Phase II Randomized, Double-Blind Study of mFOLFIRINOX plus Ramucirumab versus mFOLFIRINOX plus placebo in Advanced Pancreatic Cancer Patients
HCRN GI14-198

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PROTOCOL SIGNATURE PAGE

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VERSION DATE: 13AUG2018

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the site investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to HCRN and keep a record for your files.

_____ _____

Signature of Site Investigator Date

_____

Site Investigator Name (printed)

_____

Site Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

_____ ❑ Not Submitting to IRB

Expected IRB Approval Date

PLEASE COMPLETE AND EMAIL COPY TO HCRN

SYNOPSIS

TITLE	Phase II Randomized, Double-Blind Study of mFOLFIRINOX plus Ramucirumab versus mFOLFIRINOX plus placebo in Advanced Pancreatic Cancer Patients
SHORT TITLE	Phase II Randomized Trial of mFOLFIRINOX +/- Ramucirumab in Advanced Pancreatic Cancer
PHASE	II
OBJECTIVES	Primary Objective: Estimate and compare progression free survival (PFS) of mFOLFIRINOX plus Ramucirumab (RAM) versus mFOLFIRINOX plus placebo in subjects with recurrent or metastatic pancreas cancer (PCA) who present for first line chemotherapy treatment. Secondary Objectives: • Estimate and compare the median overall survival (mOS) in each arm. • Evaluate and compare the response rate (RR) in each arm. • Evaluate and compare the toxicities in each arm.
STUDY DESIGN	Phase II, multicenter, double-blinded, randomized, 2-arm trial evaluating efficacy and safety of mFOLFIRINOX plus ramucirumab (Arm A) vs. mFOLFIRINOX plus placebo (Arm B) in 85 subjects with advanced PCA, not amenable to curative treatment. Both arms will continue treatment until disease progression or unacceptable toxicity.
ELIGIBILITY CRITERIA	Each of the criteria in the checklist that follows must be met in order for a subject to be considered eligible for this study. **Inclusion Criteria** 1. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately. 2. Age ≥ 18 years at the time of consent. 3. ECOG Performance Status of 0-1 within 7 days prior to registration. 4. Histologic or cytological diagnosis of recurrent or metastatic pancreas adenocarcinoma (PCA) who present for first line chemotherapy treatment. 5. No prior first line systemic treatment (prior adjuvant or neoadjuvant treatment is permitted). Subjects whose disease has progressed after 6 months of last systemic chemotherapy or

chemo-radiation in the adjuvant or neoadjuvant setting are eligible.

6. Measurable disease determined using guidelines of RECIST 1.1. Baseline tumor assessment should be performed using high resolution CT scans or MRI.
7. Urine protein < 1+ on dipstick test or routine urinalysis. If the proteinuria on these tests is ≥ 2+, then a 24-hour urine test must be collected and must demonstrate < 1 g protein in 24 hours to allow participation
8. Estimated life expectancy of > 12 weeks, as assessed by the site investigator.
9. If sexually active, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods) due to unknown risk of teratogenicity of ramucirumab
10. Demonstrate adequate organ function as defined in Table 1 below; all screening labs to be obtained within 7 days prior to registration.

Table 1: Organ Function Requirements

System	Laboratory Value
Hematological	
Hemoglobin	≥ 9 g/dL
Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count (PLT)	≥ 100,000/mm^3
Renal	
Creatinine or Creatinine clearance[1]	≤ 1.5 mg/dL ≥ 40 mL/min
Albumin	≥ 2.5 g/dL
Hepatic	
Bilirubin	≤ 1.5 mg/dL
Aspartate aminotransferase (AST)	≤ 3 × ULN or <5 xULN in the setting of liver metastases
Alanine aminotransferase (ALT)	≤ 3 × ULN or <5 xULN in the setting of liver metastases
Coagulation	
International Normalized Ratio (INR) Patients receiving warfarin must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to first dose of protocol therapy.	The subject has adequate coagulation function as defined by International Normalized Ratio (INR) ≤1.5 and a partial thromboplastin time (PTT) (PTT/aPTT) < 1.5 x ULN.).

[1]: If serum creatinine is >1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed

	Exclusion Criteria 11. Subjects with histology other than adenocarcinoma; Examples include: neuroendocrine tumors, acinar cell cancer, sarcoma or lymphoma of the pancreas 12. Ongoing or active infection 13. Symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia. Symptomatic heart failure (NYHA Class II-IV) 14. Uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management. 15. Acute or sub-acute intestinal obstruction 16. Interstitial pneumonia or interstitial fibrosis of the lung, which in the opinion of the site investigator could compromise the subject or the study 17. Pleural effusion or ascites that causes > grade 1 dyspnea 18. Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) with a history of hepatic encephalopathy or clinical meaningful ascites resulting from cirrhosis; clinically meaningful ascites is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis 19. Grade 3 or higher bleeding event ≤ 3 months prior to randomization. 20. Experience of any arterial thrombotic or arterial thromboembolic events, including, but not limited to myocardial infarction, transient ischemic attack, or cerebrovascular accident, ≤ 6 months prior to randomization. 21. 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 randomization. 22. GI perforation/fistula 23. Documented and/or symptomatic or known brain or leptomeningeal metastases. 24. Severely immune-compromised (other than being on steroids) including known HIV infection 25. Concurrent active malignancy, other than adequately treated non-melanoma skin cancer, other noninvasive carcinoma, or in situ neoplasm. A subject with previous history of malignancy is eligible, provided that he/she has been disease-free for > 3 years. 26. Breast-feeding or pregnant. Serum pregnancy test for women of child-bearing potential must be performed within 7 days prior to first dose of study treatment 27. Prior autologous or allogeneic organ or tissue transplantation. 28. Known allergy to any of the treatment components 29. The patient has undergone major surgery within 28 days prior to

	first dose of protocol therapy, or minor surgery/subcutaneous venous access device placement within 2 days prior to first dose of protocol therapy. The patient has elective or planned major surgery to be performed during the course of the clinical trial. 30. Have any condition that does not permit compliance with the study schedule including psychological, geographical, or medical. 31. Receiving medications that can affect clotting ability: including warfarin, aspirin (once-daily aspirin use- maximum dose 325 mg/day is permitted), nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. 32. Serious or non-healing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy.
STATISTICAL CONSIDERATIONS	We aim to test the null hypothesis of PFS at 6 months. Using a one-sided log-rank test we have estimated a sample size of 85 patients (43 in one and 42 in another arm) which will provide 80% power under a type 1 error of 20%. This is an estimation on 24 months accrual and 9 months follow up after accrual for the primary endpoint. Sample size may increase to 95 to account for a 10% drop out rate. The primary endpoint of this clinical trial is PFS. PFS is defined as the time from enrollment to the time of progression or death. An interim analysis with Kaplan Meier method and Logrank test will be conducted after 23 subjects have been enrolled in each arm and followed up for 9 months. The trial will stop if it detects a significant difference of 3 months in PFS between the study arm-mFOLFIRINOX/RAM, as compared to the standard arm-mFOLFIRINOX at the significance level of 0.0013 according to the O'Brien-Fleming approach. Otherwise the trial will continue until the targeted sample size has been completed. RR, PFS and OS will be reported with 95% confidence intervals. Response is defined as a complete or partial response according to CT/MRI evaluations based on RECIST 1.1 criteria. Toxicity will be graded using CTCAE v4 **Early stopping:** In the case of excessive toxicity, safety-stopping rules will be used. A grade ≥3 or adverse event that will lead to stop or termination of treatment is defined as suspected treatment related toxicity observed in the first 4 weeks of enrollment after dose modification, but excluding: nausea or vomiting and hematologic toxicities if not adequately treated. Ramucirumab will be held for drug related adverse events grade ≥ 3 until recovery to grade ≤ 1 and then resumed with a lower dose level -1 (6 mg/kg). If the grade ≥ 3 related adverse events does not resolve within 3 weeks of holding treatment, subject will be taken off the trial. In the case of prolonged or medically concerning grade 2 toxicity related to chemotherapy combination, treatment will be interrupted until

	recovery to grade ≤ 1, at which time treatment will be resumed at the same dose. If the adverse event does not resolve in or within 2 weeks with medical intervention, then the subject will be taken off trial. In case of excessive toxicity, safety-stopping rules will be used. An acceptable toxicity rate will be assumed at 0.20. The study will be stopped based on an unacceptable excessive toxicity rate of 0.40. A sequential probability ratio test will be used where a likelihood ratio of 8 in favor of an excessive toxicity rate of 0.40 (vs. 0.20) provides sufficient evidence to stop the study due to excessive toxicity. Toxicity will be continuously reviewed for excessive toxicity and statistical analysis performed if excessive toxicity is suspected. In the interim safety analysis, the study will be closed to accrual after the first 20 subjects (10 in each arm) are analyzed, if within the first cycle of treatment n/10 subjects developed any of the following grade ≥ 3 toxicity: 2/10 febrile neutropenia, 3/10 neuropathy, 3/10 hypertensive emergency or urgency, 3/10 life threatening thromboembolic event, 2/10 GI perforation or 2/10 bleeding or hemorrhage, the regimen mFOLFIRINOX RAM will be considered toxic and the trial will stop.
TOTAL NUMBER OF SUBJECTS	N = 85 to 95
ESTIMATED ENROLLMENT PERIOD	Estimated 24 months
ESTIMATED STUDY DURATION	Estimated 33 months

