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DIVISION OF CANCER MEDICINE

TITLE PAGE

Protocol 2015-0393: A Phase II Study of Ramucirumab for Advanced, Pre-treated Biliary Cancers

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1. STUDY RATIONALE

Biliary cancers are a heterogeneous group of malignancies with a limited number of chemotherapeutic options in advanced disease. The current standard of care for palliative treatment of biliary cancers is the combination of gemcitabine and cisplatin[1]. There is no clear second-line therapy in biliary cancers after progression on gemcitabine and cisplatin. A retrospective study of second-line therapies at MD Anderson demonstrated a median progression free survival in this population of 2.7 months with a multitude of therapies used[2]. Angiogenesis has been shown to be a potential target for biliary cancers in a variety of small phase II studies[3-5]. Ramucirumab is a novel monoclonal antibody that targets the vascular endothelial growth factor receptor 2 (VEGFR2). It is FDA-approved for the treatment of advanced gastric cancer, and inhibits tumor-induced angiogenesis through high affinity binding to VEGFR2[6].

2. BACKGROUND

2.1 Biliary Cancers

Biliary cancers are comprised of intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder carcinoma. They are an aggressive group of malignancies but heterogeneous in their presentations and clinical pictures. The majority of patients present at an advanced stage, and median survival of locally-advanced or metastatic biliary tract cancers is less than one year. These malignancies are characterized by lymph node involvement and distant metastases[7].

Gallbladder cancer (GBC) is the most common form of biliary tract cancers. Internationally, Israel has the highest incidence worldwide, with 7.5 cases per 100,000 men and 13.8 cases per 100,000 women. Other countries with significant incidence rates include Mexico, Bolivia, Chile, and northern Japan[8]. In the US, about five thousand new cases are reported every year. The incidence has been on the decline owing to the increase in the number of cholecystectomies for other reasons like acute or chronic symptomatic cholecystitis. Less than 10 percent of patients with GBC live more than five years after diagnosis. The mortality is very high and is attributed to the late diagnosis and an advanced stage of the disease[9].

At the same time, cholangiocarcinoma is a highly fatal cancer of the biliary tree. In the United States, approximately 5,000 new cases of cholangiocarcinoma are diagnosed annually; these cases are equally distributed between intra-hepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC)[10]. Data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) indicate that the incidence of ICC is increasing[11]. The incidence of ICC in the US almost tripled between 1975 and 1999[12]. The reasons behind this increase are not clear.

Chemotherapy for biliary cancers

Gemcitabine has been the mainstay of chemotherapy in biliary cancers. The ABC-01 study was a phase II trial that examined the combination of gemcitabine and cisplatin in advanced biliary cancers. 86 patients were randomized to gemcitabine alone versus the doublet regimen. The primary endpoint of 6-month progression-free survival was 45.5% vs. 57.1% in the two arms with median time to progression being 8 months with the gemcitabine and cisplatin combination[13]. The benefit of the addition of cisplatin to gemcitabine was verified with the ABC-02 study, a randomized phase III trial of 410 patients with overall survival as the primary endpoint. The authors found that the combination of gemcitabine and cisplatin significantly improved median overall survival (11.7 months vs. 8.1 months) and progression-free survival (8.0 months vs. 5.0 months) compared to gemcitabine alone[1].

Therapy in refractory biliary cancers

There has not been any randomized controlled phase II or III trials of second or third-line therapies in biliary cancers thus far. A recent review of second-line therapy that included 14 phase II trials indicated a mean overall survival (OS) of 7.2 months, progression-free survival (PFS) of 3.2 months and response rate (RR) of 7.7% with second-line therapy[14]. Similarly, a large retrospective review of second line therapy for 300 BC patients from Italy also showed a median OS of 7.2 months[15]. A retrospective review from MD Anderson Cancer Center indicated a median PFS of 2.7 months (95% CI 2.3-3.8 months) with a median OS of 13.8 months (95% CI 12-19.3 months) in those receiving second-line chemotherapy for cholangiocarcinoma[2]. There is no “standard” second-line chemotherapy after gemcitabine and cisplatin; FOLFOX, irinotecan, capecitabine and erlotinib are used in practice[16-20].

Rationale for targeting angiogenesis in biliary cancers

Expression of pro-angiogenic factors such as VEGFs and angiogenesis play an important role in biliary cancers. VEGF and VEGFR overexpression has been reported in 30-50% of biliary cancer cases and are associated with worse prognosis[21-23]. Estrogens interact with insulin-like growth factor (IGF1) and its receptor (IGF1-R) to simulate the growth of cholangiocarcinoma. Estrogens also stimulate the expression and secretion of VEGF-A, VEGF-C and VEGFRs in cholangiocarcinoma cell lines potentially altering cholangiocarcinoma proliferation and tumor neoangiogenesis[24]. Conversely, inhibition of cholangiocarcinoma proliferation also inhibits VEGF expression. Endothelin 1 (ET-1) inhibited the proliferation of cholangiocarcinoma xenografts in nude mice, which was associated with a down-regulation of VEGF-A and VEGF-C expression[25].

A phase II trial of gemcitabine, oxaliplatin, and bevacizumab enrolled 35 patients with biliary cancers and resulted in a RR of 40% and PFS/OS of 7.0/12.7 months, which compared favorably with historic controls[5]. Lubner and colleagues reported a multicenter phase II trial of bevacizumab and erlotinib in patients with unresectable biliary cancer. The confirmed partial response rate in this study was 12%, median OS was 9.9 months, and TTP was 4.4 months, suggesting an effect of bevacizumab in this disease[4]. In the ABC-03 trial, Valle and colleagues examined the effects of adding cediranib, a pan-VEGF receptor tyrosine kinase inhibitor, to traditional treatment with cisplatin/gemcitabine. This group performed a randomized phase II

study that included 124 chemotherapy-naive biliary cancer patients who received cisplatin/gemcitabine with or without cediranib. Patients assigned to cediranib had a significantly improved RR compared with patients assigned to placebo. (44% vs. 19%, respectively (p = .0036). Patients receiving placebo were also more likely to progress (28% progressive disease vs 10% for cediranib). However, this did not result in improved OS[26]. Modest anti-tumor efficacy against biliary cancers was also demonstrated with multi-targeted anti-angiogenic tyrosine kinase inhibitors including sorafenib and sunitinib[3,27-29].

