If values are above the therapeutic range the anticoagulant doses should be modified and assessments should be repeated until stable. (See Exclusion Criteria 15 for anticoagulant therapy information for patients receiving cabozantinib).
10. Male patients with female partners of childbearing potential and women patients of childbearing potential are required to use two forms of **acceptable** contraception, including one barrier method, during their participation in the study and for 90 days following last dose of study drug(s). Male patients must also refrain from donating

sperm during their participation in the study and for 90 days after the last dose of study drug (Appendix C).

11. Willingness and ability to comply with study and follow-up procedures.
12. Ability to understand the nature of this study and give written informed consent.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Two or more prior chemotherapy regimens in the metastatic setting.
2. Most recent chemotherapy ≤ 3 weeks and > Grade 1 chemotherapy-related side effects, with the exception of neuropathy (> grade 2 excluded) and alopecia.
3. Use of a study drug or targeted therapy ≤21 days or 5 half-lives (whichever is shorter) prior to the first dose of study treatment. For study drugs for which 5 half-lives is ≤21 days, a minimum of 10 days between termination of the study drug and administration of study treatment is required.
4. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy.
5. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement.
6. Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 2 weeks prior to study entry and there is no evidence of central nervous system disease progression, mild neurologic symptoms, and no requirement for chronic corticosteroid therapy. Enzyme-inducing anticonvulsants are contraindicated.
7. Pregnant or lactating
8. Acute or chronic liver, renal, or pancreas disease.
9. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea Grade ≥2, and malabsorption syndrome).
10. Any of the following cardiac diseases currently or within the last 6 months:
    - Unstable angina pectoris
    - Congestive heart failure (New York Heart Association (NYHA) ≥ Grade 2 [Appendix B])
    - Acute myocardial infarction

- Conduction abnormality not controlled with pacemaker or medication
- Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)
- Valvular disease with significant compromise in cardiac function

11. Inadequately controlled hypertension (i.e., systolic blood pressure [SBP] >180 mmHg or diastolic blood pressure (DBP) >100 mmHg) (patients with values above these levels must have their blood pressure (BP) controlled with medication prior to starting treatment).
12. Thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks) deep vein thrombosis or pulmonary embolism within 6 months of start of treatment.
13. Evidence or history of bleeding diathesis or coagulopathy; any haemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 4 weeks prior to start of treatment.
14. **For patients receiving cabozantinib only**: Do not administer cabozantinib to patients that have high risk or at high risk for severe haemorrhage. Examples include:
    a. The patient has radiographic evidence of cavitating pulmonary lesion(s).
    b. The patient has tumor invading or encasing any major blood vessels.
    c. The patient has had hemoptysis of ≥ 0.5 teaspoon (2.5ml) of red blood within 3 months before the first dose of study treatment.
    d. The patient has experienced clinically significant GI bleeding within 6 months of the first dose of study treatment.
    e. The patient has experienced any other signs indicative of pulmonary hemorrhage within 3 months of the first dose of study treatment.
15. **For patients receiving cabozantinib only**: Do not administer cabozantinib to patients that have high risk or at high risk of perforation or fistula:
    a. The patient has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction.
    b. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose.

       Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose.
    c. The patient has pre-existing fistula of head and neck area.

Note: Treatment areas should be healed with no sequelae from prior radiation therapy that would predispose to fistula formation.

d. The patient has pre-existing osteonecrosis of the jaw.

16. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel). **[Patients receiving cabozantinib only]**
17. Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (< 1 mg/day), and low dose, low molecular weight heparins (LMWH) are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects without radiographic evidence of brain metastasis, who are on a stable dose of LMWH for at least 12 weeks before randomization, and who have had no complications from a thromboembolic event or the anticoagulation regimen.Presence of a non-healing wound, non-healing ulcer, or bone fracture.
18. Patients with phaeochromocytoma.
19. Serious active infection at the time of treatment, or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment.
20. Known diagnosis of human immunodeficiency virus, hepatitis B, or hepatitis C.
21. Presence of other active cancers unless indolent and not requiring therapy. Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.
22. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

3.3 Discontinuation from Study Treatment

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the investigator's discretion)
- Inability of the patient to comply with study requirements
- Patient requests to discontinue treatment
- Patient withdraws consent from the study
- Non-compliance/lost to follow-up
- Pregnancy

After discontinuation from protocol treatment, patients must be followed for adverse events (AEs) for 30 days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve, because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patients' medical records and as a comment in the electronic Case Report Form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v 4.03 at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment in the eCRF.

4. STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, treatment alternatives, side-effects, risks, and discomforts. Human protection committee (Institutional Review Board/Independent Ethics Committee [IRB/EC]) approval of this protocol and consent form is required. Eligible patients who wish to participate in the study will be enrolled into the study.

Registration must occur prior to the initiation of protocol therapy. Patients eligible to participate in the study may be enrolled through the Sarah Cannon Development Innovations Central Enrollment Desk. The enrollment desk may be reached by calling (877) MY-1-SCRI. Registration may be done via fax (866) 699 0258 Monday through Friday, 8:30 a.m. to 4:30 p.m., Central Standard Time. Patient registration will be confirmed via email within 24 hours, or by the next business day.

5. STUDY DESIGN

This four-arm pilot phase II study will evaluate the preliminary antitumor activity of selected commercially available molecularly matched targeted therapies in patients who have failed first line treatment for one of the following tumor types: (1) non-small cell lung cancer, (2) urothelial carcinoma, (3) non-colon gastrointestinal cancers, and (4) upper aerodigestive tract cancers. Patients will be profiled with next-generation sequencing technology results known prior to consideration for enrollment on this protocol. Patients with the specified tumor types demonstrating one of the genomic alterations described in Table 1 may be assessed for protocol eligibility and treatment. Patients with a genomic alteration that is not described in Table 1 but is covered by a targeted agent in Table 2 will also be eligible. All eligible patients will receive one of the FDA-approved targeted agents at the recommended dose outlined in Table 2. Dose modifications will be implemented based on criteria outlined in the product package insert for each individual agent. Patients will be re-evaluated for treatment response after receiving 8

weeks of oral therapy (with the exception of regorafenib which is dosed intermittently for 21 out of every 28 days). Response to therapy will be assigned using RECIST v1.1 (see Appendix E). Patients who have objective response (OR) or stable disease (SD) will continue treatment with re-evaluations every 8 weeks, until the time of tumor progression or intolerable treatment-related side effects. If a patient was not profiled with Foundation One® prior to study enrolment, Sarah Cannon Development Innovations shall use reasonable efforts to collect and send to Foundation Medicine adequate tumor tissue meeting the tissue specimen requirements for Foundation One® for retrospective profiling that will be completed and compared to the profiling report provided at study entry.

A total of 160 patients are planned to be enrolled on the trial (40 patients per study arm).

5.1 Treatment Plan

5.1.1 FDA-Approved Targeted Agents

The FDA-approved targeted agents that will be administered during the study are outlined in Table 2. Study drugs will be provided by the manufacturer and will not be billed to the patient's insurance as the proposed usage is considered off-label for the agent. The treating physician will decide which targeted agent will be prescribed based on the genomic alterations per tumor type and the targets listed in the package insert for each agent that are outlined in Tables 1 and 2. Patients with a genomic alteration that is not described in Table 1 but is covered by a targeted agent in Table 2 will also be eligible. The Medical Monitor will verify the genomic alteration and prescribed targeted agent when the patient is registered for the trial.

All patients entering this study will receive one of the targeted agents orally either daily continuously at the prescribed dose listed in Table 2 (except for regorafenib which is dosed daily for 21 out of every 28 days). Patients will be instructed to take the medication with or without food as directed in the product package insert. The time of day for administration of study drug should be consistent.

If the patient misses a dose of study drug, the patient should skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking the study medication, the patient should be instructed not to retake the dose. Patients should take the next scheduled dose of study drug. If vomiting persists the patient should contact the investigator.

No routine prophylactic antiemetics will be given. However, antiemetics may be administered for the treatment of nausea and vomiting when they occur, and may be given prophylactically afterwards.

Study drug compliance will be assessed by pill counts on Day 1 of each cycle. The research staff will count and document the amount of study drug taken and returned by the patient.

5.2 Treatment Duration

Patients will continue to receive treatment until disease progression, the patient requests to discontinue treatment, or the treating physician feels it is in the best interest of the patient to discontinue.

For the purposes of the study, a treatment cycle is defined as 28 days. Patients will be evaluated for toxicity at the start of each cycle. Every 2 cycles restaging will occur with imaging, laboratory tests will be assessed as defined in Appendix E.