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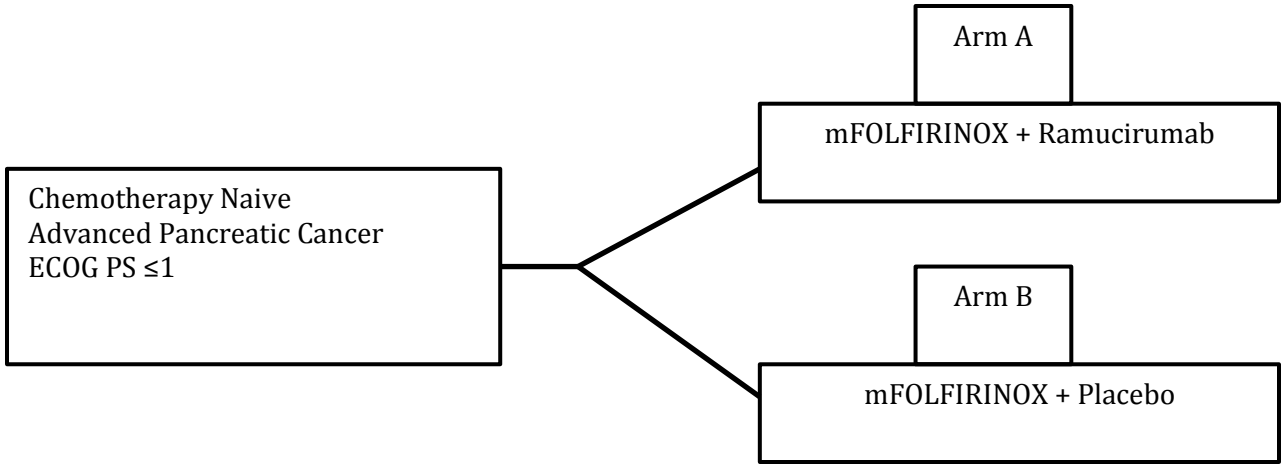
SCHEMA


Arm A
mFOLFIRINOX + Ramucirumab
Chemotherapy Naive
Advanced Pancreatic Cancer
ECOG PS ≤1
Arm B
mFOLFIRINOX + Placebo

1. BACKGROUND AND RATIONALE

1.1 Disease Background

The prognosis of pancreas adenocarcinoma (PCA) remains poor with little progress made in the last few decades with the exception of FOLFIRINOX (PRODIGE 4/ACCORD 11) [1] and gemcitabine/nab-Paclitaxel (MPACT trial) [2] treatments in 2011 and 2013, respectively, changing the PCA management paradigm with a median overall survival (OS), at best, reaching 11.1 months. Despite these advances, there is a continuous need to improve survival through the investigation of molecularly targeted agents.

Vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR)-mediated signaling and angiogenesis contribute to the pathogenesis and progression of PCA. [3,4] VEGF is expressed in all PCA tumors. [5] VEGF-A/VEGFR-2 signaling plays an important role in inducing invasion and migration of PCA cells. [6,7] VEGFR-2 and phosphorylated-VEGFR-2 (pVEGFR-2) are expressed in 69% and 50% of 107 PCA. The pVEGFR-2 is significantly associated with invasion of the anterior capsule of pancreas and arteries. It is proposed that the expression of these receptors is an important predictive and prognostic factor in PCA treatment. [6,8]

Results from anti-angiogenic agents studied in advanced PCA failed to significantly improve primary outcomes. The use of bevacizumab was evaluated in the AViTA Trial (Addition of bevacizumab to gemcitabine and erlotinib) and the reported negative primary outcome (OS). [9] Another phase III trial with gemcitabine and bevacizumab (10 mg/kg) combination compared to gemcitabine alone (CALGB 80303) proved same outcomes (P= 0.95). [10] Axitinib, in a phase III trial, compared gemcitabine/Axitinib to gemcitabine alone in the same setting, and yielded no significant difference in overall survival (OS). [11] Interestingly, and challenging the findings from single agent backbone studies, the combination of gemcitabine and a fluoropyrimidine (5FU or capecitabine) with bevacizumab reached their primary endpoints in two separate single arm phase II trials. [4,12] Additionally, a pooled analysis of 300 subjects enrolled in all single arm phase II trials utilizing gemcitabine-based doublets with bevacizumab proved survival advantage compared to historical controls. [13] These studies demonstrate the feasibility of building upon more intensive chemotherapy backbones, specifically those including a fluoropyrimidine with bevacizumab combinations in PCA.

As suggested above, the choice of a chemotherapeutic backbone may impact the efficacy of anti-angiogenic therapy in PCA. In a preclinical study, the anti-tumor activity of fluoropyrimidines but not that of gemcitabine caused the release of bone marrow derived circulating endothelial progenitor cells (CEPs) and Tie-2 expressing monocytes (TEMs) as well as the induction of pro-angiogenic growth factors. Anti-angiogenic agents inhibit the CEP and TEM mobilization and pro-angiogenic signaling and thus enhance significantly the anti-tumor activity of fluoropyrimidines but not that of gemcitabine. [14] Additionally, gemcitabine-induced myelosuppression in subjects with PCA was found to interfere with the mobilization of pro-angiogenic cell types targeted by bevacizumab and may further counteract anti-angiogenic therapy by substantially reducing the angiogenesis inhibitor TSP-1. [15] These findings may explain why gemcitabine does not elicit TEM and CEP recruitment and may therefore lack synergy with anti-VEGF agents. This phenomenon is not known to

occur with fluoropyrimidines. FOLFIRINOX, a combination of a fluoropyrimidine, oxaliplatin and irinotecan, proved to have a large and significant survival advantage over gemcitabine alone in advanced PCA, [1] thus the choice of FOLFIRINOX combination in our proposed trial. The AViTA Trial (Addition of bevacizumab to gemcitabine and erlotinib) suggests that a subset of PCA subjects with elevated VEGF-A or VEGFR-2 levels may benefit from bevacizumab. [9,16]

1.2 Ramucirumab Clinical Experience

Ramucirumab (RAM) (IMC-1121B, trade name Cyramza) is a fully human monoclonal antibody (IgG1) directed mainly against VEGFR-2. RAM also blocks binding of VEGFR ligands, VEGF-A, VEGF-C, and VEGF-D. As a result, RAM inhibits ligand-stimulated activation of VEGFR-2, thereby inhibiting ligand-induced proliferation, and migration of human endothelial cells. RAM received its first global approval by the FDA on April 21, 2014 as monotherapy in the treatment of advanced or metastatic gastric cancer or gastro-esophageal junction (GEJ) adenocarcinoma subjects who experience disease progression on or after 5FU- or platinum-containing chemotherapy. This approval was granted following the results of the REGARD trial, which compared RAM, as a single agent, to placebo in second line treatment of gastric and GEJ adenocarcinomas. [17] RAM had significant OS benefit when combined to paclitaxel in advanced/metastatic gastric and GEJ adenocarcinoma in the second line setting (RAINBOW trial). [17,18] These results have shifted the treatment paradigm in the treatment of gastric and GEJ cancers despite the initial disappointments with phase II trials utilizing another anti-angiogenic agent, bevacizumab. [19-22] These negative results were reflected in the international, randomized phase III AVAGAST (Avastin for Advanced Gastric Cancer) study, in which 774 subjects with advanced gastric or GEJ adenocarcinoma were randomized to a cisplatin/capecitabine with bevacizumab or placebo. [23] Given these opposing results between bevacizumab and RAM in gastric and GEJ cancers, it is becoming clearer that blocking VEGFR-2 (RAM) has a likely advantage over blocking VEGF-A (bevacizumab). More recently, the RAISE trial demonstrated the benefit of using ramucirumab in the setting of metastatic colorectal cancer. This trial compared ramucirumab versus placebo in combination with FOLFIRI in the second line setting for subjects with metastatic colorectal carcinoma. In this study, 536 subjects were assigned to each arm and ramucirumab plus FOLFIRI significantly improved OS with a manageable side effect profile.[24]

Currently there are no validated predictive biomarkers for selecting which cancer subjects will benefit from anti-angiogenic therapy.[25] Albumin has shown to play a role as a prognostic factor in advanced stage bevacizumab treated PCA subjects. A pooled analysis of 7 prospective trials showed that normal albumin levels (>3.4 g/dL) were associated with significantly improved median OS (10.2 months vs. 4.1 months; P=0.0001), median time to tumor progression (TTP) of 6.2 vs. 3.7 months (P=0.0488), and disease control rate (71% vs. 46%; P=0.007) for subjects receiving bevacizumab, but not for those treated without bevacizumab. [26]

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

Estimate and compare PFS of mFOLFIRINOX plus ramucirumab (RAM) versus mFOLFIRINOX plus placebo in subjects with recurrent or metastatic pancreas cancer (PCA) who present for first line chemotherapy treatment.

2.1.2 Secondary Objectives

- Estimate and compare the median overall survival (mOS) in each arm.
- Evaluate and compare the response rate (RR) in each arm.
- Evaluate and compare the toxicities in each arm.