Ramucirumab is a fully human IgG1 monoclonal antibody that is a specific and direct inhibitor of VEGFR-2, where it binds to the extracellular VEGF-binding domain with high degree of specificity and affinity, at picomolar dose range. It thus prevents the binding of the VEGF ligand to the VEGF-R2 receptor. In the phase I trial for patients with advanced solid tumors, (n=37) ramucirumab demonstrated encouraging early evidence of efficacy at a range of dose levels including the one enrolled patient with biliary cancer who experienced stable disease lasting over 5 months[30]. Ramucirumab was recently shown to improve survival compared with placebo in advanced gastric cancer, with a median overall survival of 5.2 months in the ramucirumab arm, and 3.8 months in the placebo arm. The main toxicity seen was an increase in hypertension in the ramucirumab group[31]. Additionally, a double-blind, randomized, phase III study of previously treated gastric and gastroesophageal junction cancers included 665 patients randomized to raumucirumab plus paclitaxel versus placebo plus paclitaxel[32]. In this study, the combination arm showed an improvement in overall survival (9.6 months vs. 7.4 mths, p=0.017), providing further rationale for the use of ramucirumab in refractory gastric cancer.

Initial data with ramucirumab in biliary cancer

In the initial 43 patient cohort that was enrolled in this phase II trial, 42 patients with cholangiocarcinoma and gallbladder cancers received treatment. Ramucirumab was well tolerated with 9 grade 3 toxicities including anorexia, dehydration, hypertension, hyponatremia, proteinuria and vomiting. There were no grade 4 toxicities. The median PFS for all patients who received treatment was 2.73 months (95% CI 1.91-8.03 months) and median OS was 6.31 months (95% CI 4.7 months – not reached). The overall response rate was 0% and disease control rate (SD + PR + CR) was 44%. Importantly, 6 patients (13%) were on treatment for > 24 weeks. Of these, 3 were on treatment for at least 44 weeks. In reviewing the genomic data on the 6 patients with prolonged periods of stable disease, we noted that 4 of the 6 harbored mutations in DNA repair pathways (BRCA, FANCA, ARID1A) and 1 patient had an FGFR alteration

3. DRUG INFORMATION

3.1 RAMUCIRUMAB

1. The Product

   Ramucirumab is an anti-VEGF Receptor 2 recombinant human monoclonal antibody of the IgG1 subclass. Ramucirumab drug product is a sterile, preservative-free solution for infusion oframucirumab formulated in an aqueous solution at a concentration of 10 mg/mL (500 mg/50-mL vial). The buffer contains 10 mM histidine, 75 mM sodium chloride, 133 mM glycine, and 0.01% polysorbate 80. It is administered as an intravenous infusion at a dose of 8 mg/kg over 60 minutes every two weeks.

2. Indication

In the United States, ramucirumab is indicated for the treatment of advanced gastric and gastroesophageal cancers either alone or in combination with paclitaxel after prior fluoropyrimidine- or platinum-containing chemotherapy.

It is also indicated in combination with docetaxel for treatment of metastatic non-small cell lung cancer with disease progression after platinum-therapy.

Accessed via: http://pi.lilly.com/us/cyramza-pi.pdf

3. Introduction

Ramucirumab is a recombinant human monoclonal antibody of the immunoglobulin G subclass 1 that specifically binds to the extracellular domain of the VEGFR2. This prevents the binding of activating ligands (VEGF-A, VEGF-C, VEGF-D) to the receptor. This inhibition results in inactivation of downstream signaling pathways that promote migration and proliferation of human endothelial cells.

4. Preclinical Studies with Ramucirumab

Preclinical pharmacodynamic data demonstrated that ramucirumab binds specifically and with high affinity to human VEGFR2, and not to murine VEGFR2 or the related human VEGF receptors, VEGFR-1 and VEGFR-3. Furthermore, a surrogate antibody for ramucirumab was tested with demonstration of potent antiangiogenic effects in multiple mouse xenograft solid tumor models, including gastric, hepatic, breast, colorectal, non-small cell lung, and pancreatic cancer models (Ramucirumab investigator's brochure).

5. Clinical Studies In Gastrointestinal malignancies with Ramucirumab

The REGARD trial randomized patients with advanced gastric or GE junction cancers in a 2:1 fashion to ramucirumab versus best supportive care. These patients had previously received platinum or fluoropyrimidine therapy. Patients who received ramucirumab has an improvement in 12-week PFS from 15.8% to 40.1% with overall survival being significantly improved as well (5.2 vs. 3.8 months)[31].

The RAINBOW trial randomized 665 advanced, refractory gastric or GE junction patients to receive paclitaxel plus ramucirumab versus paclitaxel plus placebo. The addition of ramucirumab to paclitaxel significantly improved median PFS from 2.9 months to 4.4 months. Objective response rate was similarly improved from 16% to 28%. Further, the combination of paclitaxel with ramucirumab resulted in a significant improvement in overall survival from 7.4 months to 9.6 months[32].

6. Potential Risks of Ramucirumab Toxicities

The most common toxicities reported with Ramucirumab as monotherapy include hypertension (16%), diarrhea (14%), headache (9%), and hyponatremia (6%). Class-related effects such as hemorrhage (3.4%), arterial thromboembolic events (1.7%), and gastrointestinal perforations (0.7%) were rarely noted. Infusion-related reactions were initially seen in 16% of patients prior to the institution of premedication recommendations.

7. Further Information and Storage
   See Appendix 2 for Package Insert and Investigator's Brochure

4. OBJECTIVES

PRIMARY
Determine the progression-free survival (PFS) of ramucirumab in advanced biliary cancers (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer) who have received prior chemotherapy.

SECONDARY

- Determine the response rate (RR) and disease control rate (partial response + complete response + stable disease) of ramucirumab in advanced biliary cancers
- Determine overall survival (OS) of ramucirumab in advanced biliary cancers
- Evaluate the toxicity of ramucirumab in advanced biliary cancers

EXPLORATORY

- Correlate the carbohydrate antigen (CA) 19-9 response (defined as >50% decrease from baseline) with tumor response, PFS and OS
- Correlate baseline tumor gene expression profile with PFS
- Correlate pre- and post-therapy CT imaging to quantify iodine content, atomic numbers, and Z-values and correlate with response

5. PATIENT ELIGIBILITY

Patients will be included in the study based on the following inclusion and exclusion criteria.

INCLUSION CRITERIA

1. Patient must have cholangiocarcinoma, gallbladder cancer or adenocarcinoma on liver biopsy with clinical features consistent with biliary primary/ cholangiocarcinoma.

2. Metastatic or unresectable disease documented on diagnostic imaging studies.

3. Must have received at least one regimen containing gemcitabine chemotherapy.

4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 (Appendix 1).

5. The patient has adequate hepatic function as defined by a total bilirubin ≤1.5 mg/dL (25.65 µmol/L), and aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 times the upper limit of normal (ULN; or 5.0 times the ULN in the setting of liver metastases).

6. The patient has adequate hematologic function, as evidenced by an absolute neutrophil count (ANC) ≥1000/µL, hemoglobin ≥9 g/dL (5.58 mmol/L), and platelets ≥100,000/µL.

