NCI Protocol #: **NCT02795858**

DF/HCC Protocol #: 16-072

TITLE: A Phase II Study of Ramucirumab with Somatostatin Analog Therapy in Patients with Advanced, Progressive Carcinoid Tumors

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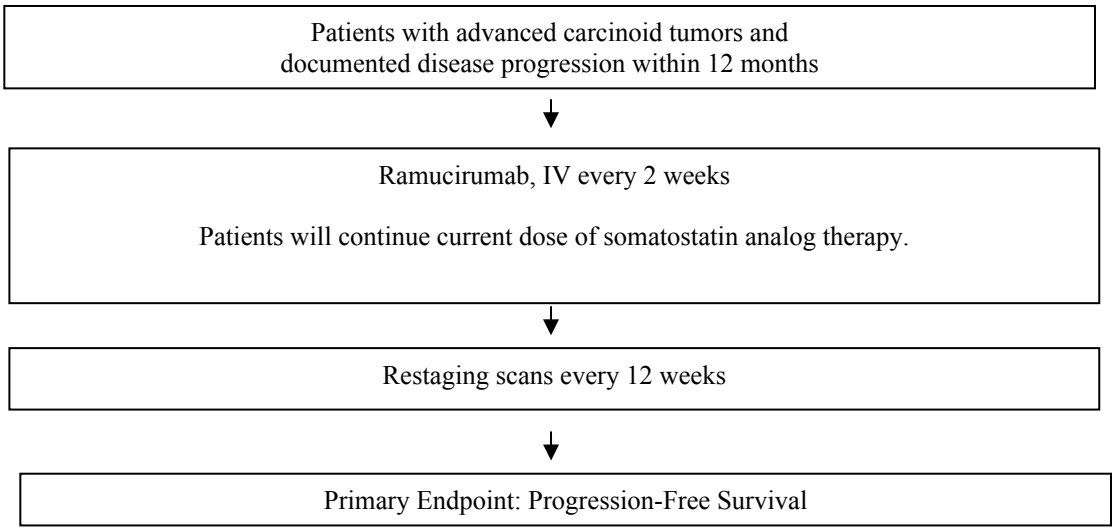
Agent: Ramucirumab (Eli Lilly)

Study Exempt from IND Requirements per 21 CFR 312.2(b).

Protocol Type / Version # / Version Date: *Original / Version #3 /February 1, 2021*

SCHEMA


Patients with advanced carcinoid tumors and documented disease progression within 12 months
Ramucirumab, IV every 2 weeks
Patients will continue current dose of somatostatin analog therapy.
Restaging scans every 12 weeks
Primary Endpoint: Progression-Free Survival

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1. OBJECTIVES

1.1 Study Design

This is an open-label phase II study to evaluate the safety and efficacy of ramucirumab in patients with advanced carcinoid tumors.

1.2 Primary Objectives

- To assess the progression-free survival duration of patients with advanced, progressive carcinoid tumors treated with ramucirumab in combination with somatostatin analog therapy.

1.3 Secondary Objectives

- To determine the safety and tolerability of ramucirumab in combination with somatostatin analog therapy in patients with advanced carcinoid tumors.
- To assess the overall radiographic and biochemical response rate associated with ramucirumab in combination with somatostatin analog therapy in patients with advanced carcinoid tumors
- To assess the overall survival duration of patients with advanced, progressive carcinoid tumors treated with ramucirumab in combination with somatostatin analog therapy.

2. BACKGROUND

2.1 Overview of Neuroendocrine Tumors

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies characterized by variable but most often indolent biologic behavior. Well-differentiated NETs can be broadly classified as either carcinoid or pancreatic NET.

The treatment of advanced NET has undergone a rapid evolution in recent years. In addition to controlling symptoms related to hormone hypersecretion, somatostatin analogs have also been shown to control tumor growth. In the PROMID trial, patients with advanced small bowel carcinoid tumors receiving octreotide had a longer median time to tumor progression compared with those receiving placebo (14.3 vs. 6 months).(Rinke, Muller et al. 2009) Further support for the antiproliferative effect of somatostatin analogs in patients NET was demonstrated in the CLARINET trial, a randomized, placebo-controlled phase III trial evaluating the antiproliferative effects of lanreotide in patients with advanced well- or moderately-differentiated, non-functioning gastroenteropancreatic NETs, including both gastrointestinal NET and pancreatic NET. Patients receiving lanreotide had improved progression-free survival (PFS) compared to those receiving placebo (median not reached vs. median of 18 months).(Caplin, Pavel et al.

2014)

Agents targeting the VEGF- and mTOR-pathway signaling pathways are also active in the treatment of NET. In advanced pancreatic NET, independent randomized, placebo-controlled studies of everolimus and sunitinib demonstrated clear improvements in progression-free survival (PFS), leading to the approval of both agents for this indication.(Raymond, Dahan et al. 2011, Yao, Shah et al. 2011) In advanced carcinoid tumors, however, there remains no approved drug for tumor control, and the development of effective systemic therapy for this patient population represents a clear and unmet medical need.

VEGF Inhibition in Carcinoid Tumors

Several studies suggest that vascular endothelial growth factor (VEGF) pathway inhibition is a promising approach in treating patients with advanced carcinoid tumors. A key role for angiogenesis and VEGF pathway signaling in NET has been suggested by clinical observations that NET are vascular tumors. Additionally, pre-clinical studies have demonstrated that NET have increased expression of VEGF, VEGF receptor-2 (VEGFR-2), and other growth factor receptors including platelet-derived growth factor receptors (PDGFRs) α and β, stem-cell factor receptor (c-kit).(Fjallskog, Lejonklou et al. 2003, Hansel, Rahman et al. 2003, Fjallskog, Hessman et al. 2007, Bowen, Silva et al. 2009, Silva, Bowen et al. 2011)

The VEGF pathway inhibitors bevacizumab, sunitinib, sorafenib, and pazopanib have been evaluated in advanced carcinoid tumors in the phase II setting.(Hobday, Rubin et al. 2007, Kulke, Lenz et al. 2008, Yao, Phan et al. 2008, Phan, Yao et al. 2010) These drugs have shown low radiographic response rates, but a relatively high rate of disease stabilization and encouraging median progression-free survival durations (8-14 months).

We have evaluated the prognostic significance of expression of VEGF pathway components, including VEGF-A, VEGFR-1, and VEFGR-2, in NET (Fig 1) and found that expression of VEGFR-2 appears to be an adverse prognostic factor associated with shorter overall survival (Fig 2).

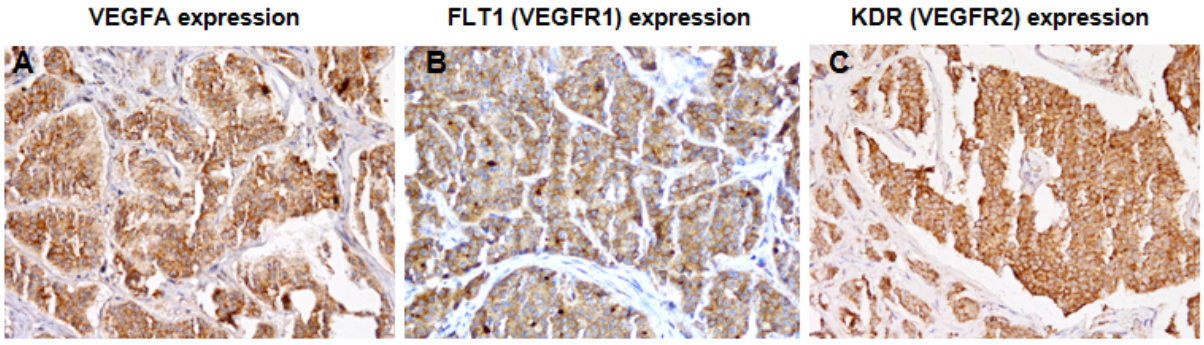

Figure 1: Expression of VEGF-A, VEGFR-1 and VEGFR-2 by immunohistochemistry.