2.2 Endpoints

2.2.1 Primary Endpoint

Nine month PFS is based upon the time of registration until progression or death. Disease is evaluated by CT/MRI scans of the organ(s) with the target lesion(s) based on RECIST 1.1 criteria.

2.2.2 Secondary Endpoints

- Median overall survival (mOS) will be measured using the Kaplan-Meier method.
- Response rate (RR) will be evaluated per RECIST 1.1
- Toxicity evaluation will be assessed per CTCAE v4

3. ELIGIBILITY CRITERIA

Each of the criteria in the checklist that follows must be met in order for a subject to be considered eligible for this study.

3.1 Inclusion Criteria

1. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.
2. Age ≥ 18 years at the time of consent.
3. ECOG Performance Status of 0-1 within 7 days prior to registration.
4. Histologic or cytological diagnosis of recurrent or metastatic pancreas adenocarcinoma (PCA) who present for first line chemotherapy treatment.
5. No prior first line systemic treatment (prior adjuvant or neoadjuvant treatment is permitted). Subjects whose disease has progressed after 6 months of last systemic chemotherapy or chemo-radiation in the adjuvant or neoadjuvant setting are eligible.
6. Measurable disease determined using guidelines of RECIST 1.1. Baseline tumor assessment should be performed using high resolution CT scans or MRI.
7. Urine protein < 1+ on dipstick test or routine urinalysis. If the proteinuria on these tests is ≥ 2+, then a 24-hour urine test must be collected and must demonstrate < 1 g protein in 24 hours to allow participation

8. Estimated life expectancy of > 12 weeks, as assessed by the site investigator.
9. If sexually active, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods) due to unknown risk of teratogenicity of ramucirumab
10. Demonstrate adequate organ function as defined in Table 1 below; all screening labs to be obtained within 7 days prior to registration. Include additional labs or remove as needed below and ensure they are included in the Study Calendar and Evaluations Section

Table 1: Organ Function Requirements

System	Laboratory Value
Hematological	
Hemoglobin	≥ 9 g/dL
Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
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International Normalized Ratio (INR) Patients receiving warfarin must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to first dose of protocol therapy	The subject has adequate coagulation function as defined by International Normalized Ratio (INR) ≤1.5 and a partial thromboplastin time (PTT) (PTT/aPTT) < 1.5 x ULN.).

[1:] If serum creatinine is >1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed.

3.2 Exclusion Criteria

1. Subjects with histology other than adenocarcinoma; Examples include: neuroendocrine tumors, acinar cell cancer, sarcoma or lymphoma of the pancreas
2. Ongoing or active infection
3. Symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia. Symptomatic heart failure (NYHA Class II-IV)

4. Uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management.
5. Acute or sub-acute intestinal obstruction
6. Interstitial pneumonia or interstitial fibrosis of the lung, which in the opinion of the site investigator could compromise the subject or the study
7. Pleural effusion or ascites that causes > grade 1 dyspnea
8. Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) with a history of hepatic encephalopathy or clinical meaningful ascites resulting from cirrhosis; clinically meaningful ascites is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis
9. Grade 3 or higher bleeding event ≤ 3 months prior to randomization.
10. Experience of any arterial thrombotic or arterial thromboembolic events, including, but not limited to myocardial infarction, transient ischemic attack, or cerebrovascular accident, ≤ 6 months prior to randomization.
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16. Breast-feeding or pregnant. Serum pregnancy test for women of child-bearing potential must be performed within 7 days prior to first dose of study treatment
17. Prior autologous or allogeneic organ or tissue transplantation.
18. Known allergy to any of the treatment components
19. The patient has undergone major surgery within 28 days prior to first dose of protocol therapy, or minor surgery/subcutaneous venous access device placement within 2 days prior to first dose of protocol therapy. The patient has elective or planned major surgery to be performed during the course of the clinical trial.
20. Have any condition that does not permit compliance with the study schedule including psychological, geographical, or medical.
21. Receiving medications that can effect clotting ability: warfarin, aspirin (once-daily aspirin use- maximum dose 325 mg/day is permitted), nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents.
22. The patient has a serious or non-healing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy.

4. SUBJECT REGISTRATION

All subjects must be registered through HCRN electronic data capture (EDC) system. A subject is considered registered when an "On Study" date is entered into the EDC system.

Subjects must be registered and randomized prior to starting protocol therapy. Subjects must be randomized **within one business day** of registration and begin therapy **within 5 business days** of randomization.

4.1 Blinding

Site pharmacy staff and HCRN EDC administrative team will be unblinded to the study treatment. Subjects, site investigators, site analysis teams, and other site personnel will be blinded to the study treatment.

Unblinding of site personnel may occur for emergency purposes only. Site investigators should note that the occurrence of a serious adverse event or progressive disease should not routinely precipitate the immediate unblinding of the label. The site investigator will contact HCRN to unblind a subject. If this is not feasible, HCRN must be notified **within 24 hours** of unblinding.

In compliance with applicable regulations, in the event of a serious adverse event (SAE), the subject's treatment assignment may be unblinded before reporting to the health authorities, ethic committees, and site investigators if the SAE was related (possibly, probably, definitely) to the blinded treatment.

5. TREATMENT PLAN

5.1 Treatment Regimen

One cycle will be equal to 28 days. The ramucirumab/placebo will be administered prior to the mFOLFIRINOX regimen. Both arms will receive mFOLFIRINOX regimen given per institutional standards (suggested administration sequence below), which will be a modification of the previously published regimen. [27] mFOLFIRINOX will be administered every 2 weeks. Dose modifications for all medications are outlined in Section 6:

- Arm A will receive ramucirumab administered as an intravenous infusion over 60 minutes (infusion rate should not exceed 25 mg/min), at a fixed dose of 8 mg/kg every 2 weeks.
- Arm B will receive a placebo infusion. Due to the double-blinded nature of this study, the volume of placebo will be calculated as if it were ramucirumab.
- Oxaliplatin 85 mg/m^2 over 2-4 hours
- Irinotecan 165 mg/m^2 over 90 minutes
- 5-FU 2,400 mg/m^2 as a 46-hour continuous infusion without the 5-FU bolus to decrease the risk of neutropenia.

Leucovorin is not included in this regimen since the 5-FU is administered as a continuous infusion and not in bolus form.

5.2 Pre-medications and Home Medications

5.2.1 Pre-medications

The following medications will be administered:

- Palonosetron 250 mcg IV within 30 minutes prior to oxaliplatin and 5-FU
- Dexamethasone 20 mg IV or PO within 30 minutes prior to oxaliplatin and 5-FU
- Atropine 0.4 mg IV within 30 minutes prior to Irinotecan. May repeat 1 dose for cramping or diarrhea.
- Diphenhydramine 50 mg IV within 30 minutes prior to ramucirumab/placebo.

5.2.2 Home Medications

The following are suggested medications to be provided to the subject to take home:

- Prochlorperazine 10 mg PO every 6 hours PRN nausea/vomiting.
- Loperamide PRN diarrhea. Subject will be instructed to take 4 mg PO at onset of diarrhea, followed by 2 mg PO every 2 hours (or 4 mg every 4 hours at night) until 12 hours have passed without a bowel movement.

5.3 Drug Administration

Table 2. Drug Administration

Drug	Dose	Frequency of administration	Route of administration
Ramucirumab or Placebo	8 mg/kg	Every 2 weeks	IV; infusion rate should not exceed 25 mg/min
Oxaliplatin	85 mg/m^2	Every 2 weeks	IV over 2 to 4 hrs
Irinotecan	165 mg/m^2	Every 2 weeks	IV over 90 min
5-FU	2,400 mg/m^2	Every 2 weeks	IV 46-hour continuous infusion

Body surface area and drug doses should be recalculated for subject's whose weight changes by ≥ 10% during the course of the study.

Leucovorin is not included in this regimen since the 5-FU is administered as a continuous infusion and not in bolus form.

5.3.1 Missed Doses

All medications are given on Day 1. A missed dose implies delay of that cycle. Infusions may be given within 3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. It should be clearly documented in subject's chart and case report forms.

5.4 Supportive Care

Subjects should receive full supportive care in accordance with ASCO or equivalent guidelines on supportive care for solid tumors, if necessary. Supportive care measures may include but are not limited to anti-diarrheal agents, anti-emetic agents, opiate and non-opiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Subjects will receive supportive care as judged by their treating physician. If it is unclear whether a therapy should be regarded as supportive care, the site investigator should consult with HCRN. Use of any supportive care therapy should be reported on the eCRFs.

5.4.1 Analgesic agents

The use of analgesic agents during the study is permitted at the discretion of the site investigator. The subject is receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents will be excluded. Once-daily aspirin use (maximum dose 325 mg/day) is permitted. Chronic use of analgesic agents with no or low bleeding risk (for example acetaminophen) is acceptable. See exclusion criteria above for additional information.

5.4.2 Antiemetic therapy

The use of antiemetic agents is permitted during this study and at the discretion of the site investigator. However, it is recommended to follow the guidelines of the Multinational Association of Supportive Care in Cancer (MASCC) and ASCO.

5.4.3 Appetite Stimulants

The use of appetite stimulants is permitted at the discretion of the site investigator.

5.4.4 Blood Product Transfusions

Transfusions of red blood cells, platelets or other blood products are permitted at the site investigators discretion during the conduct of the study.