5.3 Concomitant Medications

Patients will be instructed not to take any additional medications during the course of the study without prior consultation with the research team. At each visit, the patient will be asked about any new medications he is taking or has taken after the start of the study drug.

5.3.1 Permitted Concomitant Medications

No routine prophylactic antiemetics will be given. However, antiemetics may be administered for the treatment of nausea and vomiting when they occur, and may be given prophylactically afterwards. Anti-emetics may be administered according to standard practice guidelines.

Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following:

- Bisphosphonate use, as recommended according to practice guidelines
- Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor use, as recommended according to practice guidelines

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator.

5.3.2 Prohibited Concomitant Medications

The following treatments are prohibited or should be used with caution while in this study:

- No other investigational therapy should be given to patients. No anticancer agents other than the study medications should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study.
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.
- Regorafenib and cabozantinib are metabolized by the cytochrome P450 (CYP) system. Therefore, drugs that are strong inducers or inhibitors of CYP3A4 should be avoided. These drugs are listed in Appendix F. Other potential drug interactions are described in the

product package inserts for the individual agents and should be reviewed prior to the start of study treatment.

- Afatinib is a substrate of the P-glycoprotein transporter (MDR1). Caution should be exercised when combining afatinib with P-gp modulators. Below are the lists of potent P-gp inhibitors and inducers. Additional information can be found in the afatinib product package insert in Appendix H.

  Potent P-glycoprotein Inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, nelfinavir, ritonavir, quinidine, ranolazine, saquinavir, tacrolimus, ticagrelor, verapamil.

  Potent P-glycoprotein Inducers: carbamazepine, phenytoin, rifampicin, St John's Wort, phenobarbital salt, tipranavir, ritonavir.

6. DOSE MODIFICATIONS

If toxicity occurs, the toxicity will be graded utilizing the NCI CTCAE v4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

Doses of study drug will be modified based on hematologic and non-hematologic toxicity as outlined in the product package insert for each FDA-approved targeted agent. If dose reductions are necessary, they will be permanent for the remainder of the treatment. Any patient requiring a toxicity-related dose delay of more than 28 days from the intended day of the next scheduled dose must be discontinued from the study.

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study is shown in Appendix D. The baseline physical examination, medical history, ECOG PS, and laboratory assessments should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated. A pregnancy test must be performed within 72 hours of Cycle 1 Day 1. CT scans should be performed ≤28 days prior to initiation of treatment, as should tumor markers, if appropriate.

7.2 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at screening:

- Written informed consent
- Medical history
- Physical examination, measurements of height (first visit), weight, and vital signs (resting heart rate, blood pressure [BP], respiratory rate, and oral temperature)
- ECOG performance status (see Appendix A)
- Concomitant medication review
- CBC (complete blood count) including hemoglobin, hematocrit, WBC with 3-part differential and platelets
- CMP to include: glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), alkaline phosphatase (ALT), AST, ALT, total bilirubin, total protein, and albumin plus magnesium.
- Coagulation analysis: prothrombin time (PT)/International Normalization Ratio (INR) and partial thromboplastin time (PTT)
- Serum or urine pregnancy test in women of child-bearing potential only (must be performed within 72 hours of Cycle 1 Day 1)
- CT scans of chest, abdomen and pelvis.
- Tumor markers (if applicable)
- Head CT or MRI scan **[Required for patients with a history of treated brain metastases]**

7.3 Study Treatment Assessments

7.3.1 Day 1 of each cycle

- Update of medical history
- Physical examination, including measurement of weight and vital signs
- ECOG performance status
- Adverse event (AE) assessment
- Concomitant medication review
- Study drug compliance review (Cycle 2 and beyond)
- CBC, including 3-part differential and platelets (may be done up to 72 hours prior to treatment)

- CMP plus magnesium (may be done up to 72 hours prior to treatment)
- Serum or urine pregnancy test in women of child-bearing potential only
- Tumor markers (if applicable)
- CT scans of chest, abdomen, and pelvis (if abnormal at baseline) **[Every 2 cycles]**

7.3.2 Day 15 of Cycle 1 Only

- AE assessment
- Concomitant medication review
- Vital signs
- Study drug compliance review
- CBC, including 3-part differential and platelets
- CMP plus magnesium

7.4 End of Study Treatment

The follow-up evaluations required after treatment ends due to completion of the planned study treatment period, disease progression, or once the patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the study physician are specified in Appendix D.