7. The patient does not have:
    a. Cirrhosis at a level of Child-Pugh B (or worse) or
    b. Cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.

8. The patient has adequate renal function as defined by a serum creatinine ≤1.5 times the ULN, or creatinine clearance (measured via 24-hour urine collection) ≥40 mL/minute (that is, if serum creatinine is >1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed).

9. The patient's urinary protein is ≤1+ (≤30-100 mg/dl) on dipstick or routine urinalysis (UA; if urine dipstick or routine analysis is ≥2+ (≥100-300 mg/dl), a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours to allow participation in this protocol).

10. The patient must have adequate coagulation function as defined by International Normalized Ratio (INR) ≤1.5 and a partial thromboplastin time (PTT) (PTT/aPTT) < 1.5 x ULN.). Patients on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin. If receiving warfarin, the patient must have an INR ≤3.0 and no active bleeding (that is, no bleeding within 14 days prior to first dose of protocol therapy) or pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices).

11. Because the teratogenicity of ramucirumab is not known, the patient, if sexually active, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods).

12. Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to enrollment.

13. Patients must sign an Informed Consent and Authorization indicating that they are aware of the investigational nature of this study and the known risks involved.

14. Patient is ≥ 18 years of age on the day of consenting to the study.

15. In the ten patient expanded cohort, patients diagnosed with DNA repair or FGFR genetic aberrations will be enrolled.

EXCLUSION CRITERIA

1. The patient has experienced any Grade 3-4 GI bleeding within 3 months prior to enrollment.

2. Prior therapy with any agent targeting the VEGFR pathway to include bevacizumab, pazopanib, and other anti-angiogenesis inhibitors.

3. The patient has a history of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism, including portal venous thrombosis (venous port or catheter thrombosis, incidental pulmonary embolism diagnosed on imaging studies or superficial venous thrombosis are not considered "significant") during the 3 months prior to randomization.

4. The patient has 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.

5. The patient has uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management.

6. The patient has a serious or non-healing wound, ulcer, or bone fracture within 28 days prior to enrollment.

7. The patient has undergone major surgery within 28 days prior to enrollment, or subcutaneous venous access device placement within 7 days prior to enrollment.

8. The patient is 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.

9. The patient has elective or planned major surgery to be performed during the course of the clinical trial.

10. The patient is pregnant or breast-feeding.

6. TREATMENT PLAN

This is an open-label phase II study. Patients with advanced biliary cancers will be enrolled. All patients must be registered on the M. D. Anderson Cancer Center Clinical Oncology Research (CORe) system prior to initiation of treatment.

This study will enroll up to 60 patients to at MD Anderson Cancer Center. Accrual is projected to be 2.5 subjects per month. If this study proceeds to a future trial for patients with DNA repair gene of FGFR mutations, data obtained from this expanded cohort of 10 patients will be included in final analysis.

This will be an open-label, single arm study with each cycle being 14 days. Ramucirumab will be administered at 8 mg/kg intravenously on day 1 of the cycle. Restaging will be done every 4 cycles (+/- 1week). Treatment will be continued until progression unless other reasons for study discontinuation occur as listed in section 8 "Criteria for Removal from the Study." Additionally, patients who have therapy interrupted for consolidative therapies (including, but not limited to radiation therapy, radioembolization, and chemoembolization) or at the physician's discretion, will remain on study for survival analyses.

Table 2: Starting Dose Level

Drug	Dose	Infusion Time	Schedule (in 14-day cycle)
IV Ramucirumab	8 mg/kg	60 min (+/- 5 min)	Day 1

Dosing and Administration

The study drug will be provided by the sponsor and administered in the following order with the specified pre-medications:

- Premedication should be with an IV H_1 agonist, diphenhydramine 50 mg in NS 50 mL IV within 30 minutes prior to treatment
- Ramucirumab 8 mg/kg in NS to final volume of 250 mL IV over 60 minute on day 1 repeated every 14 days

Dose Modifications and Toxicity Management

Dose modifications and treatment delays based on observed drug-related toxicity will be performed as described below. Any toxicity associated or possibly associated with ramucirumab treatment should be managed according to standard medical practice.

Specific adverse events of concern, which may or may not be associated with ramucirumab therapy, include infusion reactions, hypertension, arterial or venous thrombotic events, bleeding (hemorrhagic) events, and proteinuria. These are specified in greater detail below.

A cycle of therapy may be delayed up to 3 weeks to allow for weather events, patient's personal emergencies, observation of holidays, or other unforeseen delays that the Investigator deems to be in the best interest of the patient. For any dose interruptions, re-initiation of therapy may be delayed for a maximum of 30 days to allow recovery from any toxicity. In exceptional cases where subjects are responding, re-initiation of therapy after missing > 30 consecutive days of treatment may be done on a case-by-case basis after confirmation with the Primary Investigator.

Toxicity will be graded according to the NCI CTCAE, Version 4.0 (which is available at: http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/ctc.htm). For any event which is apparent at baseline, the dose modification will apply according to the corresponding shift in toxicity grade if the investigator feels this is appropriate, (e.g. if a patient has grade 1 asthenia at baseline which increases to grade 2 during treatment, this will be considered as a shift of 1 grade and treated as a grade 1 toxicity for dose modification purposes).

Dose modifications of ramucirumab will be done based on the specific toxicity. Once a dose of

any study drug has been reduced, it should not be increased at a later time. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in progress notes. Growth factors may be used to treat hematologic toxicity and will not constitute a dose reduction. A maximum of a 3-week treatment delay is permitted to allow recovery of toxicities.

Table 3: Dose Levels

Dose Level	Ramucirumab (mg/kg)
0 – baseline	8
-1	6
-2	5

Hematologic Toxicity

Though myelosuprression is expected to be rare, in the event dose modifications are required at the beginning of a cycle due to hematologic toxicities, dose of ramucirumab may be adjusted as detailed below.

Table 4: Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity)

ANC		Platelets	Timing
≥ 1,500 cells/mm^3	AND	≥ 75,000/uL	Treat on time
< 1,500 cells/mm^3	OR	< 75,000/uL	Delay by 1 week intervals until recovery

Special Instructions Regarding Treatment of Chemotherapy-related Toxicity

Dose modification or delay may occur in the setting of lower Grade toxicity if the treating physician believes that it is in the interest of a subject's safety. Alopecia and nausea and/or vomiting that can be controlled by antiemetics do not require dose modification or interruption. No dose reduction or interruption will be required for anemia as it can be satisfactorily managed by transfusions. Dose reductions for non-hematologic toxicity should be as below.