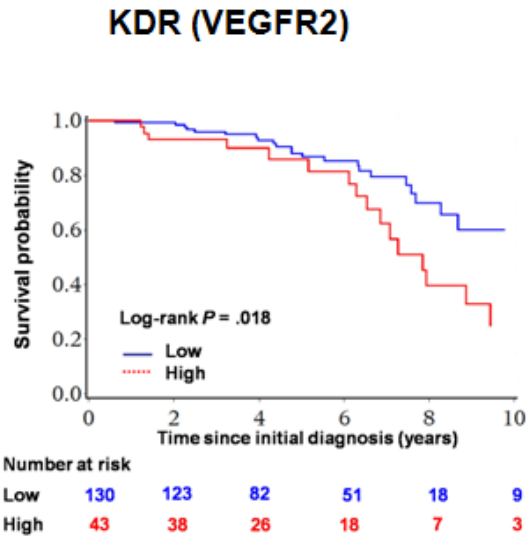

Figure 2: Overall survival of patients with NET according to VEGFR2 expression.

2.2 IND Agent

Ramucirumab has been previously evaluated as monotherapy in separate clinical studies, and a recommended schedule and dose range for monotherapy has been determined. Detailed information about the characteristics of ramucirumab is provided in the Investigator's Brochure (IB). The following sections provide a summary of the information most relevant to this phase II study.

2.2.1 Ramucirumab

Mechanism of action:
Ramucirumab (IMC-1121B [LY3009806]) is a human receptor-targeted monoclonal antibody that specifically binds VEGF Receptor 2. The binding of ramucirumab to VEGF Receptor 2 prevents its interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D). As a result, ramucirumab inhibits ligand-stimulated activation of VEGF Receptor 2and its downstream intracellular signaling components, including Erk1/Erk2, neutralizing ligand induced proliferation and migration of human endothelial cells.

Pharmacokinetics:
Trough concentrations (or minimum concentrations [Cmin]) were collected in two Phase 3 studies (REGARD and RAINBOW) in patients with gastric cancer. Following the recommended clinical dose regimen, 8 mg/kg every 2 weeks, observed Cmin values were similar between

REGARD and RAINBOW, as noted in the table below (Investigator's Brochure, Table 6.1). The geometric mean observed trough values were approximately 50 ug/mL and approximately 60 to 70 ug/mL before the fourth and seventh doses, respectively.

Table 6.1. Summary of Observed Ramucirumab Trough Concentrations for Patients with Advanced Gastric Cancer Following Administration of 8 mg/kg of Ramucirumab Every 2 Weeks as an IV Infusion over Approximately 1 Hour Alone (REGARD) or in Combination with Paclitaxel (RAINBOW)

	Trough[a] Serum Concentrations (µg/mL)			
Dose Number	4		7	
	REGARD	RAINBOW	REGARD	RAINBOW
n_{PK}	53	203	34	142
Geo Mean	49.5	45.0	74.4	62.8
Geo CV%	81	50	58	47

Abbreviations: CV% = percentage coefficient of variation; Geo = geometric; IV = intravenous; n_{PK} = number of pharmacokinetic observations included in calculation.

a Trough concentrations were obtained prior to Doses 4 and 7. They also represent C_{min} following Doses 3 and 6.

Pharmacokinetic data were from pooled from 8 studies including 497 patients with various malignancies for a population pharmacokinetic (PopPK) analysis. In these studies, ramucirumab was administered as a 1-hour I.V. infusion, at either 8 mg/kg once every 2 weeks on a 14- or 28-day cycle, or 10 mg/kg every 3 weeks on a 21-day cycle. The geometric mean (percentage coefficient of variation [CV%]) of PopPK model-derived estimates of ramucirumab clearance (CL), volume of distribution at steady state (Vss) and terminal half-life (t1/2) were 0.0140 L/h (29.8%), 5.5 L (14.4%), and 15 days (24.1%), respectively. These parameter estimates were consistent with those observed with other human monoclonal IgG1 (Keizer et al. 2010) antibodies. Results from the PopPK analyses indicate that the PK of ramucirumab following 8- and 10-mg/kg dose administrations were dose linear (absolute dose range: 169 to 1234 mg) and time independent.

Weekly doses of ramucirumab ranging from 2 to 16 mg/kg were evaluated in a Phase 1 study: I4TIE- JVBM [IMCL CP12-0401]. A maximum tolerated dose (MTD) for weekly dosing was identified as 13 mg/kg (2 dose-limiting toxicities [DLTs] were observed in patients receiving the 16-mg/kg weekly dose: Grade 3 deep vein thrombosis and Grade 3 hypertension). Preliminary activity was observed across a range of doses, including the 2-mg/kg dose. Pharmacokinetic results from this study suggested that, as with other recombinant human IgG1 monoclonal antibodies targeting cell membrane-expressed antigens, ramucirumab exhibited nonlinear PK characteristics.

Apparent nonlinear PK profiles were observed between 2 and 8 mg/kg; PK profiles appeared to be linear at and above 8 mg/kg, suggesting saturation of the target mediated (VEGF Receptor 2) clearance pathway. Every-2-week (6 to 10 mg/kg) and every-3- week (15 to 20 mg/kg) dose regimens were evaluated in an additional dose-ranging study (Study I4T-IE-JVBN [IMCL CP12-0402]). No MTD was identified for every-2-week or every-3-week dosing; all dose regimens were well tolerated, and preliminary evidence of clinical efficacy was observed across a range of dose/schedule cohorts.

Clinical Experience and Activity:

Ramucirumab has been studied and/or continues to be investigated in ongoing clinical studies for the indications as indicated in the Investigator's Brochure. As of 31 December 2013, ramucirumab or ramucirumab/placebo has been administered either as a single agent or in combination with various antineoplastic agents to approximately7000 patients with different oncologic conditions in Phase 1/1b, Phase 2, and Phase 3 clinical trials.

Ramucirumab demonstrated significant and clinically meaningful benefit in overall survival (OS) as a single agent at a dose of 8 mg/kg every 14 days in patients with advanced gastric cancer in the REGARD study, a randomized Phase 3 trial of ramucirumab monotherapy with best supportive care [BSC] versus placebo with best supportive care.(Fuchs, Tomasek et al. 2014) Ramucirumab also has shown clinical efficacy in patients with gastric cancer in combination with paclitaxel in a phase III study of paclitaxel with ramucirumab compared with paclitaxel with placebo (RAINBOW).(Wilke, Muro et al. 2014) A Phase 3 trial (ROSE) examining the combination of ramucirumab with docetaxel in previously untreated metastatic breast cancer failed to meet its primary endpoint of investigator-assessed progression-free survival (PFS). In ROSE, while investigator-assessed PFS numerically favored ramucirumab, this difference was not statistically significant.(Mackey, Ramos-Vazquez et al. 2015)

Please refer to the current version of the Investigator's Brochure for updated information regarding the clinical experience and activity of ramucirumab.

Adverse Events:

As of 31 December 2013, AE information was available for 2485 patients receiving ramucirumab drug product (DP) on 7 Phase 1/1b studies, 18 open-label or unblinded Phase 2 studies, and 3 completed Phase 3 studies, including monotherapy and combination therapy with cytotoxic chemotherapy agents. Placebo-controlled blinded clinical trials are ongoing (1 Phase 2 study, 3 Phase 3 studies); unblinded safety data for these studies are not available. Detailed AE information based on a review of Phase 1/1b, Phase 2, and completed Phase 3 clinical studies of ramucirumab DP (N=2485) are available in the Investigator Brochure.