If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no study treatment is administered, that visit may fulfil the End-of-Treatment Visit.

After withdrawal from or completion of protocol treatment, patients must be followed for AEs for 30 calendar days after the last dose of study drug. The following assessments will be performed:

- Update of medical history
- Physical examination, including measurement of weight and vital signs
- ECOG performance status
- AE assessment
- Concomitant medication review
- Review study drug compliance with the patient, and collect unused study drug
- CBC, including 3-part differential and platelets
- CMP plus magnesium

Patients who discontinue study treatment prior to the occurrence of disease progression will be followed for disease assessment only every 3 months (±1 month) from the date of last dose of study drug until disease progression.

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

8.1 FDA-Approved Targeted Agents

Study Drug	Dosage Form and Strength	Manufacturer
Regorafenib	40 mg tablet	Bayer
Afatinib	40 mg, 30 mg, and 20 mg tablets	Boehringer Ingelheim
Cabozantinib	20 mg, 40 mg and 60 mg tablets	Exelixis

8.1.1 Labeling, Packaging, and Supply

The study drugs described in Section 8.1 will be supplied to Sarah Cannon Research Institute by the manufacturers.

At each visit, patients will be dispensed sufficient supplies until the next visit. Study drug compliance will be assessed at each patient visit. The research staff will count and document the amount of study drug taken and returned by the patient.

The immediate packaging will contain a statement to conform with U.S. Food and Drug Administration (FDA) Investigational New Drug (IND) requirements as follows: Caution: New Drug - Limited by Federal (or United States) law to investigational use.

All study drugs must be kept in a secure place at controlled room temperature. Storage conditions for each study drug are included on the product label and in the product package inserts included in Appendices G and H.

8.1.2 Precautions and Risks Associated with FDA-Approved Targeted Agents

Precautions and risks are described in the product package inserts for each drug included in Appendices G and H.

8.2 Accountability for All Study drugs

The Principal Investigator (or designee) is responsible for accountability of all used and unused study drug supplies at the site.

At the end of the study, all Sarah Cannon Development Innovations Drug Accountability Record Form(s) will be completed by the site and sent to the Sarah Cannon Development Innovations Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by the Sponsor or its representative. Please contact Sarah Cannon Development Innovations regarding disposal of any study drug.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (see Appendix E). Lesions are either measurable or non-measurable according to the criteria. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This four-arm pilot phase II study will evaluate the preliminary antitumor activity of selected commercially available molecularly matched targeted therapies in patients who have failed first line treatment for one of the following tumor types: (1) non-small cell lung cancer, (2) urothelial carcinoma, (3) non-colon gastrointestinal cancers, and (4) upper aerodigestive tract cancers. Patients will be profiled with next-generation sequencing technology results known prior to consideration for enrolment on this protocol. Patients with the specified tumor types demonstrating one of the genomic alterations described in Table 1 may be assessed for protocol eligibility and treatment. Patients with a genomic alteration that is not described in Table 1 but is covered by a targeted agent in Table 2 will also be eligible. All eligible patients will receive one of the FDA-approved targeted agents at the recommended dose outlined in Table 2.

Sample Size Considerations

The design of this trial uses an exact single-stage design for each of the four arms. (A'Hern 2001) For this investigation, it has been determined that an ORR (CR + PR) of 10% or worse has low activity in line with standard of care. An ORR of 25% (or better) is considered to indicate interesting activity. Using a one-sided alpha of 5% and power of 80%, 40 evaluable patients will be required in each arm. A minimum of 8 responders in a particular arm would indicate that the corresponding tumor type would be worthy of further investigations.

10.2 Data Analysis

Descriptive statistics, including mean, median, standard deviations and ranges for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time to events endpoints will be reported using Kaplan-Meier estimates, with 95% confidence intervals (CI) for median time to event.

10.2.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized. Data to be tabulated will include demographic features such as age, sex and race, as well as disease-specific characteristics.

The number and percentages of patients screened, treated, and withdrawn from treatment/study for any reason will be presented overall and also by study arm.

10.2.2 Efficacy Analysis

All efficacy analyses will be performed using the Intent-To-Treat Population.

- Overall Response Rate (ORR) is defined as the proportion of patients with confirmed complete response (CR) or partial response (PR (i.e. 2 CRs or PRs at least 4 weeks apart) according to the RECIST v1.1.