Table 5: Dose Modifications for Ramucirumab on Day 1 of Each Cycle (Non-Hematologic Toxicity)*

Toxicity/Dose Held	Ramucirumab dose this cycle
Grade 0-2 toxicity	Same as Day 1 previous cycle
Grade 3 toxicity	Decrease ramucirumab to next lower dose level
Grade 4 toxicity	Off protocol treatment
Dose held in 2 previous consecutive cycles	Decrease ramucirumab to next lower dose level and continue throughout the rest of treatment

* Drug-specific toxicities are explained in greater detail below with appropriate modifications

6.1 G-CSF Administration

The exact dosage amount and schedule for G-CSF support will be left to the treating physician's discretion. A recommended approach would be to administer G-CSF 5

mcg/kg/day (rounded to the nearest vial size per investigator's standard of care) 24 hours after chemotherapy until recovery to the predetermined neutrophil count.

6.2 Infusion-related reactions

Infusion reactions are defined according to the NCI-CTCAE Version 4.02 definition of infusion-related reactions, (General disorders and administration site conditions, p. 23). Symptoms occurring during or following infusion of investigational therapy may also be defined according to adverse event categories such as allergic reaction, anaphylaxis, or cytokine release syndrome (Immune system disorders, p. 26). In the setting of symptoms occurring during or following infusion of investigational therapy, the adverse event term "Infusion-related Reaction" and any additional terms (including those not listed here) that best describe the event should be used. Those described above should be graded as follows:

Table 6: NCI-CTCAE v 4.02 Infusion-related Reactions

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-related 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, I.V. fluids); prophylactic medications indicated for ≤ 24 hrs	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
Definition: A disorder characterized by an adverse reaction to the infusion of pharmacological or biological substances.					
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤ 24 hrs	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
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: 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.					
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, I.V. fluids); prophylactic medications indicated for ≤ 24 hrs	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; pressor or ventilator support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cell.					

If a patient experiences a Grade 1 or 2 infusion reaction, the infusion rate should be decreased for the duration of the infusion and all subsequent infusions, as directed in the protocol. In addition, patients with Grade 1 and 2 infusion reactions should be treated according to standard medical practices. After a Grade 1 or 2 infusion reaction, patients should be premedicated with antihistamines, steroids, acetaminophen, etc, as appropriate for subsequent infusions.

A Grade 3 or 4 infusion reaction will require immediate treatment, including the use of epinephrine, bronchodilators, and/or glucocorticoids for symptomatic bronchospasm, I.V. fluids and/or pressors for hypotension, and immediate and permanent discontinuation of ramucirumab with appropriate supportive care.

Consistent with usual medical practice, selected parenteral medications may be utilized for Grade 2 infusion-related reactions as detailed below.

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

Grade1

- Slow the infusion rate by 50%
- Monitor the patient for worsening of condition
- For subsequent infusions, continue to premedicate with diphenhydramine hydrochloride 50 mg
  I.V. (or equivalent); additional premedication may be administered at the investigator's discretion

Grade2

- Stop the infusion
- Administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally for fever, and oxygen
- Resume the infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to Grade 1; the infusion duration should not exceed 2 hours
- Monitor for worsening of condition
- For subsequent infusions, continue to premedicate with diphenhydramine hydrochloride 50 mg
  I.V. (or equivalent); additional premedication may be administered at the investigator's discretion

For a second Grade 1 or 2 infusion reaction, administer dexamethasone 8-10 mg I.V. (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally, and dexamethasone 8-10 mg I.V. (or equivalent).

Grade 3

- Stop the infusion and disconnect the infusion tubing from the patient
- Administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), dexamethasone 10 mg I.V. (or equivalent), bronchodilators for bronchospasm, and other medications/treatment as medically indicated
- Patients who have a Grade 3 infusion reaction will not receive further ramucirumab treatment, but will continue to be followed on the protocol

Grade 4

- Stop the infusion and disconnect the infusion tubing from the patient
- Administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), dexamethasone 10 mg I.V. (or equivalent), 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 reaction will not receive further ramucirumab treatment, but will continue to be followed on the protocol

6.3 Hypertension

If a patient develops hypertension during the study, he/she should be treated with antihypertensive medications according to standard medical practice.

Grade<3

- If the hypertension is not associated with symptoms, continue ramucirumab and initiate anti-hypertensive therapy.

- If the hypertension is associated with symptoms, hold ramucirumab until symptoms resolve and initiate anti-hypertensive therapy.
- If ramucirumab therapy is held more than once for hypertension (ie, symptomatic hypertension, markedly elevated blood pressure unresponsive to anti- hypertensive therapy), the dose of ramucirumab should be reduced upon re- treatment (refer to protocol for dose and frequency). A second dose-reduction (refer to protocol for dose and frequency) should be undertaken if an additional postponement of therapy is required.

Grade 3 (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated)

- For Grade 3 hypertension not associated with symptoms, continue ramucirumab with more intensive anti-hypertensive therapy. If systolic BP remains ≥ 160 or diastolic BP ≥ 100 mmHg > 2 weeks after initiation of additional anti-hypertensive therapy, hold ramucirumab while continuing appropriate anti-hypertensive therapy.
- If the hypertension is associated with symptoms, hold ramucirumab until symptoms resolve and initiate anti-hypertensive therapy.
- If ramucirumab therapy is held more than once for hypertension (ie, symptomatic hypertension, markedly elevated blood pressure unresponsive to anti-hypertensive therapy), the dose of ramucirumab should be reduced upon re- treatment . A second dose-reduction should be undertaken if an additional postponement of therapy is required.

Grade 4 or refractory

Patients with Grade 4 hypertension (life-threatening consequences, eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis; or urgent intervention indicated) or patients whose hypertension is poorly controlled (> 160 mmHg systolic or > 100 mmHg diastolic for > 4 weeks) despite appropriate oral medication (> 2 oral agents at maximum tolerated dose) will be discontinued from study therapy.

6.4 Thrombotic Events

Investigators should perform all testing required to fully characterize arterial or venous thrombotic/vascular events. The incidence, type, and diagnostic tests used for the diagnostic confirmation of thrombotic/vascular events will be collected and reported. Because of the high rate of venous thrombotic events in patients with upper gastrointestinal malignancies, and because therapy with antiangiogenic agents has been shown to be feasible in the setting of anticoagulation in patients with upper gastrointestinal malignancies, patients who develop Grade 3-4 venous thrombotic events (deep vein thrombosis [DVT] or pulmonary embolism [PE]) may continue study therapy if the event is not considered to be life-threatening in the opinion of the investigator, the patient is asymptomatic, and/or the event can be adequately treated with low molecular weight heparin-based therapy.

Grade 3-4 arterial thromboembolic events, or any PE/DVT occurring or intensifying during anticoagulant therapy, will warrant discontinuation of study therapy.

6.5 Hemorrhagic Events

Ramucirumab therapy should be discontinued in the event of any Grade 3-4 bleeding (hemorrhagic) event.