5.4.5 Treatment of Diarrhea

In the event of diarrhea, the following supportive measures are strongly recommended:

Subjects should be advised to drink at least 3 L of fluids per day. Frequent small meals are recommended.

Upon the subject experiencing the first episode of a loose stool, the subject should take an initial dose of loperamide 2 capsules (4 mg) by mouth, then l capsule (2 mg) by mouth every 2 hours or 2 capsules every 4 hours overnight for at least 12 hours after the first liquid stool and up to 12 hours after the last liquid stool without exceeding total treatment duration of 48 hours.

For uncomplicated Grade 1 or 2 diarrhea that does not resolve after 24 hours, start a broad spectrum antibiotic such as a fluoroquinolone for a 7-day course. After 48 hours of unresolved uncomplicated Grade 1 or 2 diarrhea the subject should stop loperamide and be evaluated in the out subject setting with a stool workup, complete blood count (CBC) and

replacement of fluids and electrolytes as clinically indicated. A second-line agent, such as octreotide, should then be considered.

Octreotide has been shown to be effective in the control of diarrhea induced by fluoropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. Octreotide can be administered at doses starting from 100 mcg 3 times daily and escalating to 500 mcg 3 times daily.

Subjects should be admitted to the hospital whenever they present with Grade 3 or 4 diarrhea, or when they have complicated Grade 1 or 2 diarrhea, defined as having diarrhea *plus* one or more of the following symptoms: cramping, nausea/vomiting grade ≥ 2, decreased performance status, fever, sepsis, neutropenia, frank bleeding or dehydration. If the subject is already on loperamide, it should be stopped, and the subject should be started on octreotide, intravenous fluids and undergo a stool workup CBC and electrolyte evaluation, with repletion as clinically indicated. In addition, if the subject is febrile or has an ANC < 500 a broad-spectrum antibiotic should be started for at least 7 days and until the resolution of fever and an ANC ≥ 1000. Events that require a subject to be hospitalized are considered SAEs.

It is imperative that subjects have access to loperamide for home use prior to the start of each cycle. In addition, subjects should receive oral and written information about the risk for diarrhea, associated symptoms and instructions on how to manage diarrhea. This includes the need for oral hydration, when and how to take medications, when to notify the site physician and when to report to the hospital for further treatment. These recommendations have been adapted from the ASCO guidelines (Benson et al. 2004)

5.4.6 Erythroid Growth Factors

The use of erythroid-stimulating factors is permitted at the discretion of the site investigator based on ASCO and FDA guidelines (FDA 2009; Rizzo et al.2010) or according to local guidelines.

5.4.7 Therapy for Febrile Neutropenia

Subjects experiencing febrile neutropenia, especially with diarrhea or dyspnea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of intravenous antibiotic therapy.

5.4.8 Granulocyte Colony-Stimulating Factors

The use of granulocyte-colony stimulating factor (G-CSF) or similar agents is permitted during this study, at the discretion of the site investigator based on local guidelines or ASCO (Smith et al. 2006), European Society for Medical Oncology (Crawford et al. 2009). Note that prophylactic use of G-CSF or similar agents is also permitted.

5.4.9 Hand-Foot Syndrome

Also called palmar-plantar erythrodysesthesia is a side effect of some types of chemotherapy. Treatment with pyridoxine (B6) at a dose of 100 to 150 mg per day is allowed.

5.4.10 Hypersensitivity Reactions

Premedication for ramucirumab/placebo administration: H1 antagonist (for example, diphenhydramine hydrochloride) intravenously. Additional premedication and treatment may be provided at site investigator discretion. All premedication administered must be adequately documented in the eCRF.

Premedication after first episode of grade 1 or 2 infusion-related reaction: Subjects should be premedicated within 30 minutes prior to infusion with antihistamines, corticosteroids, acetaminophen, etc.

Treatment for second episode of grade 1 or 2 infusion-related reaction: administer dexamethasone 8 to 10 mg I.V. (or equivalent). For subsequent infusions pre-medicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally and dexamethasone 8 to 10 mg I.V. (or equivalent). Reduce the ramucirumab infusion rate by 50% for the duration of the infusion and all subsequent infusions if the patient experiences a Grade 1 or 2 IRR (per NCI-CTCAE).

Treatment for grade 3 or 4 infusion-related reaction: Subjects should be treated with epinephrine, bronchodilators and/or glucocorticoids for symptomatic bronchospasm and I.V. fluids and/or pressors for hypotension. Subjects with grade 3 or 4 infusion reaction must not receive further treatment with ramucirumab.

5.4.11 Contraception

Ramucirumab may have adverse effects on a fetus in utero. Furthermore, it is not known if ramucirumab has transient adverse effects on the composition of sperm. Subjects should start using birth control from time of consent throughout the study period up to 90 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.5 Treatment Compliance

Ramucirumab/placebo, 5-FU, Irinotecan, oxaliplatin will be administered only at HCRN sites by the authorized study personnel. As a result, treatment compliance is ensured.

5.6 Concurrent Therapy

Additional concurrent chemotherapy or radiation therapy, biologic response modifiers, or other investigational agents may not be administered to subjects on this study. However, palliative radiation during the study is allowed if clinically indicated.

5.7 Concomitant Medications

Medications allowed:

- Medications required for supportive care during the study (See Section 5.4)
- Medications subject requires for treatment of previous comorbidities.

6. Toxicity Monitoring and Dose Modifications

The NCI Common Terminology Criteria for Adverse Events CTCAE v4 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

6.1 Dose Modifications for Ramucirumab/placebo

Ramucirumab/placebo will be held for Grade ≥ 3 study drug related adverse events until recovery to Grade ≤ 1 and then resume with a dose reduction (level -1; 6 mg/kg) if site investigator evaluation relates toxicity to ramucirumab/placebo. If a second Grade ≥ 3 drug related adverse event is experienced and does not resolve within 2 weeks of the initial dose reduction, an additional dose reduction (level -2; 5mg/kg) will be made. If Grade ≥ 3 related adverse event does not resolve within 2 weeks of the second dose reduction, the subject will be taken off the trial.

Table 3. Modified dose of ramucirumab

Dose level	Ramucirumab
Starting dose	8 mg/kg
Level -1 dose reduction	6 mg/kg
Level -2 dose reduction	5 mg/kg

Table 4. Dosing level of ramucirumab/placebo for treatment related adverse events

Toxicity NCI Grade (value)	Worst Interval Toxicity	Day of Treatment
1	Maintain dose level	Continue treatment per protocol schedule.
2	Maintain dose level	Hold until resolved to grade 1 or less.
3	Reduce to dose level -1 6 mg/kg	Hold until resolved to grade 1 or less.
4	Reduce to dose level -2 5 mg/kg	Hold until resolved to grade 1 or less.

6.1.1 Management of Hypertension

Interrupt ramucirumab/placebo for severe hypertension until controlled with medical management. Permanently discontinue ramucirumab/placebo for severe hypertension that cannot be controlled with antihypertensive therapy. The subject will continue to be followed per guidelines in Section 7. Subjects with grade 4 hypertension must not receive further treatment with ramucirumab

6.1.2 Proteinuria

Interrupt ramucirumab/placebo for urine protein levels ≥ 2 g/24 hours. Reinitiate treatment at a dose level -1 reduction (see Table 3) once the urine protein level returns to <2 g/24 hours. If the protein level ≥ 2 g/24 hours reoccurs, interrupt ramucirumab/placebo and reduce the dose to dose level -2 (table 4) once the urine protein level returns to < 2 g/24 hours. Permanently 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. Permanently discontinue ramucirumab/placebo for urine protein level >3 g/24 hours or in the setting of nephrotic syndrome

6.1.3 Wound Healing Complications

Interrupt ramucirumab/placebo prior to scheduled surgery until the wound is fully healed

6.1.4 Thyroid Dysfunction

Monitor thyroid function during treatment with ramucirumab. In Study 4, the incidence of hypothyroidism reported as an adverse event was 2.6% in the ramucirumab plus FOLFIRI treated subjects and 0.9% in the placebo plus FOLFIRI treated subjects.

6.1.5 Venous Thromboembolic Events

Ramucirumab therapy should be discontinued in the event of any Grade 3/4 VTE that is considered by the site investigator to be life threatening, or symptomatic and not adequately treated by anticoagulation therapy. 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. Ramucirumab should

also be discontinued in the setting of a deep vein thrombosis or pulmonary embolism that occurs or intensifies while the patient is receiving therapeutic anticoagulation therapy. Any venous event leading to discontinuation of ramucirumab therapy will be considered serious and should be reported via the serious adverse event (SAE) mechanism.

6.1.6 Conditions for permanent discontinuation of ramucirumab/placebo

Listed below are clinical conditions in which ramucirumab/placebo should be permanently discontinued.

- Grade 3 and 4 arterial thromboembolic events, or any PE/DVT occurring or worsening during anticoagulant therapy. Any arterial event leading to discontinuation of ramucirumab therapy will be considered serious and should be reported via the serious adverse event (SAE) mechanism.
- Subjects with Grade 4 hypertension must not receive further treatment with ramucirumab
- Gastrointestinal Perforation
- Grade 3 or 4 Bleeding
- Grade 3 or 4 Infusion Reaction
- Hepatic encephalopathy or other serious signs of liver impairment such as hepatorenal syndrome
- Fistula Formation
- Reversible Posterior Leukoencephalopathy (RPLS); All cases of RPLS must be reported via the SAE reporting guidelines.