Adverse drug reactions (ADRs; AEs for which a causal relationship to the investigational drug was considered at least possible) of special interest include AEs which have been associated with antiangiogenic agents and therapeutic monoclonal antibodies and include the following categories: infusion-related reaction (IRR), hypertension, proteinuria, arterial thromboembolic events (ATEs), venous thromboembolic events (VTEs), bleeding/hemorrhagic events, gastrointestinal (GI) perforation, and congestive heart failure (CHF) when used in combination with mitoxantrone or following prior anthracycline therapy.

Infusion-related reaction is considered an adverse event of special interest (AESI), as it has been observed in association with other approved and investigational therapeutic monoclonal antibodies. With the exception of liver injury/liver failure, the AESIs discussed are potentially associated with other agents that inhibit VEGF- or VEGF Receptor 2-mediated angiogenesis.

Some AESIs also have been reported in clinical trials of ramucirumab DP, although in some instances a causal association with ramucirumab DP could not be clearly established. Liver failure and/or other significant liver injury events were included as an AESI in August 2012, following the independent data monitoring committee (IDMC) recommendations in an ongoing Phase 3 study in patients with advanced hepatocellular carcinoma (HCC; Study I4T-IE-JVBF [IMCL CP12-0919; REACH]).

Animal studies have not been specifically conducted to evaluate the effect of ramucirumab on female reproduction and fetal development, and there are no studies in pregnant women.

Please refer to Section 7 or the protocol and the current version of the Investigator's Brochure for updated information regarding the adverse events associated with ramucirumab.

2.3 Rationale

Ramucirumab is a fully human monoclonal antibody targeting VEGFR-2 that prevents ligand binding and receptor-mediated pathway activation. In light of pre-clinical data demonstrating prognostic significance for VEGFR-2 expression in NET and preliminary evidence of activity of VEGF pathway inhibitors in carcinoid, we propose a 43 patient single-arm phase II study of ramucirumab in advanced carcinoid tumors. Because somatostatin analogs also have antitumor activity, concurrent treatment with a somatostatin analog will be required in all patients.

A future randomized, placebo-controlled phase II study or phase III study could be planned if ramucirumab demonstrates efficacy in this study.

Because prior studies of targeted agents have demonstrated low RECIST-defined tumor response rates in advanced carcinoid, we propose enrolling patients with documented disease progression and will use progression-free survival (PFS) as a primary endpoint. Assessment of efficacy will be made by comparing our results to the PFS of patients in the placebo arm of the RADIANT-2 study, a randomized phase III study of everolimus plus octreotide LAR vs. placebo plus octreotide LAR in patients with progressive carcinoid tumors with carcinoid syndrome.

We hypothesize that ramucirumab in combination with a somatostatin analog will be active in the treatment of advanced carcinoid tumors and will be associated with a median PFS duration of 12 months or greater.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have histologically or cytologically confirmed low- to intermediate-grade neuroendocrine tumor (carcinoid tumor).

3.1.2 Carcinoid tumors of any site are eligible. Patients with pancreatic neuroendocrine tumors are excluded.

3.1.3 Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 10 for the evaluation of measurable disease.

3.1.4 Locally advanced, unresectable or metastatic disease.

3.1.5 Patients must have evidence of radiographic disease progression within the past 12 months. Progressive disease by RECIST criteria is not required.

3.1.6 Age ≥ 18 years.

3.1.7 ECOG performance status 0-1 (see Appendix A).

3.1.8 Participants must have normal organ and marrow function as defined below:

– absolute neutrophil count	≥1,000/ mm^3
– platelets	≥100,000/ mm^3
– hemoglobin	≥ 9 g/dL
– total bilirubin	≤ 1.5 × institutional upper limit of normal
– AST(SGOT)/ALT(SGPT)	≤ 3 × institutional upper limit of normal, or ≤ 5× institutional upper limit of normal in the setting of liver metastases
– creatinine	≤ 1.5 × upper limit of normal
– urinary protein	≤ 1+ on dipstick or routine urinalysis (if urine dipstick or routine urinalysis is 2+, a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours)
– coagulation function	Adequate coagulation function as defined by International Normalized Ratio (INR) ≤ 1.5 and a partial thromboplastin time (PTT) < 1.5 x institutional upper limit of normal. Patients on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin.

3.1.9 The effects of ramucirumab on the developing human fetus are unknown. For this reason and because anti-antiangiogenic agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of ramucirumab administration.

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.2 Patients who have undergone major surgery within 28 days or subcutaneous venous access device placement within 7 days prior to study enrollment.

3.2.3 Patients with elective or planned major surgery to be performed during the course of the clinical trial.

3.2.4 Patients who are receiving any other investigational agents.

3.2.5 Patients with any Grade 3-4 gastrointestinal bleeding within 3 months prior to enrollment.

3.2.6 Patients with a history of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered “significant”) during the 3 months prior to registration.

3.2.7 Patients who have experienced any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to enrollment.

3.2.8 Patients with uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management.

3.2.9 Patients who have congestive heart failure (NYHA Class III or IV), sustained ventricular tachycardia, ventricular fibrillation, clinically significant bradycardia, advanced heart block within the six months preceding enrollment.

3.2.10 Patients who have cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis.

3.2.11 Patients with a serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to enrollment.

3.2.12 Patients receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.

3.2.13 Patients with uncontrolled brain or leptomeningeal metastases, including patients who continue to require glucocorticoids for brain or leptomeningeal metastases.

3.2.14 Patients with prior or concurrent malignancy except for the following: adequately treated basal cell or squamous cell skin cancer, or other adequately treated in situ cancer, or any other cancer from which the patient has been disease free for five years.

3.2.15 Patients with symptomatic cholelithiasis.

3.2.16 Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

- Severely impaired lung function
- Any active (acute or chronic) or uncontrolled infection/ disorders.
- Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with the study therapy
- Psychiatric illness/social situations that would limit compliance with study requirement

3.2.17 History of allergic reactions attributed to compounds of similar chemical or biologic composition to ramucirumab .

3.2.18 Pregnant and breastfeeding women are excluded from this study because ramucirumab is associated with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ramucirumab, breastfeeding should be discontinued if the mother is treated with ramucirumab. These potential risks may also apply to other agents used in this study.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

N/A

4.4 Registration Process for Other Investigative Sites

N/A

5. TREATMENT PLAN

5.1 Treatment Regimen

Patients will receive treatment with ramucirumab at a dose of 8 mg/kg intravenously every 14 days of a 28-day treatment cycle.

Patients already receiving a somatostatin analog may continue at their current dose. Patients not already receiving a somatostatin analog should initiate treatment at an approved dose, according to institutional guidelines.

No other investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Patients will continue treatment until progression, unacceptable toxicity, or withdrawal of consent.

Because adverse events associated with the combination of ramucirumab and a somatostatin analog have not examined previously, toxicity and adverse events will be examined in the first 10 patients who complete one cycle of therapy before expanding enrollment.

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1: Participants must meet eligibility criteria on the first day of treatment and have completed all of the required activities by the first day of treatment (Section 9).

5.2.2 Subsequent Cycles: Participants must complete all required assessments (Section 9). Any treatment-related adverse events must meet parameters for re-treatment with required dose adjustment as specified in Section 6.3.

5.3 Agent Administration

5.3.1 *Ramucirumab*

Ramucirumab will be administered as a 1-hour IV infusion on Days 1 and 15 of a 28-day cycle. The infusion rate of ramucirumab should not exceed 25 mg/min.