- Clinical Benefit Rate (CBR) is defined as the proportion of patients with CR, PR or SD ≥ 6 months according to the RECIST v1.1.

    - For ORR and CBR, patients without a post-baseline tumor assessment will be classed as not evaluable (NE) and considered as non-responder.

- Time to treatment failure (TTF) is measured from the first day of treatment until the patient is removed from study for toxicity, disease progression, patient choice, or death.

- Progression Free Survival (PFS) is defined as the time from the first day of study drug administration (Day 1) to disease progression as defined by the RECIST v1.1, or death on study. Patients who are alive and free from disease progression will be censored at the date of last tumor assessment.

For ORR and CBR, the estimates and the associated 95% CI (based on the Clopper-Pearson method) in each treatment group will be calculated.

For PFS, Kaplan-Meier curves will be generated and the median time to event and the associated 95% CI will be provided.

10.2.3 Safety Analysis

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy, and will be graded according to NCI CTCAE v. 4.03. A copy of CTCAE scoring system may be downloaded from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), and summarized using system organ class and preferred term by treatment arm for all patients in the

Safety Population. In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented by treatment arm.

Other safety endpoints including laboratory results, vital signs and ECG findings will be summarized for all patients in the Safety Population

10.3 Analysis Time Points

10.3.1 Final Analysis

The final analysis of the study will occur when the required number of response evaluable patients has been reached in each treatment arm.

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and Serious Adverse Events (SAEs), measurement of protocol-specified laboratory tests and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for recognizing and reporting AEs to the Sarah Cannon Development Innovations Safety Department. It is the Sponsor's responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRB/EC according to the policies of that IRB/EC.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1 Definitions

11.1.1 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also known as adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgement about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, dose or including overdose.

11.1.2 Serious Adverse Event

An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:

- **Death**
- **A life-threatening AE**
- **Inpatient hospitalization of at least 24-hours or prolongation of existing hospitalization**
- **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
- **A congenital anomaly/birth defect**

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" AE, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. Seriousness serves as the guide for defining regulatory reporting obligations. "Serious" is a regulatory definition and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

11.1.3 Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is a reason to conclude that the drug caused the event.

11.1.4 Suspected Adverse Reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

11.1.5 Recording and Reporting of Adverse Events

Recording of Adverse Events

All AEs of any patient during the course of the research study will be recorded in the eCRF, and the investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes a serious adverse event (SAE) or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the investigator's assessment of causality (i.e., the relationship to the study treatment[s]). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE v4.03, and changes will be documented.

If the AE is serious, it should be reported immediately to Sarah Cannon Development Innovations Safety Department. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms; abnormal test findings; changes in physical examination; hypersensitivity; and other measurements that occur will be reported as an AE, and collected on the relevant eCRF screen.

Test findings will be reported as an AE if: the test result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or test findings require additional testing or surgical intervention, a test result or finding is associated with accompanying symptoms, or a test result is considered to be an AE by the investigator.

Reporting Period for Adverse Events

All AEs regardless of seriousness or relationship to the FDA-approved targeted agents (called study treatment), spanning from the start of study treatment, until 30 calendar days after discontinuation or completion of study treatment as defined by the clinical study for that patient, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF screen.

After 30 days of completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

11.1.6 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

> **YES:** There is a plausible temporal relationship between the onset of the AE and administration of the study medication, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies, and/or the AE follows a known pattern of response to the study drug, and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
>
> **NO:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

11.2 Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating investigator as serious require expeditious handling and reporting to Sarah Cannon Development Innovations Safety Department in order to comply with regulatory requirements. Determination of life-threatening or serious is based on the opinion of either the Sponsor or the Investigator.

Serious AEs may occur at any time from the start of study treatment through the 30 day follow-up period after the last study treatment. **The Sarah Cannon Development Innovations Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.**

To report a SAE, the SAE Report Form should be completed with the necessary information.

The SAE report should be sent to Sarah Cannon Development Innovations Safety Department via fax or e-mail using the using the following contact information (during both business and non-business hours):

Sarah Cannon Development Innovations Safety Department

Safety Dept. Fax #: 1-866-807-4325

Safety Dept. Email: CANN.SAE@SCRI-Innovations.com

Transmission of the SAE report should be confirmed by the site personnel submitting the report, and a copy of the confirmation should be retained with the patient's records.