6.2 Dose Modification for mFOLFIRINOX

Toxicities to 5-Fluorouracil (5-FU), oxaliplatin and irinotecan may include hematologic and non-hematologic events. The dose adjustment of 5-Fluorouracil, oxaliplatin, and irinotecan for hematologic toxicity is shown in Table 5.

Table 5: Modified dosing of the mFOLFIRINOX combination

Dose level	Oxaliplatin	Irinotecan	5-FU Infusion
Starting dose	85 mg/m^2	165 mg/m^2	2400 mg/m^2
First dose reduction	50 mg/m^2	150 mg/m^2	1800 mg/m^2
Second dose reduction	40 mg/m^2	127 mg/m^2	1200 mg/m^2

6.2.1 Dose Modifications of mFOLFIRINOX for Hematologic Toxicity

Dose adjustments of oxaliplatin, irinotecan and 5-FU on subsequent treatment cycles, will be based on the worst hematologic toxicity due to any of the chemotherapy agents on any day of the previous cycle. See Table 6.

Table 6: Dosing level of Oxaliplatin, Irinotecan and 5-FU for hematologic toxicity

Toxicity NCI Grade (value)	Worst Interval Toxicity	Day of Treatment
Neutropenia Grade 1 (ANC< LLN-1500/mm^3) Grade 2 (ANC<1499-1000/ mm^3) Grade 3 (ANC<999-500/ mm^3) Grade 4 (ANC<500/ mm^3)	G1 Maintain dose level G2 Maintain dose level G3 Maintain dose level G4 Reduce 5-FU, oxaliplatin and irinotecan 1 dose level	If ANC < 1000 mm3 on day of treatment, hold and check weekly until >1000 mm3. Then treat based on interval toxicity
Thrombocytopenia Grade 1 (PLT < 75,000/mm^3) Grade 2 (PLT 74,999-50,000/mm^3) Grade 3 (PLT 49,999-25,000/mm^3) Grade 4 (PLT<25,000/ mm^3)	G1 Maintain dose level G2 Maintain dose level G3 Reduce 5-FU, oxaliplatin, irinotecan 1 dose level G4 Reduce 5-FU, oxaliplatin and irinotecan 1 dose level	If PLT < 75,000 on day of treatment, hold and check weekly until > 75,000. Then treat based on interval toxicity
Recommend red cell transfusion for hemoglobin < 8 g/dL, no dose adjustment required.		

6.2.2 Dose Modifications for Other Treatment Related Non-Hematological Toxicity

Dose adjustments of oxaliplatin, irinotecan and 5-FU on subsequent treatment cycles will be based on the worst non-hematologic toxicity due to any of the chemotherapy agents on any day of the previous cycle. If neurologic toxicity appears, only oxaliplatin dose should be modified. See Table 7 for all non-hematologic toxicities except neurologic toxicity and Table 8 for neurologic toxicity.

Table 7: Dosing level of Oxaliplatin, Irinotecan, and 5-FU for non-hematologic toxicity (except diarrhea and neurologic toxicity)

Toxicity NCI Grade	Worst Interval Toxicity	Day of Treatment
Non-Hematologic Toxicity (Except diarrhea and neurologic toxicity) Grade 1 Grade 2 Grade 3 Grade 4	G1: Maintain dose level G2: Maintain dose level G3: Reduce irinotecan, 5-FU and/or oxaliplatin 1 dose level. G4: Reduce irinotecan, 5-FU and/or oxaliplatin 1 dose level.	G1: Continue treatment per protocol schedule. G2: Hold until resolved to grade 1 or less. G3: Hold until resolved to grade 1 or less. G4: Hold until resolved to grade 1 or less.
Toxicity NCI Grade	**Worst Interval Toxicity**	**Day of Treatment**
Diarrhea Grade 1 Grade 2 Grade 3 Grade 4	G1: Maintain dose level G2: Reduce 5-FU, oxaliplatin, irinotecan 1 dose level G3: Reduce 5-FU, oxaliplatin, irinotecan 1 dose level G4: Reduce 5-FU, oxaliplatin, irinotecan 1 dose level	Hold chemotherapy if any grade of diarrhea above baseline is present with the subject not taking anti-diarrheal agents within 24 hours of treatment. Decrease irinotecan and oxaliplatin 1 dose level upon resolution of diarrhea. If diarrhea has not resolved within 2 weeks of scheduled treatment day, discontinue therapy.

Table 8. Modified dosing of oxaliplatin for neurologic toxicity.

Toxicity	Duration of Toxicity		
Parasthesia/dysesthesia	1-7 Days	> 7 Days	Persistent Between Doses
Grade 1 Short duration that resolves and does not interfere with function	No change	No change	No change
Grade 2 Interferes with function but not activities of daily living (ADL)	No change	No change	Reduce oxaliplatin 1 dose level
Grade 3 With pain or with functional impairment that also interferes with ADL	1st time: reduce 1 dose level 2nd time: reduce another dose level	1st time: reduce 1 dose level 2nd time: reduce another dose level	Discontinue oxaliplatin
Grade 4 Persistent symptoms that are disabling or life-threatening	Discontinue oxaliplatin	Discontinue oxaliplatin	Discontinue oxaliplatin

6.3 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities, a subject will also be discontinued from protocol therapy and followed up per protocol under the following circumstances:

- Evidence of disease progression
- The site physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - In case a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant
- If protocol therapy is interrupted for ≥ 30 days.

6.4 Study Withdrawal

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The site investigator should contact the subject or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the subject's study withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

CYCLE = 28 DAYS

Examination	Screening	Cycle 1–2		Cycle 3–4		Cycle 5+		End of Treatment Visit	Follow up
	Within 28 days of registration	Day 1 (±7)	Day 15 (±3)	Day 1 (±3)	Day 15 (±3)	Day 1 (±3)	Day 15 (±3)	30 days (± 7) after last dose of study drug	
REQUIRED ASSESSMENTS									
Demographics and Medical History/Height	X								
Physical Examination	X	X	X	X	X	X	X	X	
Vital Signs and ECOG PS[1]	X	X	X	X	X	X	X	X	
Comprehensive Metabolic Panel[2]	X	X	X	X	X	X	X	X	
Magnesium and uric acid	X	X	X	X	X	X	X	X	
CBC with Differential and platelet[3]	X	X	X	X	X	X	X	X	
PT, PTT, INR[11]	X								
CA19-9[4]	X	X		X		X			
Pregnancy Test (Urine or Serum β-HCG)[5]	X								
Urinalysis[6]	X	X		X		X			
AEs and Con Meds	X	X	X	X	X	X	X	X	
Thyroid function (TSH, total T_3, free T_4)[10]	X		X		X		X		
Diagnosis Confirmation[7]	X								
DISEASE ASSESSMENT									
CT or MRI of Chest, Abdomen and Pelvis[8]	X			X		X		X	X[9]
TREATMENT									
mFOLFIRINOX every 2 weeks		X	X	X	X	X	X		
Ramucirumab/placebo every 2 weeks		X	X	X	X	X	X		
FOLLOW-UP									
For progression, start of additional cancer treatment, and survival[9]									X[9]

1: Vital signs to include blood pressure, weight, height (screen only) and ECOG performance status.

2: CMP to include Sodium, potassium, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, calcium, random glucose, albumin

3: CBC to include Hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume, mean cell hemoglobin concentration, leukocytes (WBC), neutrophils, lymphocytes, monocytes, basophils, platelets

4: CA19-9 at screening and every 2 cycles

5: Serum pregnancy test for women of child-bearing potential must be performed within 7 days prior to first dose of study treatment

6: Protein in the urine should be monitored prior to each cycle. Urine dipstick may be used to quantify the amount if necessary.

7: Confirmation of diagnosis must be obtained during screening. A pathology report with staging information will be obtained from the institution that performed the diagnosis procedure.

8: Scans to be repeated every 8 weeks (± 7 days) until progression of disease. Pre-treatment scans to be performed within 28 days prior to registration.

9: For subjects who discontinue study treatment without radiographically documented PD, the investigative sites will continue to evaluate tumor response every 8 weeks (± 7 days) by the same method used at baseline and throughout the study until time of disease progression, death or until study completion, except when not feasible in the opinion of the site investigator due to subject's clinical status. After the subject has documented PD, radiologic assessments are no longer required and the subject will be followed every 8 weeks (± 7 days) until the subject's death or study completion, whichever is earlier.

10: If the TSH is abnormal, a total T3 and free T4 should be ordered.

11: Coagulation tests should be periodically repeated during the course of the study per site investigator discretion.