Premedication: Prior to each infusion of ramucirumab, premedicate all patients with an intravenous histamine H1 antagonist, such as diphenhydramine hydrochloride. Additional premedication may be provided at investigator discretion.

If a patient experiences a Grade 1 or 2 infusion-related reaction (IRR), premedication **must** be given for all subsequent infusions, as outlined in Section 6 of the protocol.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Use of other cancer treatments

Other than a somatostatin analog, no other antineoplastic agents will be permitted during this study. No concurrent radiation treatment will be permitted, except for palliation or symptom relief after completion of Cycle 2.

The use of erythropoietin or other specific red blood cell growth factors and red blood cell transfusions will be permitted as clinically indicated during the study. The use of bone marrow colony stimulating factors (such as granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) is not permitted.

5.4.2 **Supportive medications**

Other concomitant medications may be given as clinically indicated, including supportive medications for diarrhea, nausea/vomiting, or other supportive medications.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) or adverse event(s) requiring discontinuation of therapy as specified in the dose modification section of this protocol
- Participant demonstrates an inability or unwillingness to comply with the treatment regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Jennifer Chan, MD at 617-632-6315.

5.6 Duration of Follow Up

Subject survival and subsequent therapy information will be collected, preferably via office visit or telephone contact, every 6 months +/- 1 week from the date of last dose of study drug until the subject’s death or until the subject is lost to follow-up, or until study closure. For patients who discontinue therapy prior to disease progression, a physical exam, performance status, Chromogranin A, and radiographic imaging will be assessed every 12 weeks +/- 1 week until tumor progression or start of new anticancer therapy.

Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1 Dose Adjustment and Delays

Beginning with cycle 1, if a patient experiences a toxicity warranting a dosing delay, ramucirumab may be held for up to 28 days to allow sufficient time for recovery from toxicity.

6.2 Dose levels

Dose Level	Ramucirumab Dose, IV
-2	5 mg/kg, every 14 days
-1	6 mg/kg, every 14 days
0	8 mg/kg, every 14 days

6.3 Dose Modification Guidelines

6.3.1 **Hematologic toxicity**

If the ANC is <1,000 or the platelet count is <50,000 during study therapy, therapy with ramucirumab will be delayed. If therapy cannot be administered on the scheduled day of dosing, the CBC will be repeated weekly for up to and including 4 weeks until the ANC is ≥ 1000/mm^3 and the platelet count ≥ 50,000mm^3. At that time, ramucirumab will be reinitiated at one reduced dose level.

Growth factors cannot be used to induce elevations in neutrophil count for the purposes of administration of treatment on the scheduled dosing OR to allow treatment.

Neutropenia	**Management for Ramucirumab**
≤ Grade 1 (<LLN - 1500/mm^3)	No change in dose
Grade 2 (<1500 - 1000/mm^3)	No change in dose
Grade 3 (<1000 - 500/mm^3)	Hold* until ≥ 1000/mm^3. Resume at one dose level lower.**
Grade 4	Discontinue ramucirumab
* Participants requiring a delay of >4 weeks should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	

Thrombocytopenia	**Management for Ramucirumab**
≤ Grade 1 (<LLN - 75,000/mm^3)	No change in dose
Grade 2 (<75,000 - 50,000/mm^3)	No change in dose
Grade 3 (<50,000 - 25,000/mm^3)	Hold* until ≥ 50,000 mm^3. Resume at one dose level lower.**
Grade 4 (<25,000/mm^3)	Discontinue ramucirumab
*Participants requiring a delay of >4 weeks must go off protocol therapy. **Participants requiring > two dose reductions must go off protocol therapy.	

6.3.2 **Infusion-related reaction**

As with other monoclonal antibodies, infusion-related reactions may occur during or following ramucirumab. The NCI CTCAE Version 4 description and grade of Infusion-Related Reactions are described in the following table:

Adverse Event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Infusion-related	A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.				

reaction					
	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Allergic Reaction	A disorder characterized by an adverse local or general response from exposure to an allergen.				
	Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Anaphylaxis	A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a				

	hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death				
	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Cytokine release syndrome	A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.				
	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death

Patients should be closely monitored for signs and symptoms indicative of an infusion-related reaction, starting with the initiation of the infusion until at least 30 minutes after the infusion. Monitoring should be performed in an area where resuscitation equipment and other agents (eg, epinephrine, corticosteroids) are readily available.

The following are treatment guidelines for infusion-related reactions due to ramucirumab:

Grade 1

- Slow the infusion rate by 50%.
- Monitor the patient for worsening of condition.
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV; additional premedication may be administered at the investigator's discretion.

Grade 2

- Stop the infusion.
- Administer diphenhydramine hydrochloride 50 mg IV and oxygen. Other medications, including methylprednisolone 50 mg IV, ranitidine 50 mg IV, acetaminophen 650 mg orally for fever, and meperidine 12.5 mg-25 mg IV for rigors can be administered as medically indicated.
- Resume the infusion at 50% of the prior rate once the infusion-related reaction has resolved or decreased to Grade 1; the infusion duration should not exceed 2 hours.
- Monitor for worsening of condition.
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV; additional premedication may be administered at the investigator's discretion.
- For a second Grade 1 or 2 infusion-related reaction, administer diphenhydramine 50 mg IV, methylprednisolone 50 mg IV. Other medications, including ranitidine 50 mg IV, acetaminophen 650 mg orally for fever, and meperidine 12.5 mg-25 mg IV for rigors can be administered as medically indicated. For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV and methylprednisolone 50 mg IV. Additional premedication may be administered at the investigator's discretion.

Grade 3

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg IV, methylprednisolone 50 mg IV, ranitidine 50 mg IV, oxygen. Other medications/treatment, including acetaminophen 650 mg orally for fever, meperidine 12.5 mg-25 mg IV for rigors, and bronchodilators for bronchospasm can be administered as medically indicated.
- Patients who have a Grade 3 infusion-related reaction will not receive further ramucirumab

Grade 4

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg IV, methylprednisolone 50 mg IV, ranitidine 50 mg IV and other medications/treatment as medically indicated.
- Give epinephrine or bronchodilators as indicated.
- Hospital admission for observation may be indicated.
- Patients who have a Grade 4 infusion-related reaction will not receive further ramucirumab

6.3.3 **Hypertension**

Hypertension	**Definition**	**Recommended**

CTCAE version:4.0		**management**
Grade 1	Prehypertension: systolic 120-139 mm Hg or diastolic 80-89 mm Hg	No dose modification or delay
Grade 2	Stage 1 hypertension: systolic: 140-159 mm Hg **or** diastolic: 90-99 mm Hg • Medical intervention indicated • Recurrent or persistent (≥24 hours) • Symptomatic increase by >20 mmHg (diastolic) • >140/90 mm Hg if previously normal • Monotherapy indicated	No dose modification or delay. Medical management of hypertension.
Grade 3	Stage 2 hypertension: Systolic ≥160 mm Hg or Diastolic ≥100 • Medical intervention indicated • More than one antihypertensive drug • **or** more intensive therapy than previously indicated	Delay treatment with ramucirumab for a maximum of 4 weeks. First occurrence: When BP is controlled to < 140/90, resume ramucirumab at same dose. Second occurrence: When BP is controlled to < 140/90 resume ramucirumab at one reduced dose level. Third occurrence: A second dose reduction of ramucirumab should be undertaken if additional postponement of ramucirumab is required.

Grade 4	Life threatening consequences (e.g., malignant hypertension, transient or permanent neurological deficit, hypertensive crisis); urgent intervention indicated	Discontinue ramucirumab.

6.3.4 **Proteinuria**

For proteinuria ≥2+ per a dipstick or routine urinalysis: Confirm total urine protein with a 24-hr urine collection.