6.6 Proteinuria

If, while on therapy, a patient has proteinuria ≥ 2+ per a dipstick (equivalent to ≥ 100-300 mg/dl) or routine urinalysis, ramucirumab therapy will continue as scheduled, and a 24-hour urine collection will be conducted prior to the subsequent scheduled treatment cycle. If the protein level is < 2g/24 hours, the patient will continue on study therapy at the same dose without interruption. If the protein level is 2 to 3 g/24 hours, study therapy for the subsequent cycle will be held for up to 2 weeks and a 24-hour urine collection will be repeated. Treatment will resume at a reduced dose level (6 mg/kg every other week) once the protein level returns to < 2g/24 hours. A second dose reduction (to 5 mg/kg every other week) is permitted if the protein level > 2g/24 hours recurs. The patient will be discontinued from the study if the protein level is > 3g/24 hours, if there is a third occurrence of proteinuria > 2 g/24 hours, or if the protein level does not return to < 2g/24 hours within 2 weeks.

6.7 Gastrointestinal Perforation

An infrequent incidence of gastrointestinal perforations has been associated with some antiangiogenic therapeutic agents, most specifically in the context of colorectal cancer (treated with combination regimens including anti-VEGF antibodies and cytotoxic chemotherapy) and in advanced ovarian cancer. These events may be associated with

extensive abdominal/peritoneal disease burden. Gastrointestinal perforation has been reported from clinical studies investigating ramucirumab. The incidences of these events to date and presence of significant comorbidities and risk factors preclude any definitive association with ramucirumab, although ongoing surveillance remains essential. Three gastrointestinal perforations have been reported in Phase 2 studies investigating ramucirumab (overall incidence, 0.8% of patients). Two of these events occurred on the ovarian cancer study (CP12-0711) and one on the prostate cancer study (CP18-0601). All three cases were reported as SAEs; the events on the ovarian cancer study included a Grade 4 colonic perforation (considered probably related by the investigator) and a Grade 5 bowel perforation (considered unrelated); the perforation occurring on the prostate cancer study was a Grade 3 rectal perforation (possibly related). Each of these events was characterized by extensive abdominal and/or pelvic tumor burden, including an obstructing lesion immediately distal to an area of dilated intestine and perforation (Grade 5 event on the ovarian cancer study), a diffusely infiltrated peritoneum (Grade 4 event on the ovarian cancer study), and prior pelvic radiation (Grade 3 event on the prostate cancer study). Ramucirumab should be permanently discontinued in the event of a gastrointestinal perforation.

Concomitant Medications

Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator. Erythropoietin and G-CSF may be administered at the discretion of the investigator, consistent with institutional guidelines.

7. EVALUATION DURING STUDY

- Patients must begin Cycle 1 within 14 days of signing the informed consent document and after the screening assessments. Treatment will be administered by qualified and trained site personnel in a hospital, clinic, or other out-patient setting appropriate for chemotherapeutic infusions. All assessments should be performed within 72 hours of each specified time parameter, with the exception of Cycle 1 in which assessments must be conducted within 24 hours (except those noted), or if medical or scheduling conditions require a delay. Request of 20 unstained tumor slides of 5 to 10 microns thick will be sent at enrollment.

Day 1 of each cycle (except where noted)

- Inclusion/exclusion review (Cycle 1 only)
- Directed physical exam
- Vital Signs
- Measurement of weight (kg) and BSA calculation prior to dosing.
- ECOG Performance Status (see Appendix 1)
- Hematology: CBC with differential and platelet count

- Serum chemistries: glucose, creatinine, BUN, total bilirubin, AST, ALT, alkaline phosphatase albumin, LDH, total protein, and electrolytes (sodium, potassium, phosphorus, chloride, C02, magnesium, calcium). In patients with known Gilbert's syndrome, it is recommended to perform a direct bilirubin and indirect bilirubin.
- CA 19-9
- Urinalysis
- AEs using the NCI CTCAE (http://ctep.info.nih.gov)
- Concomitant medication notation

Prior to Cycles 4, 8, 12, etc.

- In order to more precisely determine time to progression, the investigator is encouraged to obtain radiological assessments earlier if there is a strong clinical suspicion of disease progression, in order to either confirm or refute the clinical impression.
- Reassessment of the extent of tumor should be made by the same imaging methods used to establish baseline tumor measurements.

Table 7: Study Assessments (treatment cycle is 14 days)

Evaluation or Procedure	Screening[1]	Study Treatment	End of Treatment Evaluation[11]	30-day Post-Treatment Evaluation[12]/Long Term Follow-up
		On or before Day 1 of each cycle		
Informed consent	X			
Medical History	X			
Physical Examination	X	X[3,4]	X	
Inclusion/Exclusion criteria	X			
Height	X			
Weight	X	X[3,4]	X	
Vital Signs (Blood Pressure)	X	X[3,4]	X	
ECOG Performance Status	X	X [3,4]	X	
Hematology[10]	X	X[3,4]	X	
Biochemistry[10]	X	X[3,4]	X	
Urinalysis[10]	X	X[3,4]	X	
Serum or urine pregnancy test (for females of child-bearing potential)	X			
Tumor Tissue Collection	X[2]			
Toxicity assessment	X	X[3.4]	X	X[8]
Diagnostic Imaging for Tumor Assessment, preferably dual-energy CT[7]	X	Every 4 cycles[5]	X[6]	X[6]
Survival				X[9]

1. Informed consent must be obtained before any evaluations are initiated. Diagnostic imaging studies must be completed within 28 days prior to first day of study treatment. All other baseline evaluations, except for height (which can be obtained at

any time prior to enrollment), must be completed within 7 days prior to first dose of study drug.