7.1 Screening

7.1.1 Within 28 Days Prior to Registration for Protocol Therapy:

The following should be collected before registration for protocol therapy:

- Prior to the subject being registered to the study, confirmation of diagnosis must be obtained via pathology report including staging information.
- Medical history and Height
- Physical examination
- Vitals Signs (including blood pressure), Weight [kg] and ECOG PS
- Laboratory Testing:
  - CBC with differential: Hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume, mean cell hemoglobin concentration, leukocytes (WBC), neutrophils, lymphocytes, monocytes, basophils, platelets.
  - CMP: Sodium, potassium, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, calcium, random glucose, albumin
  - Magnesium and uric acid
  - Coagulation tests: PT, INR and PTT; coagulation tests should be periodically repeated during the course of the study per site investigator discretion.
  - CA 19-9
  - Thyroid function (TSH, total T_3, free T_4). If the TSH is abnormal, a total T3 and free T4 should be ordered.
  - Serum pregnancy test for women of child-bearing potential must be performed within 7 days prior to first dose of study treatment
  - Urinalysis including a urine dipstick for protein if quantification needed
- Radiological assessment (CT or MRI of chest, abdomen, and pelvis) with tumor measurements. Pre-treatment scans to be performed within 28 days prior to registration.

7.1.2 On Treatment; Day 1 of each cycle

Note: Day 1 lab testing need not be repeated if completed within 7 days of starting protocol therapy.

- Physical examination
- Vitals Signs (including blood pressure), Weight [kg] and ECOG PS
- Laboratory Testing:
  - CBC with differential: Hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume, mean cell hemoglobin concentration, leukocytes (WBC), neutrophils, lymphocytes, monocytes, basophils, platelets.
  - CMP: Sodium, potassium, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, calcium, random glucose, albumin
  - Magnesium and uric acid
  - CA 19-9 every 2 cycles
  - Urinalysis including a urine dipstick for protein if quantification needed
- CT or MRI of chest, abdomen/pelvis after every 2 cycles of treatment
- mFOLFIRINOX and ramucirumab/placebo

7.1.3 On Treatment; Day 15 of each cycle

- Physical examination
- Vitals Signs (including blood pressure), Weight [kg] and ECOG PS
- Laboratory Testing:
  - CBC with differential: Hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume, mean cell hemoglobin concentration, leukocytes (WBC), neutrophils, lymphocytes, monocytes, basophils, platelets.
  - CMP: Sodium, potassium, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, calcium, random glucose, albumin
  - Magnesium and uric acid
  - Thyroid function (TSH, total T_3, free T_4). If the TSH is abnormal, a total T3 and free T4 should be ordered.
- mFOLFIRINOX and ramucirumab/placebo

7.1.4 Protocol therapy discontinuation:

A subject will be discontinued from the protocol therapy under the following circumstances:

- Evidence of disease progression (per RECIST 1.1)
- Site physician determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy
- Subject exhibits unacceptable toxicity
- Female subject becomes pregnant
- Protocol therapy is interrupted for ≥ 30 days.

7.1.5 Safety follow up visit 30 days (±7 days) after last dose of study treatment

Subjects will be evaluated 30 days (± 7) after the last dose of study drug. Suggested testing includes:

- Physical examination
- Vitals Signs (including blood pressure), Weight [kg] and ECOG PS
- Laboratory Testing:
  - CBC with differential: Hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume, mean cell hemoglobin concentration, leukocytes (WBC), neutrophils, lymphocytes, monocytes, basophils, platelets.
  - CMP: Sodium, potassium, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, calcium, random glucose, albumin
  - Magnesium and uric acid

7.1.6 Follow-up

For subjects who discontinue study treatment without radiographically documented PD, the investigative sites will continue to evaluate tumor response every 8 weeks by the same method used at baseline and throughout the study until time of disease progression, death or until study completion, except when not feasible in the opinion of the site investigator due to subject's clinical status.

After the subject has documented PD, radiologic assessments are no longer required and the subject will be followed up every 8 weeks (+/- 7 days) until the subject's death or study completion, whichever is earlier.

8. CRITERIA FOR DISEASE EVALUATION

8.1 Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [28]

8.1.1 Measurable disease

The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

8.1.2 Measurable lesions

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, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

8.1.3 Non-measurable lesions

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, and abdominal masses (not followed by CT or MRI), are considered as 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 subject, these are preferred for selection as target lesions.

8.1.4 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.

8.1.5 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.

8.1.6 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.

8.2 Response Criteria

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

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 subject 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 sponsor-investigator.

Evaluation of best overall response

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
	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

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

Subjects 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) to confirm the complete response status.

8.3 Definitions for Response Evaluation – RECIST version 1.1

8.3.1 First Documentation of Response
The time between initiation of therapy and first documentation of PR or CR.

8.3.2 Duration of Response
Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

8.3.3 Duration of Overall Complete Response
The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

8.3.4 Objective response rate
The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST v1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

8.3.5 Disease Control Rate
The disease control rate is the proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST v1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

8.3.6 Time to Progression
A measurement from the date of randomization until the criteria for disease progression is met as defined by RECIST 1.1. Subjects who have not progressed or have died due to any cause will be right-censored at the date of the last disease evaluation or date of death.

8.3.7 Progression Free Survival
A measurement from the date of randomization until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

8.3.8 Overall Survival
Overall survival is defined by the date of randomization to date of death from any cause.

9. DRUG INFORMATION

9.1 Ramucirumab (Cyramza)

9.1.1 Formulation and Storage

Ramucirumab 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). The buffer contains 10 mM histidine, 75 mM sodium chloride, 133 mM glycine and 0.01% polysorbate 80, pH 6.0.

Vials of ramucirumab should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. The vial should be kept in the outer carton in order to protect from light. For product diluted in 0.9% sodium chloride, the chemical and physical stability have been demonstrated for up to 24 hours at 2°C to 8°C (36°F to 46°F) or for 4 hours at room temperature (below 25°C [77°F]). The diluted product should not be frozen or shaken.

9.1.2 Preparation and Administration

Inspect vial contents for particulate matter and discoloration prior to dilution. Discard the vial, if particulate matter or discolorations are identified. Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light.

- Calculate the dose and the required volume of ramucirumab needed to prepare the infusion solution. Vials contain either 100 mg/10 mL or 500 mg/50 mL at a concentration of 10 mg/mL solution of ramucirumab.
- Withdraw the required volume of ramucirumab and further dilute with only 0.9% Sodium Chloride Injection in an intravenous infusion container to a final volume of 250 mL. Do not use dextrose containing solutions.
- Gently invert the container 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.
- Store diluted infusion for no more than 24 hours at 2°C to 8°C (36°F to 46°F) or 4 hours at room temperature (below 25°C [77°F]).
- Discard vial with any unused portion of ramucirumab.

Visually inspect the diluted solution for particulate matter and discoloration prior to administration. If particulate matter or discolorations are identified, discard the solution.

Administer diluted RAM infusion via infusion pump over 60 minutes through a separate infusion line. Use of a protein sparing 0.22 micron filter is recommended. Flush the line with sterile sodium chloride (0.9%) solution for injection at the end of the infusion.

9.1.3 Dosage Information

Injection:
100 mg/10 mL (10 mg per mL) solution, single-dose vial
500 mg/50 mL (10 mg per mL) solution, single-dose vial

9.1.4 Handling and Disposal

The vial of ramucirumab should be kept in the outer carton in order to protect from light. Neither the vial nor the diluted solution should be frozen or shaken.

9.1.5 Adverse Events

For a comprehensive list of adverse events please refer to the package insert for ramucirumab.

The following are adverse events that have been reported:

- Cardiovascular: Hypertension, arterial thrombosis.
- Hematologic: neutropenia, anemia, hemorrhage.
- Respiratory: Epistaxis
- Gastrointestinal: Diarrhea (14%), intestinal obstruction (2%)
- Genitourinary: Proteinuria
- Endocrine & metabolic: Hyponatremia
- Central nervous system: Headache.
- Immunologic: Antibody development.
- Dermatologic: Skin rash.
- Miscellaneous: Infusion related reaction
- Thyroid Dysfunction: Hypothyroidism 2.6%

9.2 5-Fluorouracil/Adrucil

9.2.1 Formulation and Storage

Fluorouracil injection is a sterile, nonpyrogenic injectable solution for intravenous administration. Each 10 mL contains 500 mg fluorouracil; pH is adjusted to approximately 9.2 with sodium hydroxide.

Fluorouracil should be stored at room temperature 15° to 30°C (59° to 86°F). Protect from light. Retain in carton until time of use.

NOTE: Although fluorouracil solution may discolor slightly during storage, the potency and safety are not adversely affected.

9.2.2 Adverse Events

For a comprehensive list of adverse events please refer to the package insert for 5-Fluorouracil. The following are the adverse reactions most likely to occur on this study.
Hematologic: Agranulocytosis, anemia, leukopenia (nadir: days 9-14; recovery by day 30), pancytopenia, thrombocytopenia

- Central nervous system: Acute cerebellar syndrome, confusion, disorientation, euphoria, headache, nystagmus, stroke

- Cardiovascular: Angina, arrhythmia, heart failure, MI, myocardial ischemia, vasospasm, ventricular ectopy
- Respiratory: Epistaxis
- Gastrointestinal: Anorexia, bleeding, diarrhea, esophagopharyngitis, mesenteric ischemia (acute), nausea, sloughing, stomatitis, ulceration, vomiting
- Dermatologic: Alopecia, dermatitis, dry skin, fissuring, nail changes (nail loss), palmar-plantar erythrodysesthesia syndrome, pruritic maculopapular rash, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, vein pigmentation
- Ocular: Lacrimation, lacrimal duct stenosis, photophobia, visual changes
- Local: Thrombophlebitis
- Miscellaneous: Anaphylaxis, generalized allergic reactions

9.3 Irinotecan/Camptosar

9.3.1 Formulation and Storage

Irinotecan is a sterile, pale yellow, clear, aqueous solution. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol, NF, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Irinotecan is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

Irinotecan should be stored at controlled room temperature 15° to 30°C (59° to 86°F) and protected from light. Keep the vial in the carton until the time of use.