The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product (s), if available. Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to Sarah Cannon Development Innovations Safety Department as soon as it is available; these reports should be submitted using the Sarah Cannon Development Innovations SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

The Sponsor Safety department (SCRI Innovations) shall report all SAEs and non-serious AEs which are relevant to a reported SAE by FAX using MEDWATCH form with accompanying BI cover letter form to the BI Unique Entry Point as detailed below in accordance with the following timelines as specified in the pharmacovigilance agreement:

- Within five (5) calendar days upon receipt of initial and follw-up SAEs containing at least one fatal or immediately life-threatening event;
- Within ten (10) calendar days upon receipt of any other initial and follow-up SAEs.

Boehringer Ingelheim Pharmaceuticals, Inc.

900 Ridgebury Road

Ridgefield, CT 06877

FAX: 1-203-837-4329

Expedited Reporting by Investigator to Pharmaceutical Companies Providing Drug Supply (Bayer, Boehringer Ingelheim, or Exelixis)

Expedited reporting will be completed by the Sponsor Safety Department of Sarah Cannon Development Innovations Safety Department. Expedited reports will not be sent to Bayer, Boehringer Ingelheim, or Exelixis by the Site investigator. SAE reports are submitted by the participating site investigator within 24 hours of awareness to the Sarah Cannon Development Innovations Safety Department. The Expedited Reporting responsibilities belong to Sarah Cannon Development Innovations Safety Department. Upon fax confirmation receipt from the submission of the expedited report, a copy will be forwarded to Bayer, Boehringer Ingelheim, or Exelixis.

Drug Safety and Pharmacovigilance Contact Information:

Bayer Healthcare Pharmaceuticals Email at DrugSafety.GPV.US@Bayer.com or 973-709-2185 (FAX).

Boehringer Ingelheim Pharmaceuticals 1-203-837-4329 (FAX).

Exelixis at drugsafety@exelixis.com (e-mail) or (650) 837-7392.

11.3 Recording of Adverse Events and Serious Adverse Events

11.3.1 Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF screen). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as an SAE.

11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF screen.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF screen.

11.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF screen.

Abnormal laboratory values will be reported as an AE if: the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms, or a laboratory result is considered to be an AE by the investigator.

11.3.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "Study Discontinuation" eCRF screen. All other on study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the Sarah Cannon Development Innovations Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and Adverse Event screen of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF Adverse Event screen. During post-study survival follow-up, deaths attributed to progression of disease will be recorded only on the "After Progressive Disease Follow-Up" eCRF screen.

11.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as an SAE to the Sarah Cannon Development Innovations Safety Department.

11.3.6 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History eCRF screen. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.7 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria. New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.3.8 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form should be completed and faxed to the Sarah Cannon Innovations Safety Department. Sarah Cannon Development Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to Sarah Cannon Development Innovations Safety Department.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the Sarah Cannon Development Innovations Safety Department immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

11.3.9 FDA-Approved Targeted Agent Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Sarah Cannon Development Innovations Safety Department no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting if the overdose is symptomatic.

For information on how to manage an overdose of the FDA-approved targeted agents, see the product package insert for each individual agent included in Appendices G and H.

11.4 Sarah Cannon Development Innovations Safety Department Serious Adverse Event Reporting

Sarah Cannon Development Innovations Safety Department will forward SAE information to the appropriate pharmaceutical company within 1 business day of Sarah Cannon Development Innovations Safety Department becoming aware of the SAE.

Sarah Cannon Development Innovations Safety Department is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with International Conference on Harmonization (ICH) guidelines, FDA regulations, and/or local regulatory requirements.

11.4.1 Sarah Cannon Development Innovations Safety Department Assessment of Unexpected

Sarah Cannon Development Innovations is responsible for assessing an AE or SAR as "unexpected".

An AE or SAR is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the IB (or current USPI)
- Event(s) is not listed at the specificity or severity that has been observed
- An event(s) is not consistent with the General Investigative Plan or in the current application
- Includes AEs or SAR that may be anticipated from the pharmacological properties of the study drug, or that occur with members of the drug class, but that have previously been observed under investigation.

When applicable, an unexpected AE may also apply to an event that is not listed in the current USPI or an event that may be mentioned in the USPI, but differs from the event because of greater severity or specificity.