2. When patients are enrolled, we will collect their pre-existing tissue biopsies, if available, for testing. The Oligo GEArray® Human Angiogenesis Microarray profiles the expression of 113 genes involved in modulating the biological processes of angiogenesis and will be investigated for correlation with outcome, include PFS. Archival tumor biopsy specimens will be used. This investigation will be performed at MD Anderson Core Facility.
3. For Cycle 1, baseline evaluations will suffice as they are performed within 7 days prior to first dose of study drug (except for imaging studies which are performed within 28 days prior).
4. Within 72 hours prior to start of the cycle (except for Cycle 1 as noted above).
5. Imaging should be obtained every 4 cycles (+/- 1week). Evaluations earlier than every 4 cycles are allowed if, in the investigator's opinion, this evaluation is in the patient's best interest.
6. The end of treatment imaging does not have to be repeated if recent imaging has been completed within 4 weeks. For patients discontinued from the study for reasons other than progression, it is recommend to perform every 12 weeks (+/- 5 week) after the End of Treatment Evaluation visit until documentation of progression or for 12 months after their first dose of study drug, whichever comes first, if no other anti-cancer treatment is given.
7. CT of the chest, abdomen, and pelvis. MRI may be used in cases where it is felt to be unsafe to perform CT secondary to patient's history of dye allergy, or if the tumor is not adequately seen on CT for the purposes of this study.
8. Treatment-related adverse events occurring during study treatment or within 30 days (window of 28-35 days allowed) after the last administration of study drug(s) will be followed until resolution or stabilization. If the patient is unable or unwilling to return to M. D. Anderson for this assessment, the patient will be contacted by phone for this assessment.
9. Every 3 months (+/- 5 weeks) from Post-Treatment Evaluation.
10. Hematology: complete blood count with differential. Chemistry: glucose, creatinine, BUN, total bilirubin, AST, ALT, alkaline phosphatase, albumin, LDH, total protein, and electrolytes (sodium, potassium, phosphorus, chloride, C02, magnesium, calcium). Tumor markers (CA19-9) as indicated. Tumor markers are performed every 2 cycles. In patients with known Gilbert's syndrome, it is recommended to perform a direct bilirubin and indirect bilirubin.
11. Within 10 days of decision to discontinue study treatment.
12. At 28-45 days from last dose of study medication.

7.1 End of treatment evaluations

Within 10 days of decision to discontinue treatment

- The investigator will evaluate the results of the following clinical and laboratory assessments to be conducted at the time the patient discontinues study treatment:
- Physical examination with neuropathy assessment
- ECOG Performance Status
- Weight
- Vital signs (blood pressure)
- Hematology: complete blood count with differential
- Biochemistry: glucose, creatinine, BUN, total bilirubin, AST, ALT, alkaline phosphatase albumin, LDH, total protein, and electrolytes (sodium, potassium, phosphorus, chloride, C02, magnesium, calcium). Tumor markers (CA19-9) as indicated. In patients with known Gilbert's syndrome, it is recommended to perform a direct bilirubin and indirect bilirubin.
- Urinalysis
- Concomitant medication notation
- Toxicity (adverse events) assessment (including neurologic toxicities) using NCT CTCAE Version 4.0
- Tumor evaluations including CT scan or MRI of the chest, abdomen, and pelvis (if recent imaging within 4 weeks, tumor evaluation does not need to be repeated)

7.2 Follow-up (off-treatment)

Follow-up/observation for all treatment related adverse events will be through Day 30 (Day 28 to Day 45 allowed) following the last dose of study drug or until resolution or stabilization of the toxicity or start of another treatment regimen. If it is not feasible for the patient to return to M. D. Anderson for the Day 30 toxicity assessment, the patient will be contacted by phone for this assessment.

Patients with documented (radiological) disease progression at any point during the study will discontinue treatment with study drugs under this protocol. Objective evidence of progressive disease will be recorded at the time of progression. Patients without evidence of progression while on study, regardless of the number of treatment cycles received, will be followed for progression until it is documented. If a patient is off treatment with no documented disease progression and no subsequent anti-cancer treatment is received, he/she should be followed every 12 weeks (+/- 5 weeks) after the End of Treatment Evaluation visit with tumor evaluations until disease progression is documented or for 12 months after their first dose of study drug, whichever comes first.

7.3 Long-term followup

All patients will be followed for survival status approximately every 3 months 30-day post-treatment evaluation. Survival status may be obtained by checking the electronic medical record or by telephone call.

8. CRITERIA FOR REMOVAL FROM THE STUDY

Subjects who meet the following criteria should be discontinued from study treatment:

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

9. RESPONSE EVALUATION

9.1 Measurement of effect

Response and progression will be evaluated in this study using the new international RECIST criteria (version 1.1, 2009) proposed by the RECIST committee[33]. All patients who have measurable disease according to the RECIST criteria and who have their disease re-evaluated will be evaluable for response. For the purposes of this study, patients should be reevaluated for response approximately every 4 cycles. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

9.2 Definitions

All sites of disease should be followed as either target or non-target lesions, as categorized at baseline. All measurable lesions up to a maximum of 2 lesions per organ or 5 lesions in total, representative of all involved organs should be identified as target lesions, while all other lesions (either additional measurable lesions or non-measurable lesions) should be classified as non-target lesions. In cases where a target lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. To ensure comparability, the baseline radiology/scans and subsequent radiology/scans to assess response should be performed using identical techniques (eg, scans performed immediately following bolus contrast administration should be made with a standard volume of contrast, the identical contrast agent, and preferably the same scanner). The same method, radiological or physical, should be employed and assessed by the same individual on each occasion, when possible.

9.3 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >10 mm with CT scan (with minimum slice thickness no greater than 5mm, or 10mm caliper measurement by clinical exam, or 20mm by chest X-ray). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Pathological lymph nodes may also be considered as target or non-target lesions. To be considered pathologically enlarged and measurable (target lesion), 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). Lymph nodes with a short axis ≥ 10 mm but < 15 mm

should be considered non-target lesions. Lymph nodes that have a short axis < 10 mm are considered non-pathologic and should not be recorded. The short axis measurement of any lymph node that is considered a target lesion should continue to be recorded regardless if the node progresses to below 10 mm. This may prevent the sum of lesions from being zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. In rare circumstances, when a target lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

9.4 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI). For bone and cystic lesions, please refer to the RECIST criteria (version 1.1, 2009).

9.5 Target lesions

All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters for all target lesions (longest for non-nodal lesions, short axis for nodal lesions) will be calculated and reported as the baseline sum diameters (LD). The baseline sum diameters will be used as reference by which to characterize the objective tumor response.

9.6 Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”). Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

9.7 Guidelines for evaluation of measurable disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
Conventional CT and Magnetic Resonance Imaging. Conventional CT and MRI should be performed to obtain images of 5 mm or less slice thickness.
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 patient to be considered in complete clinical response.
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.

9.8 Response criteria
Evaluation of target lesions

- Complete Response (CR): Disappearance of all target and non-target lesions including normalization of elevated tumor marker level. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. All non-target lymph nodes must be non-pathological in size (< 10 mm short axis). Complete response must be confirmed at a second tumor assessment not less than 4 weeks apart from the assessment at which CR was observed.
- Partial Response (PR): At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD. Partial response must be confirmed at a second tumor assessment not less than 4 weeks apart from the assessment at which PR was observed.
- Progressive Disease (PD): At least a 20% increase (and an absolute increase of at least 5 mm) in the sum of LD of measured lesions taking as references the smallest sum LD recorded since the treatment started. Appearance of new lesions will also constitute PD. In exceptional circumstances, unequivocal progression of non-target lesions may be accepted as evidence of disease progression.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
- Non-CR/Non-PD: Persistence of 1 or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Evaluation of non-target lesions

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level
- Incomplete Response/ Stable Disease (SD): 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
- Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the study chair.
- Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

9.9 Time point evaluation

At each protocol specified time point, a response assessment occurs. Table 9 provides a summary of this for patients who have measurable disease at baseline. Table 10 provides a summary of this for patients with non-measurable (therefore non-target) disease.