24 hour urine protein	**Management**
<2 g/24 hours	Continue on ramucirumab at the same dose without interruption.
2 to 3 g/24 hours	Ramucirumab will be held for 2 weeks and a 24- hour urine collection will be repeated. Treatment with ramucirumab will resume at 1 lower dose level once the protein level returns to <2 g/24 hours. – A dose reduction of ramucirumab to 5 mg/kg every 2 weeks is permitted if proteinuria >2 g/24 hours recurs. – Discontinue ramucirumab if there is a third occurrence of >2 g/24 hours, or if the protein level does not return to <2 g/24 hours within 2 weeks.
>3 g/24 hours	Discontinue ramucirumab.

6.3.5 **Venous Thromboembolic Events**

Grade 3 or asymptomatic Grade 4:
Interrupt ramucirumab. If the planned duration of full-dose anticoagulation is <2 weeks, protocol treatment should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, protocol treatment may be resumed during the period of full-dose anticoagulation if all of the following criteria are met:

- The patient must have an in-range INR (usually between 2-3) on a stable dose of warfarin (or other anticoagulant) prior to restarting therapy;
- The patient must not have had a grade 3 or 4 hemorrhagic event while on study; and
- The patient must not have had evidence of a tumor involving major blood vessels on any prior CT scan.

Patients with unresected primary tumors (or local recurrence) who develop Grade 3 and 4 venous thromboembolism may also receive anticoagulation and continue ramucirumab therapy provided that the tumor does not confer an excessive bleeding risk, in the opinion of the patient's physician.

For recurrent/worsening venous thromboembolic events after resumption of treatment:
Discontinue ramucirumab.

For symptomatic grade 4:
Discontinue ramucirumab.

Any venous thrombotic event leading to discontinuation of ramucirumab therapy will be considered serious and should be reported via the SAE mechanism.

6.3.6 **Arterial thrombotic event**

Discontinue ramucirumab for any grade 3 and 4 arterial thromboembolic events.

Any arterial thrombotic event leading to discontinuation of ramucirumab therapy will be considered serious and should be reported via the SAE mechanism.

6.3.7 **Bleeding (Hemorrhagic) Events**

For Grade 3 or 4 bleeding (hemorrhagic) event bleeding: Discontinue ramucirumab.

6.3.8 **Gastrointestinal Perforations or Fistula**

Ramucirumab should be discontinued in the event of a GI perforation or fistula formation.

6.3.9 **Congestive Heart Failure**

Ramucirumab should be discontinued in the event of any Grade 3-4 events consistent with CHF.

6.3.10 **Reversible Posterior Leukoencephalopathy Syndrome**

Reversible posterior leukoencephalopathy syndrome should be identified and treated promptly in order to minimize potential for permanent neurological damage. Treatment encompasses careful control of BP, withdrawal of potentially causative medication, and administration of anticonvulsant agents to those experiencing seizures. If the diagnosis of RPLS is confirmed, ramucirumab should be permanently discontinued. All cases of RPLS must be reported via the SAE mechanism.

6.3.11 **Liver Impairment**

Any patient who experiences signs of hepatic encephalopathy or other serious signs of liver impairment such as hepatorenal syndrome must permanently discontinue ramucirumab.

6.3.12 **Other non-hematologic toxicity**

	Management for Ramucirumab
≤ Grade 1	No change in dose

	Management for Ramucirumab
Grade 2	Hold* until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at one lower dose level. If the same toxicity recurs at grade ≥ 3, protocol therapy will be stopped.
Grade 4	Discontinue ramucirumab
*Participants requiring a delay of >4 weeks should go off protocol therapy.	

Standard supportive measures for the treatment of nausea, vomiting, fatigue are encouraged, at the discretion of the treating provider.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Event List(s) for ramucirumab

Please refer to the Investigator's Brochure for up to date information regarding adverse events associated with ramucirumab.

The most frequently observed, possibly related treatment-emergent adverse events (TEAEs) associated with ramucirumab include adverse events (AEs) which have been associated with antiangiogenic agents and therapeutic mAbs, and include the following categories: infusion-related reactions, hypertension, proteinuria, arterial thromboembolic events (ATEs), venous thromboembolic events (VTEs), bleeding/hemorrhagic events, gastrointestinal (GI) perforation, impaired wound healing, reversible posterior leukoencephalopathy syndrome (RPLS), and congestive heart failure (CHF) in patients who received ramucirumab following prior anthracycline therapy.

Table 7.2 of the Investigator's Brochure, summarized below, provides the frequency and severity of adverse drug reactions (ADRs) reported in ≥5% of ramucirumab-treated patients in the REGARD study, a single-agent, placebo-controlled Phase 3 gastric cancer study. The list below presents the frequency category of ADRs reported in the pooled safety analysis. ADRs are listed according to MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each

adverse reaction: very common (≥1/10); common (≥1/100 to <1/10);uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)

Gastrointestinal Disorders Very common: abdominal pain, diarrhea	**Nervous System Disorders** Common: headache
Metabolism and Nutrition Disorders Common: hypokalemia, hyponatremia	**Vascular Disorders** Very common: hypertension

Clinically relevant ADRs reported in ≥1% and <5% of ramucirumab-treated patients in REGARD were: neutropenia, ATEs, intestinal obstruction, epistaxis, and rash.
Clinically relevant reactions (including Grade ≥3) associated with antiangiogenic therapy observed in ramucirumab-treated patients across clinical trials were proteinuria, infusion-related reactions, and GI perforations.

Table 7.3 of the Investigator's Brochure, summarized below, provides the frequency and severity of ADRs reported in ≥5% of ramucirumab-treated patients in the RAINBOW study, a phase III study of paclitaxel in combination with ramucirumab compared with paclitaxel with placebo in patients with advanced gastric cancer.

Blood and Lymphatic System Disorders Very common: leukopenia, neutropenia, thrombocytopenia	**Renal and Urinary Disorders** Very common: proteinuria
Gastrointestinal Disorders Very common: diarrhea, gastrointestinal hemorrhage, stomatitis	**Respiratory, Thoracic, Mediastinal Disorders** Very common: epistaxis
General Disorders Very common: fatigue, peripheral edema	**Vascular Disorder** Very common: hypertension
Metabolism and Nutrition Disorders Very common: hypoalbuminemia	

Clinically relevant ADRs reported in ≥1% and <5% of the ramucirumab plus paclitaxel treated patients in RAINBOW were GI perforations (1.2% for ramucirumab plus paclitaxel versus 0.3% for placebo plus paclitaxel) and sepsis (3.1% for ramucirumab plus paclitaxel versus 1.8% for placebo plus paclitaxel).

The most frequent (≥5%) ADRs observed in the open-label Phase 2 Study I4T-IE-JVBL (IMCL CP12-0917) for the nonsquamous population receiving ramucirumab plus platinum-based chemotherapy (pemetrexed plus carboplatin *or* cisplatin) are listed below.

Blood and Lymphatic System Disorders *Very Common:* anemia, neutropenia *Common:* thrombocytopenia, leukopenia	**Nervous System Disorders** *Very Common:* headache *Common:* dysgeusia, neuropathy
Gastrointestinal Disorders *Very Common:* nausea, vomiting *Common:* constipation, diarrhea, stomatitis	**Respiratory, Thoracic Disorders** *Very Common:* epistaxis *Common:* dyspnea

General Disorders *Very Common:* fatigued *Common:* peripheral edema	**Skin and Subcutaneous Tissue Disorders** *Common:* rash
Investigations *Common:* weight decrease	**Vascular Disorders** *Very Common:* hypertension
Metabolism and Nutrition Disorders *Very Common:* decreased appetite *Common:* hypomagnesemia	

7.2 Definitions

7.2.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they are determined to be of clinical significance or require treatment or further diagnostic tests.