The solution is physically and chemically stable for up to 24 hours at room temperature and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C, 36° to 46°F), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Freezing CAMPTOSAR and admixtures of CAMPTOSAR may result in precipitation of the drug and should be avoided.

9.3.2 Preparation and Administration

Inspect vial contents for particulate matter and discoloration and repeat inspection when drug product is withdrawn from vial into syringe.

Irinotecan injection 20 mg/mL is intended for single use only and any unused portion should be discarded.

Irinotecan injection must be diluted prior to infusion. Irinotecan should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 mg/mL to 2.8 mg/mL. Other drugs should not be added to the infusion solution.

The CAMPTOSAR Injection solution should be used immediately after reconstitution as it contains no antibacterial preservative. Because of possible microbial contamination during dilution, it is advisable to use the admixture prepared with 5% Dextrose Injection, USP, within 24 hours if refrigerated (2° to 8°C, 36° to 46°F). In the case of admixtures prepared with 5% Dextrose Injection, USP, or Sodium Chloride Injection, USP, the solutions should be used within 4 hours if kept at room temperature. If reconstitution and dilution are performed under strict aseptic conditions (e.g., on Laminar Air Flow bench), CAMPTOSAR Injection solution should be used (infusion completed) within 12 hours at room temperature or 24 hours if refrigerated (2° to 8°C, 36° to 46°F).

Care should be exercised in the handling and preparation of infusion solutions prepared from irinotecan injection. The use of gloves is recommended. If a solution of irinotecan contacts the skin, wash the skin immediately and thoroughly with soap and water. If CAMPTOSAR contacts the mucous membranes, flush thoroughly with water.

9.3.3 Adverse Events

For a comprehensive list of adverse events please refer to the package insert for irinotecan.

The following are the adverse events most likely to occur with this medication

- Cardiovascular: Vasodilation, edema, hypotension, thromboembolic events.
- Central nervous system: Cholinergic toxicity, fever, pain, dizziness, insomnia, headache, chills, somnolence, confusion.
- Dermatologic: Alopecia, rash
- Endocrine & metabolic: Dehydration,
- Gastrointestinal: Diarrhea, diarrhea, nausea, abdominal pain, vomiting, cramps, anorexia, constipation, mucositis, weight loss, flatulence, stomatitis, abdominal fullness, dyspepsia.
- Hematologic: Anemia, leukopenia, thrombocytopenia, neutropenia, neutropenic fever, hemorrhage, neutropenic infection.
- Hepatic: Bilirubin increased, alkaline phosphatase increased, AST increased, ascites, jaundice.
- Neuromuscular & skeletal: Weakness, back pain
- Respiratory: Dyspnea, cough, rhinitis, pneumonia.
- Miscellaneous: Diaphoresis, infection

9.4 Oxaliplatin/Eloxatin

9.4.1 Formulation and Storage

Oxaliplatin is a sterile, preservative-free, aqueous solution at a concentration of 5 mg/ml. Water for Injection, USP is present as an inactive ingredient.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Do not freeze and protect from light (keep in original outer carton).

9.4.2 Preparation and administration

Do not freeze and protect from light the concentrated solution. A final dilution must never be performed with a sodium chloride solution or other chloride containing solutions. The solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP. After dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)]. After final dilution, protection from light is not required. ELOXATIN is incompatible in solution with alkaline medications or media (such as basic solutions of 5-fluorouracil) and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with 5% Dextrose Injection, USP prior to administration of any concomitant medication. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and discarded if present. Needles or intravenous administration sets containing aluminum parts that may come in contact with ELOXATIN should not be used for the preparation or mixing of the drug. Aluminum has been reported to cause degradation of platinum compounds.

9.4.3 Handling and disposal

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from ELOXATIN. The use of gloves is recommended. If a solution of ELOXATIN contacts the skin, wash the skin immediately and thoroughly with soap and water. If ELOXATIN contacts the mucous membranes, flush thoroughly with water. Procedures for the handling and disposal of anticancer drugs should be considered.

9.4.4 Adverse Events

For a comprehensive list of adverse events please refer to the package insert for Oxaliplatin/Eloxatin

- Central nervous system: Peripheral neuropathy, fatigue, pain, headache, insomnia, rigors, dizziness.
- Cardiovascular: Edema, chest pain, peripheral edema, flushing, thromboembolism.
- Gastrointestinal: Nausea, diarrhea, vomiting, abdominal pain, constipation, anorexia, stomatitis, dyspepsia, dysgeusia, flatulence, hiccups, mucositis, gastroesophageal reflux disease, dysphagia.
- Hematologic & oncologic: Anemia, thrombocytopenia, leukopenia, neutropenia.
- Hepatic: Increased serum AST, increased serum ALT, increased serum bilirubin.
- Endocrine & metabolic: Dehydration, hypokalemia.
- Neuromuscular & skeletal: Back pain, arthralgia.
- Respiratory: Dyspnea, cough, upper respiratory tract infection, rhinitis, epistaxis, pharyngitis, pharyngolaryngeal dysesthesia.
- Renal: Increased serum creatinine
- Dermatologic: Skin rash, alopecia, palmar-plantar erythrodysesthesia
- Hypersensitivity: Hypersensitivity reaction (includes urticaria, pruritus, facial flushing, shortness of breath, bronchospasm, diaphoresis, hypotension, syncope)
- Local: Injection site reaction

- Ocular: Abnormal lacrimation
- Miscellaneous: Fever

10 ADVERSE EVENTS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be utilized for AE reporting. A copy of the CTCAE v4 can be downloaded from the CTEP website at http://ctep.cancer.gov

10.1 Definitions

10.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

10.1.2 Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence resulting in one or more of the following:

- Death- Death due to progression is not considered a SAE unless the site investigator feels the study drug contributed to disease progression.
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic

bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

10.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

10.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is not related to the study drug(s)
Unlikely	Adverse Event is doubtfully related to the study drug(s)
Possible	Adverse Event may be related to the study drug(s)
Probable	Adverse Event is likely related to the study drug(s)
Definite	Adverse Event is clearly related to the study drug(s)

10.2 Reporting adverse events

10.2.1 Adverse Event (AE)

- AEs will be recorded from time of signed informed consent until 30 days after discontinuation of study drug(s).
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within EDC system.
- AEs considered related to study drug(s) will be followed until resolution to Grade ≤ 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.

10.2.2 Serious Adverse Event (SAE)

10.2.2.1 Site Requirements for Reporting SAEs to HCRN

- SAEs will be reported from time of signed informed consent until 30 days after discontinuation of study drug(s).
- SAEs will be reported on the SAE Submission Form **within 24 hours** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within EDC system.

- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The completed SAE Submission Form must be sent electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements. The original copy of the SAE Submission Form and the email correspondence must be kept within the Trial Master File at the study site.

Once the SAE has resolved (see resolution guidelines listed in 11.2.2.1), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

10.2.2.2 HCRN Requirements for Reporting SAEs to Eli Lilly

HCRN will report all SAEs to Eli Lilly at Global Patient Safety via fax **within 24 hours** of receipt of the SAE Submission Form from the site. The fax number to send the form is 866-644-1697 or 317-453-3402. Follow-up information will be provided to Eli Lilly and Co. as reasonably requested.

10.2.2.3 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 24 hours** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

10.2.2.4 HCRN Requirements for Reporting to the Food and Drug Administration (FDA)

This protocol was determined to be exempt from the requirements of an IND by the FDA. HCRN will continue to facilitate compliance of applicable requirements for the sponsor-investigator in relation to this study. This includes but is not limited to 21 CFR 50.20 informed consent, 21 CFR Part 56 IRB, and pertinent sections of the Public Health Service Act and FDAAA.

11. STATISTICAL METHODS

11.1 Study Design

This is a phase II, multicenter, double-blinded, randomized, 2-arm trial evaluating the efficacy and safety of mFOLFIRINOX + RAM (Arm A) vs. mFOLFIRINOX + placebo (Arm B) in 85 subjects with advanced PCA, not amenable to curative treatment. Subjects will be randomized in a 1:1 ratio (i.e., there will be 43 subjects in the control group and 42 subjects in the treatment group). The primary objective of this trial is to estimate and compare PFS in Arm A versus Arm B. See section 11.10 for a description of the power/sample size analysis based on the logrank test.

11.2 Definition of Primary Endpoint

PFS is based upon the time of enrollment until progression or death. Disease is evaluated by CT/MRI scans of the organ(s) with the target lesion(s) based on RECIST 1.1 criteria.

11.3 Definitions of Secondary Endpoints

Overall survival is defined as the time of enrollment to time of death. Response is defined as a complete or partial response according to CT/MRI evaluations based on RECIST 1.1 criteria. CTCAE v4 is used to grade toxicities.

11.4 Analysis Plan for Primary Objective

PFS will be estimated for each arm using the method of Kaplan and Meier. Nine month PFS will be reported along with a 95% confidence interval. PFS will be compared between Arm A and Arm B using a one-sided logrank test. The ITT analysis dataset will be used for this analysis.