Known as Suspected Unexpected Serious Adverse Reactions (SUSAR), these events suspected (by the Investigator or Sponsor) to be related to the study drug, are unexpected (not listed in the Investigator's Brochure [IB] or USPI), and are serious (as defined by the protocol) and require expedient submission to relevant health authorities within 7 days (fatal or life-threatening event) or 15 days (all serious events), or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected AEs are those events that are listed or characterized in the USPI or current IB.

11.4.2 Sponsor Reporting for Clinical Studies under an Investigational New Drug Application

All written IND Safety Reports submitted to the FDA by the Sarah Cannon Development Innovations Safety Department must also be faxed to pharmaceutical company (ies) that are supporting the study with either funding or drug supply:

- Reports for regorafenib should be sent to Bayer Healthcare Pharmaceuticals at: DrugSafety.GPV.US@bayer.com (electronic mailbox) or (973) 709-2185 (FAX)
- Reports for afatinib should be sent to Boehringer Ingelheim at: (203) 837-4329 (FAX)

- Reports for cabozantinib should be sent to Exelixis at : drugsafety@exelixis.com (e-mail) or (650) 837-7392.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Study Monitoring, Auditing, and Inspecting

The investigator will permit study-related monitoring, quality audits, and inspections by the Sponsor or its representative(s), government regulatory authorities, and the IRB/EC of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable study-related facilities. The investigator will ensure that the study monitor or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At the Sponsor's discretion, Source Document Verification (SDV) may be performed on all data items or a percentage thereof.

Participation as an investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the Sponsor or its representative(s), or the pharmaceutical companies providing drug supply for the study.

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

13.1 Institutional Review Board Approval

The clinical study protocol, informed consent form (ICF), Patient Information Sheet (PIS), product package insert, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going, IRB study review. The Principal Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for the individual FDA-approved targeted agents will be prepared by the Sponsor or its representative as required, for distribution to the Investigator(s) and submission to the relevant IRB.

13.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

13.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form (ICF).

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

13.3.1 Confidentiality

13.3.1.1 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information

- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of the Sponsor, the regulatory authorities and the IRB/EC direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients in the eCRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

13.3.1.2 Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the Sarah Cannon Development Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub investigator, Sarah Cannon Development Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

13.4 Financial Information

The finances for this clinical study will be subject to a separate written agreement between the Sarah Cannon Development Innovations, LLC and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor. All amendments require review and approval of all pharmaceutical companies and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable, and IRB approval obtained, and specifically when an increase to dosing or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment approval from IRB and/or FDA or other regulatory authorities includes, but are not limited to, the following:

- Change to study design
- Risk to patient
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

14.2 Documentation Required to Initiate the Study

Before the study may begin certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

Sarah Cannon Development Innovations
Regulatory Department
1100 Charlotte Avenue, Suite 600
Nashville, TN 37203

Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current Curricula Vitae for the principal investigator and any associate investigator(s) who will be involved in the study
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB-approved consent form (and patient information sheet, if applicable) containing permission for audit by representatives of Sarah Cannon Development Innovations, the IRB, and the FDA and other regulatory agencies (as applicable)
- Financial disclosure forms for all investigators listed on Form FDA 1572 (if applicable)
- Site qualification reports, where applicable
- Verification of Principal Investigator acceptability from local and/or national debarment list(s)

14.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patient's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG

traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The Principal Investigator and each study staff member is responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or investigator study file [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, copies of completed eCRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

The Sponsor shall maintain adequate product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRFs, medical records), all original, signed ICFs, and copies of all eCRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor will notify the investigator(s)/institutions(s) when the study-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the study, both the Sponsor and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by the Sponsor (Sarah Cannon Development Innovations) throughout the study, and will be held by the Sponsor at the conclusion of the study.

14.4 Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable the Sponsor to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, initials and date of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Sarah Cannon Development Innovations and replaced instead with the patient number and patient's initials. The investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested in the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The investigator will sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Principal Investigator, once all data for that patient is final.

14.5 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication process.

Inclusion of the investigator in the authorship of any multicenter publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the study. The investigator acknowledges that the study is part of a multicenter study and agrees that any publication by the investigator of the results of the study conducted at research site shall not be made before the first multicenter publication. In the event there is no multicenter publication within fifteen (15) months after the study has been completed or terminated at all study sites, and all data has been received, the investigator shall have the right to publish its results from the study, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the investigator shall withhold any publication or presentation an additional

sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any Sarah Cannon Development Innovations Confidential Information from all publications.

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