7.2.2 Serious adverse event

A serious adverse event (SAE) is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

7.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version

4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.4 Expedited Adverse Event Reporting

7.4.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.4.2 DF/HCC Expedited Reporting Guidelines
Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

The DFCI IRB requires the following Adverse Events (AE) be reported for all subjects enrolled and actively participating in the trial or when the AE occurs within 30 days of the last study intervention (e.g. drug administration):

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are Unexpected and Possibly, Probably or Definitely Related / Associated with the Intervention.
- ALL Grade 4 (life threatening or disabling) Events – Unless expected AND specifically listed in protocol as not requiring reporting.
- ALL Grade 5 (fatal) Events

Notes:
- If subject is in Long Term Follow Up, death is reported at continuing review.
- Grade 2 and Grade 3 laboratory abnormalities that are considered by the investigator to be clinically insignificant and do not require therapy, or adjustment in prior therapy, do not need to be reported to the DFCI IRB.

The DFCI IRB AE Reporting Form must be used to report AEs experienced by DF/HCC participants enrolled in a DF/HCC study. The full written AE report must be submitted to OHRS

within 10 working days from notification of the event. All AE Reports must be submitted via OHRS Submit. No interoffice submissions, faxes or e-mail notifications of AEs will be accepted.

For follow Up AE Reports: When submitting follow up reports to previously reported AEs, please include the prior OHRS AE # in the reporting form.

7.4.3 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.4.4 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.4.5 Expedited Reporting to Eli Lilly and Company

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

The Global Product Safety Fax Number for all SAEs for ramucirumab studies is 866-644-1697 or 317-453-3402

A copy of all submissions to Lilly must be sent to the DF/HCC Overall Principal Investigator.

7.4.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 Ramucirumab

Ramucirumab is a recombinant human monoclonal antibody of the immunoglobulin G subclass 1 (IgG1) subclass. It is composed of 4 polypeptide chains, 2 identical heavy (γ) chains consisting of 446 amino acids each, and 2 identical light (κ) chains consisting of 214 amino acids each. The antibody contains 1 conserved N-linked glycosylation site at each heavy chain, in the Fc region.

Molecular weight: The ramucirumab molecular masses, determined by mass spectrometry, of the light chain and the heavy chain are 23.2 kDa and 50.1 kDa, respectively, resulting in a relative molecular mass for the ramucirumab monoclonal antibody of 146.8 kDa. The theoretical molecular weights predicted by complementary deoxyribonucleic acid (cDNA) of the light chain and the heavy chain are 23.2 kDa and 48.7 kDa, respectively, resulting in a theoretical relative molecular mass for the ramucirumab monoclonal antibody of 143.8 kDa. The difference between the observed and theoretical molecular weights, approximately 3 kDa, is attributed to posttranslational glycosylation.

Pharmacokinetic data from the 8 studies involving 497 patients were pooled together for a population pharmacokinetic (PopPK) analysis. In these studies, ramucirumab was administered as a 1-hour I.V. infusion, at either 8 mg/kg once every 2 weeks on a 14- or 28-day cycle, or 10 mg/kg every 3 weeks on a 21-day cycle. The studies included patients with varying cancer indications: gastric cancer (80.5% of patients), non-small cell lung cancer (NSCLC; 8.2%), breast cancer (2.2%), colorectal cancer (CRC; 1.6%), and other tumor types (7.4%). The geometric mean (percentage coefficient of variation [CV%]) of PopPK model-derived estimates of ramucirumab clearance (CL), volume of distribution at steady state (Vss) and terminal half-life (t1/2) were 0.0140 L/h (29.8%), 5.5 L (14.4%), and 15 days (24.1%), respectively.

8.1.1 Form

Ramucirumab DP is a sterile, preservative-free solution for infusion of ramucirumab formulated in an aqueous solution at a concentration of 10 mg/mL (500 mg/50-mL vial or 100mg/10mL vial). The buffer contains 10mM histidine, 75mM sodium chloride, 133mM glycine, and 0.01% polysorbate 80. Ramucirumab DP is a clear to slightly opalescent and colorless to slightly yellow liquid without visible particles. The pH is 6.0. The osmolality is 285 mmol/kg. All excipients used for the manufacture of ramucirumab DP are of pharmacopeial grade. No animal-derived components are used in the manufacture of ramucirumab DP excipients.

8.1.2 Storage and Stability

PREPARED RAMUCIRUMAB DOSING SOLUTION FOR INFUSION: Chemical and physical in-use stability for the prepared ramucirumab dosing solution has been demonstrated for up to 24 hours below 25°C (77°F). However, it is recommended that the prepared dosing solution be used immediately in order to minimize the risk of microbial

contamination. If not used immediately, the prepared ramucirumab dosing solution should be stored under refrigeration at 2°C to 8°C (36°F to 46°F), for a duration not to exceed 24 hours. If the prepared solution is held at room temperature (below 25°C [77°F]), it must be used within 4 hours. This recommendation supersedes the room temperature storage recommendation of up to 24 hours specified in some study protocols. Store protected from light. Brief exposure to ambient light is acceptable while preparation and administration is taking place. DO NOT FREEZE AND/OR SHAKE PREPARED RAMUCIRUMAB

8.1.3 Compatibility

DO NOT dilute with other solutions or co-infuse with other electrolytes or medication.

8.1.4 Handling

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

8.1.5 Availability

Ramucirumab will be provided by Eli Lilly and Company from investigational supply.

8.1.6 Preparation

1. Prepare the infusion solution using aseptic technique to ensure the sterility of the prepared solution.

2. Each vial is intended for single use only. Inspect the content of the vials for particulate matter and discoloration prior to dilution. If particulate matter or discolorations are identified, discard the vial.

3. Calculate the dose and volume of ramucirumab needed to prepare the infusion solution. Vials contain either 100 mg or 500 mg as a 10 mg/mL solution of ramucirumab. Only use sterile sodium chloride (0.9%) solution for injection as a diluent. DF/HCC sites will use their own practices with regards to calculating doses based on body weight (kg).

In case of prefilled I.V. infusion container usage:
Based on the calculated volume of ramucirumab, remove the corresponding volume of sterile sodium chloride (0.9%) solution for injection from the prefilled 250 mL I.V. container. Aseptically transfer the calculated volume of ramucirumab to the I.V. container. The final total volume in the container should be 250 mL. The container should be gently inverted to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medications.

In case of empty I.V. infusion container usage:
Aseptically transfer the calculated volume of ramucirumab into an empty I.V. container. Add a sufficient quantity of sterile sodium chloride (0.9%) solution for injection to the container to make the total volume 250 mL. The container should be gently inverted to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medication.

4. Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is identified, discard the infusion solution.

5. Discard any unused portion of ramucirumab left in a vial, as the product contains no preservatives.

8.1.7 Administration

Ramucirumab will be administered as a 1-hour IV infusion on Days 1 and 15 of a 28-day cycle. The infusion rate of ramucirumab should not exceed 25 mg/min. DF/HCC sites will use their own practices with regards to calculating doses based on body weight (kg).

Administer via infusion pump. A separate infusion line with a protein-sparing 0.22 micron filter must be used for the infusion and the line must be flushed with sterile sodium chloride (0.9%) solution for injection at the end of the infusion.

If a patient experiences a Grade 1 or 2 infusion-related reaction (IRR), premedication **must** be given for all subsequent infusions. If a patient has a second Grade 1 or 2 IRR, administer dexamethasone; for subsequent infusions, premedicate with the following or equivalent medications: diphenhydramine hydrochloride (I.V.), acetaminophen, and dexamethasone, as outlined in Section 6 of the protocol.