11.5 Analysis Plan for Secondary Objectives

OS will be estimated for each arm using the method of Kaplan and Meier. Median OS will be reported along with a 95% confidence interval. OS will be compared between the two arms using a logrank test. RR will be estimated for each arm and reported along with exact 95% confidence intervals. A Fisher's exact test will be used to compare RR between the two arms. Toxicities will be described for each arm using frequency tables. Fisher's exact tests will be used compare toxicities between arms. The ITT analysis dataset will be used for secondary analyses related to OS and RR. The safety analysis dataset will be used for analyses related to toxicities.

11.6 Excessive Toxicity – Criteria for Stopping and Interim Safety Analysis

In case of excessive toxicity, safety-stopping rules will be used. An acceptable toxicity rate will be assumed at 0.20. The study will be stopped based on an unacceptable excessive toxicity rate of 0.40. A sequential probability ratio test will be used where a likelihood ratio of 8 in favor of an excessive toxicity rate of 0.40 (vs. 0.20) provides sufficient evidence to stop the study due to excessive toxicity. Data will be continuously reviewed for excessive toxicity and statistical analysis performed if excessive toxicity is suspected. The table below provides the minimum number of patients exhibiting excessive toxicity that will trigger statistical analysis.

Total number of treated patients	Number of Patients observed with excessive toxicity
3	≥2
4-5	≥3
6-7	≥4
8-9	≥5
10-11	≥6
12-13	≥7
14-16	≥8
17-18	≥9
19-20	≥10

21-23	≥11
24-25	≥12
26-28	≥13
29-30	≥14
31-33	≥15
34-35	≥16
36-38	≥17
39-40	≥18

Ramucirumab will be held for drug related adverse events Grade ≥ 3 until recovery to Grade ≤ 1 and then resumed with a lower dose level -1 (6 mg/kg). If the Grade ≥ 3 related adverse event does not resolve within 4 weeks of holding treatment, the subject will be taken off study treatment.

In the case of prolonged or medically concerning Grade 2 toxicity related to the chemotherapy combination, treatment will be interrupted until recovery to Grade ≤ 1, at which time treatment will be resumed at the same dose. If the adverse event does not resolve in or within 2 weeks with medical intervention, then the subject will be taken off study treatment.

11.6.1 Excessive Toxicity

Excessive toxicity is defined as any adverse event that meets the following criteria:

- Any grade 3 or higher adverse event or an adverse event that leads to discontinuation of study therapy.
- The adverse event must be possibly, probably or definitely related to any of the study treatments (Ramucirumab, Oxaliplatin, Irinotecan, 5-FU)
- The adverse event occurs in the first four weeks of treatment
- The adverse event grade does not diminish to grade 1, four weeks after dose modification or dose delay. AE must have been adequately treated (e.g. nausea, vomiting, hematologic toxicities)

11.6.2 Interim Safety Analysis

The study will be closed to accrual and an interim safety analysis conducted after ten subjects are accrued to each arm. If the following rates of selected toxicities listed below are observed within the first cycle of treatment (four weeks), the regimen (Ramucirumab, Oxaliplatin, Irinotecan, 5-FU) will be considered toxic and the trial will be stopped.

Adverse Event (≥ grade 3)	**Toxicity Rate (n/10 subjects)**
Febrile Neutropenia	2/10
Peripheral Motor or Sensory Neuropathy	3/10
Hypertension	3/10
Life Threatening Thromboembolic Event	3/10
GI Perforation	2/10
Hemorrhage, Bleeding	2/10

11.7 Interim Analysis for Efficacy

An interim analysis with the Kaplan-Meier method and logrank test will be conducted after 23 subjects have been enrolled in each arm and followed up for 9 months. The trial will stop if it detects a significant difference in PFS between the two arms at the significance level of 0.0013 according to the O'Brien-Fleming approach. Otherwise the trial will continue until the targeted sample size has been completed.

11.8 Un-blinding Plan

See section 4.1.

11.9 Analysis Datasets

The intention-to-treat (ITT) analysis dataset includes all subjects who meet the eligibility criteria and are registered onto the study irrespective of their compliance to the planned course of treatment. The intention-to-treat principle asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analyzed as members of that group irrespective of their compliance to the planned course of treatment.

The safety analysis dataset includes all subjects who are randomized and receive at least one dose of study treatment (on either arm). Subjects will be analyzed for safety according to the treatment actually received.

11.10 Sample Size/Accrual/Study Duration

We aim to test the null hypothesis of PFS at 6 months. Using a one-sided log-rank test we have estimated a sample size of 85 patients (43 in one and 42 in another arm) which will provide 80% power under a type 1 error of 20%. This is an estimation on 24 months accrual and 9 months follow up after accrual for the primary endpoint. Sample size may increase to 95 to account for a 10% drop out rate.

The expected progression free survival for mFOLFIRINOX in metastatic pancreatic cancer is 6 months. The addition of RAM to mFOLFIRINOX would be expected to increase the median PFS to at least 9 months. We assume a type 1 error (α) of 0.2 and a power ($1-\beta$) of 80%.

With an exact power of 0.8014, hazard ratio of 0.6667 and endpoint of detecting 3 months PFS advantage of the mFOLFIRINOX/ramucirumab combination over mFOLFIRINOX alone (from 6 to 9 months), the sample size on each arm was calculated to be 43 in the control arm and 42 in the treatment arm (total is 85). [29,30]

The estimated enrollment period for this study is 24 months and the estimated study duration is 33 months.

11.11 Subject Characteristics and Significant Protocol Violations
Baseline, demographic, and medical history information will be summarized for each arm. Demographic and baseline data will also be provided in by-subject data listings.

11.12 Concomitant Medications
Concomitant medication use will be summarized for each arm and will be included in by-subject data listings.

11.13 Disposition
A tabulation of subject disposition will be presented, including the number in each analysis dataset, the number who withdrew from treatment and the reasons for withdrawal, and the number who withdrew during the follow-up phase and the reasons for withdrawal.

12. TRIAL MANAGEMENT

12.1 Data and Safety Monitoring Plan
The study will be conducted in accord with the Winship Cancer Institute of Emory University's Data and Safety Monitoring Plan (DSMP).

In addition, HCRN data and safety activities include**:**

- Review all adverse events requiring expedited reporting as defined in the protocol
- Notify participating sites of adverse events requiring expedited reporting
- Provide data summary reports to the sponsor-investigator on a monthly basis
- Submit data summary reports to the lead institution Data Safety Monitoring Committee for review as per their guidelines.

12.2 Winship Cancer Institute Data Safety Monitoring Committee
The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study which has been deemed Moderate Risk. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Since this study is Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review the following:

- Adverse event summary report
- Monitoring and/or audit results if applicable
- Summary of enrollment including number of subjects consented, enrolled, treated and active and discontinued
- Any regulatory compliance findings from all active sites
- Summary of investigational product accountability, handling, and dose delivery
- Summary of protocol compliance relative to tumor response evaluation
- Summary of data accuracy and timeliness of reporting

- Any site-specific concerns with elements above, with recommendation/documentation or corrective actions and re-monitoring as needed

The Winship Cancer Institute DSMC will review aggregate AE data on an annual basis. Documentation of DSMC reviews will be provided to sponsor-investigator and HCRN. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with HCRN to address the DSMC's concerns.

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the HCRN Monitor assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

12.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study by HCRN. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

On-site monitoring of the study and subjects will occur per section 13.2 of this protocol. Additional for-cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

The trial site may also be subject to quality assurance audit by Eli Lilly and Co. or its designee as well as inspection by appropriate regulatory agencies.

12.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

13. DATA HANDLING AND RECORD KEEPING

13.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform, OnCore, a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. Select data will be collected and entered into OnCore by study site personnel from participating institutions.

13.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

13.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

13.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study team. Samples that are collected will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

Subjects will be informed in writing that some organizations, including the sponsor-investigator and his/her research associates, Emory University, HCRN, Eli Lilly and Company, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subjects' identity will remain confidential.

13.5 Changes to the Protocol and Informed Consent

Study procedures will not be changed without the mutual agreement of the sponsor-investigator, Emory University, HCRN, and Eli Lilly and Company.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by HCRN and must be approved by the sponsor-investigator and Eli Lilly and Company in addition to each site's IRB. Local requirements must be followed.

If a protocol amendment requires a change to the informed consent form, then the IRB must be notified. Approval of the revised informed consent form by the IRB is required before the revised form is used.

The site investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center.

Eli Lilly and Company's willingness to supply study drug is predicated upon the review of the protocol. HCRN agrees to provide written notice to Eli Lilly and Company of any modifications to the protocol or informed consent.

14. ETHICS

14.1 Ethics Review

Each site must obtain approval of the final study protocol, including the final version of the informed consent form, from its IRB. The site investigator must submit written approval to the HCRN office before he or she can enroll any subjects into the study.

The site investigator must inform the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit

subjects for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Sites will provide progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB as required by local regulations and guidelines.

14.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles which are consistent with ICH/Good Clinical Practice E6 as adopted by the FDA, and applicable regulatory requirements.

14.3 Informed Consent Process

The site investigator will ensure the subjects is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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