Table 8: Response for measurable disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
CR	CR	No	CR	≥ 4 weeks Confirmation
CR	Non-CR/Non-PD	No	PR	≥ 4 weeks Confirmation
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	Documented at least once ≥ 6 weeks from baseline
Not All Evaluated	Non-PD	No	NE	NE
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. NE = inevaluable Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 9: Response for non-measurable disease

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

9.10 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.

Table 10: Response Assignment

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

NE = inevaluable. If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact, the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.
In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

9.11 Confirmation
To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessment at a minimum follow-up interval of 6 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

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

9.13 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.

10. STATISTICAL METHODS

10.1 Study design and sample size
This is a single arm, open label, phase II trial to assess the efficacy and toxicity of ramucirumab in patients with pre-treated, advanced bile duct cancer. The primary objective is to evaluate the efficacy of the therapy. The primary endpoint is the progression-free survival (PFS). A maximum of 60 patients will be enrolled in the study at an estimated accrual rate of 2-3 patients per month. The study will monitor for futility and safety so that it will stop early if based on the interim data, it is unlikely the PFS will be better than that estimated from historical data or the study drug is too toxic.

10.2 Primary efficacy endpoint

The primary endpoint is PFS, which is calculated as the time period from the date of treatment start to the date of disease progression or to the date of death, whichever occurs first, or to the last follow-up date if patients are alive without disease progression. It is expected that the median PFS time will be 3 months or more under this study treatment. If the trial continues to accrual of 60 patients and maintains sufficient follow-up to observe 35 events (PD/death) with a median PFS of 3 months, then the 95% credible interval for the median PFS would extend from 2.1 to 4.2 months.

10.3 Futility monitoring

For futility monitoring, we will monitor PFS using the methods of Thall et al and we will stop enrolling patients to the study if the median PFS is not likely to be longer than that from the historical data, which is around 3 months. Specifically, the trial will be stopped if Pr (lamda(E) > lamda(S) | data from the trial) < 0.05, where lamda(S) is the median PFS for historical patients under conventional care with an inverse gamma distribution IG(58.25,171.75), which corresponds to a mean of 3 months and a standard deviation of 0.4 month (variance = 0.16), the corresponding 95% CI of (2.32, 3.88) months. The prior for lamda(E) is assumed to be IG(2.5625, 4.6875), corresponding to a mean of 3 months and a larger standard deviation of 4 (variance=16, the corresponding 95% CI is 0.72-10.67). Futility monitoring will start once 5 patients have been enrolled. Assuming an accrual rate of 2 per month and an additional follow-up of 6 months, the operating characteristics for the futility stopping rule under various scenarios are summarized in Table 11 below, with results based on 5000 simulations.

Table 11: Operating characteristics for futility monitoring

Median PFS (M)	Prob(Stop Early)	Mean No. of Patients (25%, 75%)
6	0.0058	49.5 (50, 50)
4.5	0.0216	49.1 (50, 50)
3	0.1674	44.2 (50, 50)
2	0.855	23.7 (10,37)
1.5	0.9992	12.3 (7, 16)

10.4 Toxicity monitoring

Unacceptable toxicities will also be monitored closely for the study drug using the method of Thall et al (1995). Denote the probability of unacceptable toxicity by T_E, Unacceptable toxicity will be defined as follows, using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0. For the purpose of toxicity monitoring, only unacceptable toxicities that occur in the first 28 days (i.e., 2 cycles) will be counted when assessing the stopping boundary. That is, a patient will be classified as not having toxicity if the patient has been treated for 28 days and no unacceptable toxicity has been observed.

- Grade 4 neutropenia lasting ≥ 5 days or Grade 3 or 4 neutropenia with fever and/or infection

- Grade 4 thrombocytopenia (or Grade 3 with bleeding)
- Grade 4 anemia
- Grade 3 or 4 non-hematological toxicity [excluding electrolyte abnormalities, alopecia or grade 3 nausea that is correctable with usual supportive medications]
- Dosing delay greater than 14 days due to treatment-emergent AEs or related severe laboratory abnormalities
- Grade 3 hypersensitivity reaction with premedication (Grade 3 hypersensitivity reaction without premedication is not considered a DLT)
- Grade 4 hypersensitivity reaction with or without premedication
- Drug-related fever ≤ Grade 3 will not be considered a DLT.

We assume $T_E \sim$ beta (0.3, 0.7). We will stop the enrollment if at any point $Pr(P_E > 0.30 \mid \text{data}) > 0.9$. That is, we will stop the trial if, at any time during the study, we determine that there is more than 90% chance that the unacceptable toxicity rate is more than 30%. This toxicity monitoring rule will be applied after the first 5 patients have been enrolled and evaluated, and then in cohort size of 5. The corresponding stopping boundaries are to stop the trial if (number of patients with unacceptable toxicities / number of patients) ≥4/5, 6/10, 8/15, 9/20, 11/25, 13/30, 15/35, 16/40, 18/45. The operating characteristics (OCs) are listed in Table 12.

Table 12: OCs for unacceptable toxicity monitoring

True Prob(unacceptable tox)	Pr(stop)	mean # Pts (25%, 50%, 75%)
0.1	0.0006	49.97 (50, 50, 50)
0.2	0.0225	49.21 (50, 50, 50)
0.3	0.2215	43.59 (50, 50, 50)
0.4	0.6869	30.12 (15, 25, 50)
0.5	0.9597	17.77 (10, 15, 20)

Multc Lean V2.1 and OneArmTTE Version 4.1.1 were used for the trial design.

10.5 Futility monitoring in CTC website

The Department of Biostatistics will provide and maintain a website ("Clinical Trial Conduct": https://biostatistics.mdanderson.org/ClinicalTrialConduct/) for futility monitoring for this study. The Clinical Trial Conduct website resides on a secure server, and access is gained through usernames and passwords provided to personnel responsible for enrolling patients and updating patient data. The website is accessed through a browser using secure socket layer (SSL) technology. Personnel responsible for enrolling patients on trials, which includes the principal investigator(s), research nurse(s), and data coordinator(s), will be trained by members of the Department of Biostatistics in the use

of the trial website; the importance of timely updating of follow-up times and recording of events will be emphasized in training.

10.6 Analysis method

Data analysis will be performed using SAS or S-plus, as appropriate. The median PFS time will be estimated by Bayesian posterior estimates, along with the 95% credible interval. Toxicity will be reported by type, frequency and severity. Highest toxicity grades per patient per course will be tabulated for adverse events and laboratory measurements.