8.1.8 Ordering

Eli Lilly and Company provides commercially packaged material for investigator-initiated studies and provides labeling for the material to be limited to investigational use only. For Investigational Product Reorders, please send a completed form to both: data_account_usmail-sdc@lilly.com and iits_usmail-oncology@lilly.com

Allow 5-7 business days for shipment to arrive.

If a Reorder Form is not available, please send an email request to iits_usmail-oncology@lilly.com including the following in the request:

- Lilly Trial Alias –I4T-US-I005
- Principal Investigator's Name
- Institute's shipping address
- Name of the person receiving product in the pharmacy

- Email address for pharmacy contact
- Phone & Fax Number
- Name of Compound
    - Ramucirumab (Cyramza) 500 mg vials
    - Ramucirumab (Cyramza) 100 mg vials
- Number of vials needed
- Date product needed to arrive at site

8.1.9 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.10 **Destruction and Return**

At the end of the study, unused supplies of ramucirumab will be either destroyed per institutional policy or returned to Eli Lilly as directed.

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 2 days of the protocol-specified date, unless otherwise noted.

REQUIRED INFORMATION/EXAMS	Pre-Study[a]	Day 1 of each cycle[a]	Day 15 of each cycle	Restaging[b]	Off-Treatment[c]	Follow-Up (Overall Survival)
Informed consent	X					
Medical and Oncologic History	X	X	X		X	
Concurrent meds	X	X	X		X	
Physical exam (including height, weight, blood pressure, pulse)	X	X	X		X	X[c]
ECOG Performance Status	X	X	X		X	X[c]
Adverse event evaluation	X	X	X			
CBC with differential	X	X	X		X	
PT/PTT	X					
Bilirubin, ALT, AST, Albumin, Alkaline Phosphatase	X	X	X		X	
BUN, Cr, electrolytes, including Na, K, Cl, HCO3, Ca, Phosphate, Mg	X	X	X		X	
Urinalysis with assessment of urine protein	X	X			X	
β-HCG[d]	X					
EKG[f]	X				X	
Radiographic evaluation[b]	X			X	X	X[c]
Chromogranin A, 24-hr urine 5-HIAA[e]	X			X	X	X[c]

a. Screening assessments must occur within 14 days of start of ramucirumab administration. Pre-registration labs may be used for Day#1 of Cycle#1 if obtained within 7 days of starting treatment. For subsequent cycles, labs must be obtained within 48 hours of start of treatment

b. Baseline scans must be performed within 28 days of start of study therapy. Restaging scans will be performed every 12 weeks until disease progression, or end of study treatment. All patients will receive an arterial and venous phase Chest/Abdomen/Pelvic CT. A liver MRI with gadolinium may be included at the discretion of the treating physician. Please note, Multiphase CT scan (chest/abdomen/pelvis) is the preferred modality for imaging. Equivalent modalities (e.g., CXR and MRI scan of abdomen and chest) may be used at the discretion of the investigator.

c. For patients who discontinue study treatment prior to tumor progression, physical examination, performance status, chromogranin A, and radiologic imaging studies should be performed every 12 +/-1 weeks until tumor progression or the start of a new anticancer therapy. Patients who discontinue treatment at the time of tumor progression should be followed every 6 months +/- 1 week for survival, with chromogranin A and imaging studies at the discretion of the investigator.
d. Serum pregnancy test (women of childbearing potential)
e. Chromogranin A will be assessed every 12 weeks. 24-hour urine 5-HIAA will be assessed and followed as clinically indicated every 12 weeks.
f. EKG assessments will be performed with standard 12-lead EKG equipment according to standard procedures. Abnormalities in the EKG that lead to a change in subject management (eg, dose reduced or withheld, requirement for additional medication or monitoring) or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE CRF. If values meet criteria defining them as serious, they must be reported as SAEs.

10. MEASUREMENT OF EFFECT

10.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 12 weeks.

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

10.1.1 Definitions

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

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

10.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor

measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

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

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

10.1.3 Methods for Evaluation of Disease

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

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

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

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

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

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

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

progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

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

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

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

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

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

10.1.4 Response Criteria

10.1.4.1 Evaluation of Target Lesions

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

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

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

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

10.1.4.2 Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

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

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

10.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

10.1.4.4 Evaluation of Best Overall Response

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

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD***	Yes or No	PD
Any	Any	Yes	PD
* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. <u>Note</u>: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at			

that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

10.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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

10.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from registration to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from registration to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

11.1 Data Reporting

11.1.1 Method

The ODQ will collect, manage, and perform quality checks on the data for this study.

11.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

11.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

The primary objective of this study is to assess the progression-free survival duration of patients with advanced, progressive carcinoid tumors treated with ramucirumab in combination with somatostatin analog therapy. Patients will be accrued in one stage.

Progression-Free Survival (PFS) is defined as the time from registration to the earlier of progression as defined by RECIST criteria or death due to any cause. Patients will be censored in the analysis of PFS at the time they begin a new anti-cancer therapy if disease has not met the criteria for progression at the time the new treatment is started. Participants alive without disease progression are censored at date of last disease evaluation.

We will use the Kaplan-Meier method to estimate the distribution of progression-free survival.

12.2 Sample Size, Accrual Rate and Study Duration

Recent studies of targeted agents in neuroendocrine tumors suggest that while many of these agents are associated with low RECIST-defined response rates, they may be associated with significant improvements in progression-free survival. In the registration studies of sunitinib and everolimus in pancreatic neuroendocrine tumors, for example, PFS durations more than doubled while overall response rates were only 9% and 4%, respectively.(Raymond, Dahan et al. 2011, Yao, Shah et al. 2011)

In this study, we propose using PFS as the primary outcome measure. We note that all patients in our study will receive a somatostatin analog. The RADIANT 2 study provides a reasonable estimate of PFS duration in a large cohort of carcinoid tumor patients treated with either a somatostatin analog or somatostatin analog and an investigational agent.(Pavel, Hainsworth et al. 2011) RADIANT 2 randomized 429 patients with a history of symptoms attributed to carcinoid syndrome and evidence for radiographic progression within 12 months of enrollment to receive everolimus plus octreotide LAR, or placebo plus octreotide LAR. A significant PFS benefit in favor of everolimus was demonstrated based on investigator radiology review (12 vs. 8.6 months, $p<0.01$). However, the primary endpoint of the study was based on adjudicated central review, and while this analysis also favored the everolimus arm over placebo, the predefined threshold for statistical significance was not met.

Investigator radiology review will be used to determine the primary endpoint in our study. We assume that an inactive agent will be associated with a PFS of 8 months, and that an agent worthy of further investigation will be associated with a PFS of 12 months or greater. A sample size of 43 achieves 80% power to detect the difference between the null hypothesis median PFS of 8 months and the alternative hypothesis median PFS of 12 months at a 0.05 significance level (alpha) using a one-sided test. The length of follow up is 2 years.

The expected accrual rate is 6 patients per quarter with an accrual period of 2 years.

The end of the study will be defined as the time at which all protocol specified time points have passed and/or follow-up data are sufficiently mature for analysis.

12.3 Analysis of Primary Endpoints

Analysis of endpoints of this study is described in Section 12.1.

12.4 Analysis of Secondary Endpoints

Secondary objectives of this study are to:

- To determine the safety and tolerability of ramucirumab in combination with somatostatin analog therapy in patients with advanced carcinoid tumors. We will assess the rate of adverse events (as defined by Common Terminology Criteria for Adverse Events (CTCAE), version 4.0), associated with treatment.

Because adverse events associated with the combination of ramucirumab and a somatostatin analog have not examined previously, toxicity and adverse events will be examined in the first 10 patients who complete one cycle of therapy before expanding enrollment.

- To assess the overall radiographic and biochemical response rate associated with ramucirumab in patients with advanced carcinoid tumors. We will estimate the response rate and provide the associated 95% confidence interval.

- To assess the overall survival duration of patients with advanced carcinoid tumors treated with ramucirumab. We will use the Kaplan-Meier method to estimate the distribution of overall survival.

12.5 Reporting and Exclusions

12.5.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

12.5.2 Evaluation of the Primary Efficacy Endpoint

Analyses will be conducted on an intent-to-treat basis. Specifically, all eligible participants included in the study must be assessed for response/outcome to therapy, even if there are major protocol therapy deviations.

Subanalyses may then be performed on the basis of a subset of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding participants from the analysis should be clearly reported. If applicable to the endpoint, the 95% confidence intervals should also be provided.

13. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

REFERENCES

Bowen, K. A., S. R. Silva, J. N. Johnson, H. Q. Doan, L. N. Jackson, P. Gulhati, S. Qiu, T. S. Riall and B. M. Evers (2009). "An analysis of trends and growth factor receptor expression of GI carcinoid tumors." J Gastrointest Surg **13**(10): 1773-1780.

Caplin, M. E., M. Pavel, J. B. Cwikla, A. T. Phan, M. Raderer, E. Sedlackova, G. Cadiot, E. M. Wolin, J. Capdevila, L. Wall, G. Rindi, A. Langley, S. Martinez, J. Blumberg and P. Ruszniewski (2014). "Lanreotide in metastatic enteropancreatic neuroendocrine tumors." N Engl J Med **371**(3): 224-233.

Fjallskog, M. L., O. Hessman, B. Eriksson and E. T. Janson (2007). "Upregulated expression of PDGF receptor beta in endocrine pancreatic tumors and metastases compared to normal endocrine pancreas." Acta Oncol **46**(6): 741-746.

Fjallskog, M. L., M. H. Lejonklou, K. E. Oberg, B. K. Eriksson and E. T. Janson (2003). "Expression of molecular targets for tyrosine kinase receptor antagonists in malignant endocrine pancreatic tumors." Clin Cancer Res **9**(4): 1469-1473.

Fuchs, C. S., J. Tomasek, C. J. Yong, F. Dumitru, R. Passalacqua, C. Goswami, H. Safran, L. V. dos Santos, G. Aprile, D. R. Ferry, B. Melichar, M. Tehfe, E. Topuzov, J. R. Zalcberg, I. Chau, W. Campbell, C. Sivanandan, J. Pikiel, M. Koshiji, Y. Hsu, A. M. Liepa, L. Gao, J. D. Schwartz and J. Tabernero (2014). "Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial." Lancet **383**(9911): 31-39.

Hansel, D. E., A. Rahman, J. Hermans, R. R. de Krijger, R. Ashfaq, C. J. Yeo, J. L. Cameron and A. Maitra (2003). "Liver metastases arising from well-differentiated pancreatic endocrine neoplasms demonstrate increased VEGF-C expression." Mod Pathol **16**(7): 652-659.

Hobday, T. J., J. Rubin, K. Holen, J. Picus, R. Donehower, R. Marschke, W. Maples, R. Lloyd, M. Mahoney and C. Erlichman (2007). "MC044h, a phase II trial of sorafenib in patients (pts) with metastatic neuroendocrine tumors (NET): A Phase II Consortium (P2C) study." Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I **25**(18S): Abstract 4504.

Kulke, M. H., H. J. Lenz, N. J. Meropol, J. Posey, D. P. Ryan, J. Picus, E. Bergsland, K. Stuart, L. Tye, X. Huang, J. Z. Li, C. M. Baum and C. S. Fuchs (2008). "Activity of sunitinib in patients with advanced neuroendocrine tumors." J Clin Oncol **26**(20): 3403-3410.

Mackey, J. R., M. Ramos-Vazquez, O. Lipatov, N. McCarthy, D. Krasnozhon, V. Semiglazov, A. Manikhas, K. A. Gelmon, G. E. Konecny, M. Webster, R. Hegg, S. Verma, V. Gorbunova, D. Abi Gerges, F. Thireau, H. Fung, L. Simms, M. Buyse, A. Ibrahim and M. Martin (2015). "Primary results of ROSE/TRIO-12, a randomized placebo-controlled phase III trial evaluating the addition of ramucirumab to first-line docetaxel chemotherapy in metastatic breast cancer." J Clin Oncol **33**(2): 141-148.

Pavel, M. E., J. D. Hainsworth, E. Baudin, M. Peeters, D. Horsch, R. E. Winkler, J. Klimovsky, D. Lebwohl, V. Jehl, E. M. Wolin, K. Oberg, E. Van Cutsem and J. C. Yao (2011). "Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study." Lancet **378**(9808): 2005-2012.

Phan, A., J. Yao, D. Fogelman, K. Hess, C. Ng, S. Bullock, P. Malinowski, E. Regan and M. Kulke (2010). "A prospective, multi-institutional phase II study of GW786034 (pazopanib) and depot octreotide (sandostatin LAR) in advanced low-grade neuroendocrine carcinoma (LGNEC)." Journal of Clinical Oncology, 2010 ASCO Annual Meeting Proceedings **28**(15S): Abstract 4044.

Raymond, E., L. Dahan, J. L. Raoul, Y. J. Bang, I. Borbath, C. Lombard-Bohas, J. Valle, P. Metrakos, D. Smith, A. Vinik, J. S. Chen, D. Horsch, P. Hammel, B. Wiedenmann, E. Van Cutsem, S. Patyna, D. R. Lu, C. Blanckmeister, R. Chao and P. Ruszniewski (2011). "Sunitinib malate for the treatment of pancreatic neuroendocrine tumors." N Engl J Med **364**(6): 501-513.

Rinke, A., H. H. Muller, C. Schade-Brittinger, K. J. Klose, P. Barth, M. Wied, C. Mayer, B. Aminossadati, U. F. Pape, M. Blaker, J. Harder, C. Arnold, T. Gress and R. Arnold (2009). "Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group." J Clin Oncol **27**(28): 4656-4663.

Silva, S. R., K. A. Bowen, P. G. Rychahou, L. N. Jackson, H. L. Weiss, E. Y. Lee, C. M. Townsend, Jr. and B. M. Evers (2011). "VEGFR-2 expression in carcinoid cancer cells and its role in tumor growth and metastasis." Int J Cancer **128**(5): 1045-1056.

Wilke, H., K. Muro, E. Van Cutsem, S. C. Oh, G. Bodoky, Y. Shimada, S. Hironaka, N. Sugimoto, O. Lipatov, T. Y. Kim, D. Cunningham, P. Rougier, Y. Komatsu, J. Ajani, M. Emig, R. Carlesi, D. Ferry, K. Chandrawansa, J. D. Schwartz and A. Ohtsu (2014). "Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial." Lancet Oncol **15**(11): 1224-1235.

Yao, J. C., A. Phan, P. M. Hoff, H. X. Chen, C. Charnsangavej, S. C. Yeung, K. Hess, C. Ng, J. L. Abbruzzese and J. A. Ajani (2008). "Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b." J Clin Oncol **26**(8): 1316-1323.

Yao, J. C., M. H. Shah, T. Ito, C. L. Bohas, E. M. Wolin, E. Van Cutsem, T. J. Hobday, T. Okusaka, J. Capdevila, E. G. de Vries, P. Tomassetti, M. E. Pavel, S. Hoosen, T. Haas, J. Lincy, D. Lebwohl and K. Oberg (2011). "Everolimus for advanced pancreatic neuroendocrine tumors." N Engl J Med **364**(6): 514-523.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.