Demographic and baseline laboratory results will be summarized using descriptive statistics, including means with standard deviations, or medians with ranges, histograms and box-plot. Fisher's exact test and Wilcoxon rank test will be used in the data analyses of categorical and continuous variables, respectively. Progression-free survival and overall survival functions will be estimated using the Kaplan-Meier method. The two-sided log-rank test will be used to assess the differences of time to events between groups, and Cox proportional hazards model will also be fitted to evaluate the association between time-to-event outcomes and tumor gene expressions. The correlation between pre- and post- therapy CT imaging results will be assessed through Spearman correlation and Wilcoxon signed rank test will be used to assess whether the change in CT imaging between pre- and post-therapy is statistically significant. In addition, logistic regression analyses will be performed to assess the association between CT imaging results or CA19-9 response (defined as >50% decrease from baseline) and tumor response.

11. DATA AND PROTOCOL MANAGEMENT

Designated research personnel must enter the information required by the protocol onto electronic Case Report Forms (CRFs). The University of Texas MD Anderson Cancer Center's Clinical Oncology Research (CORE) system, and the University of Texas MD Anderson Cancer Center's Protocol Data Management System ©(PDMS) CRF system will be used for this study. PDMS is a clinical research information management system. The PDMS CRF is an electronic document designed to record all the protocol-required information to be reported on each trial subject.

PDMS provides data entry templates as defined in the protocol. Laboratory results are automatically transferred from MD Anderson Cancer Center Laboratory Medicine's server to PDMS each morning. Users must have clearance through the MD Anderson Cancer Center Information Services Security Department in order to access PDMS. PDMS login is password protected. The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning attribution for each event for all subjects enrolled on the trial.

12. CORRELATIVE STUDIES

All patients who sign consent for this study will provide consent for the collection of previously collected paraffin embedded tissue. Up to 20 unstained slides of 5 to 10

microns thick will be requested from the outside institution or prepared from the patient's tumor block, if applicable. Any residual tumor tissue above what is specified here will be returned to the sending institution. Collected paraffin embedded tissue will be handled by GI Medical Oncology research personnel. Only the PI and her authorized research staff will have access to the identifiable information from this study. All the samples extracted from the paraffin tissue used in this study will be coded and identifiers (name, medical record number) will not be present on any material that is undergoing analysis. Patient information and relevant data will be stored on password –protected institution computers behind the institution firewall. At the closure of this study all unused material will be either returned to the sending institution or destroyed.

When patients are enrolled, we will collect their pre-existing tissue biopsies, if available, for testing. The Oligo GEArray® Human Angiogenesis Microarray profiles the expression of 113 genes involved in modulating the biological processes of angiogenesis and will be investigated for correlation with outcome, include PFS. Archival tumor biopsy specimens will be used. This investigation will be performed at MD Anderson Core Facility. Recent data suggest that gene expression profiling may be predictive for response to anti-angiogenic agents[34]. In addition, baseline VEGF-A in plasma was suggested as a possible predictive biomarker in a trial of bevacizumab in gastric cancer. Similarly, focal amplification of VEGFA in hepatocellular carcinoma predicted sensitivity to sorafenib both in animal models and in humans[35-37].

Contrast enhanced dual-energy CT's that are triphasic or liver protocol will be utilized as standard of care imaging. This will consist of an arterial phase and a portal venous phase which will be performed on the 64-slice dual-energy CT scanner. All patients will be scanned in the cranio-caudal direction from the dome of the liver to the iliac crest during inspiratory breath-hold. Iodinated contrast medium will be intravenously administered via an automated dual-syringe power injector according to a body weight. The timing for the arterial phase scan will be determined by care bolus technique. AP scanning will start after the attenuation coefficient of abdominal aortic blood reached 100 HU. All images will be post processed to obtain the iodine and water images. Additional analysis will be done on the AW work station. This will allow for iodine content quantification pre- and post-therapy as well as calculation of atomic numbers and Z-values of the tumor in these patients[38,39]. These quantifications will then be correlated with RECIST response measurements.

13. SAFETY REPORTING OF ADVERSE EVENTS

13.1 Adverse Event Reporting and Definitions

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. Adverse events will be collected from the signing of the informed consent until 30 days after the last dose of study drug, or any time after that if the PI determines the event is related to the study drug.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- The severity grade (mild, moderate, severe or grade 1-5)
- Its relationship to the study drug(s) (suspected/not suspected)
- Its duration (start and end dates or if continuing at final exam)
- Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
- Whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.
Information about common side effects already known about drug can be found in the Investigators' Brochure or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

13.2 Adverse event attribution

- **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.

Adverse events for this protocol will be recorded using the Recommended Adverse Event Recording Guidelines for phase II protocols.

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated			Phase II	Phase II	Phase II
Unlikely			Phase II	Phase II	Phase II
Possible	Phase II	Phase II	Phase II	Phase II	Phase II
Probable	Phase II	Phase II	Phase II	Phase II	Phase II
Definitive	Phase II	Phase II	Phase II	Phase II	Phase II

The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning attribution for each event for all subjects enrolled on the trial.

13.3 Serious adverse event (SAE) reporting

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A new diagnosis of cancer during the course of a treatment should be considered as medically important.

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

Pregnancies

Pregnancies occurring while the subject (or female partner of a male subject) is on study or within 30 days after the subject's last dose of ramucirumab are considered expedited reportable events. If the subject is on ramucirumab, it is to be discontinued immediately.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for Expedited Reporting of SAEs to Lilly.

Any suspected fetal exposure to ramucirumab must be reported to Lilly within 24 hours of being made aware of the event. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in utero exposure to ramucirumab should also be reported.

Lilly Drug Safety Contact Information:

Eli Lilly
Global Product Safety Fax Number:
(866) 644-1697 or (317) 453-3402

Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements.

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to Lilly as described below.

Expedited reporting by investigator to Lilly

Serious adverse events (SAE) are defined above. The investigator must inform Lilly in writing using a Lilly SAE form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Lilly by facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Lilly tracking number (I4T-US-I004) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Lilly. A copy of the fax transmission confirmation of the SAE report to Lilly should be attached to the SAE and retained with the patient records. Participating study sites must report SAEs to Lilly as described and within 24 hours of awareness. Participating sites should also report SAEs to MD Anderson Cancer Center, the primary study site.

Report of Adverse Events to the Institutional Review Board

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

Investigator Reporting to the FDA

Serious adverse events (SAEs) that are **unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

Adverse event updates/IND safety reports

Lilly shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects. The Investigator must keep copies of all AE information, including correspondence with Lilly and the IRB/EC, on file.

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Appendix 1 – Eastern Cooperative Oncology Group Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

Appendix 2 Ramucirumab – Additional Information
SEE ATTACHED PACKAGE INSERT AND INVESTIGATOR'S BROCHURE