Academic and Community Cancer Research United (ACCRU)

Ramucirumab Plus trifluridine/tipiracil or paclitaxel for Patients With Previously Treated Advanced Gastric or Gastroesophageal Junction Adenocarcinoma: An Investigator-Initiated, Randomized Non-inferiority Phase 2 Study

For any communications regarding this protocol, please contact the person indicated on the Protocol Resource page. This is a stand-alone document found on the ACCRU web site

[redacted]

Study Chairs

ACCRU: [redacted]

FDA IND Holder/ Study Co-Chair: [redacted]

Statistician: [redacted]

Drug Availability
Commercial Agents: Paclitaxel
Drug Company Supplied: Trifluridine/tipiracil , Ramucirumab

√ Study contributor(s) not responsible for patient care.

Research Coordinating Center

[redacted]

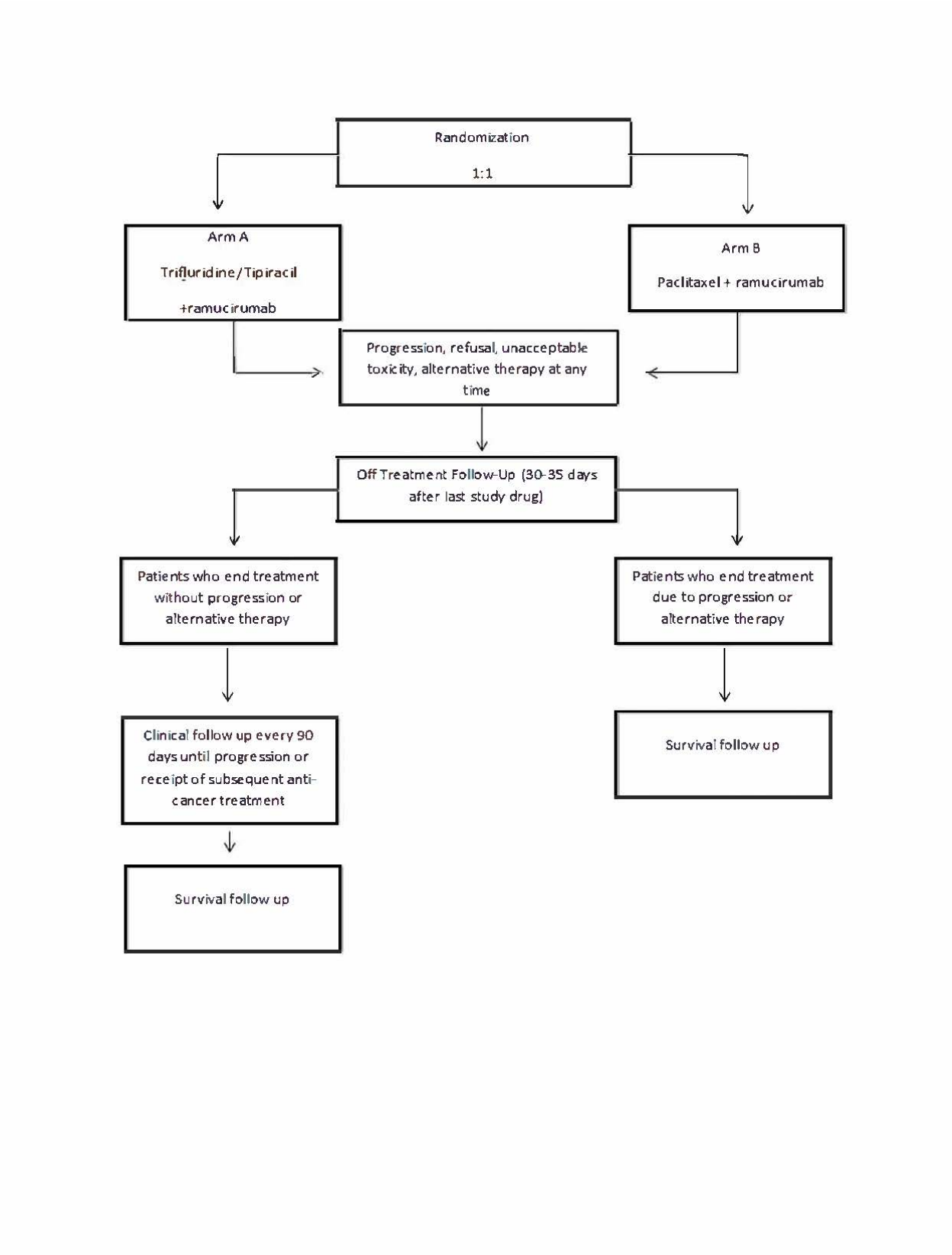
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Schema


Randomization
1:1
Arm A
Trifluridine/Tipiracil
+ramucirumab
Arm B
Paclitaxel + ramucirumab
Progression, refusal, unacceptable toxicity, alternative therapy at any time
Off Treatment Follow-Up (30-35 days after last study drug)
Patients who end treatment without progression or alternative therapy
Patients who end treatment due to progression or alternative therapy
Clinical follow up every 90 days until progression or receipt of subsequent anti-cancer treatment
Survival follow up
Survival follow up

If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

Cycle length = 28 days
Maximum of 36 treatment cycles

Generic name: trifluridine/tipiracil Brand Name: Lonsurf ® Availability: Taiho	Generic name: ramucirumab Brand Name: Cyramza ® Availability: Eli Lilly	Generic name: paclitaxel Brand Name: Taxol® Availability: Commercial

1.0 Background

1.1 Gastric and Gastroesophageal Junction Cancers

Gastric and esophageal cancers are a significant cause of mortality in the US with an estimated annual incidence of 26,240 and 17,290 cases, and 10,800 and 15,800 yearly deaths for gastric and esophageal cancers, respectively (1). Worldwide, gastric and esophageal cancers are the second highest cause of cancer deaths after lung cancer with the highest incidence in Eastern Asia, Central and Eastern Europe (2). Surgical resection is effective for complete cure of gastric cancer, but is only applicable to localized disease. The relatively high mortality rate of these cancers is attributed to the fact that most of gastroesophageal junction (GEJ) and gastric cancer patients present with advanced stage disease. For such patients, extending the duration of survival by systemic chemotherapy is the primary treatment. Therefore, there continues to be an unmet need for effective regimens in the metastatic setting.

Combination chemotherapy that include fluoropyrimidines and platinum agents have been the mainstay of treatment in the front-line metastatic setting with a median overall-survival ranging from 11.1 to a high of 13.8 months in HER2-overexpressing disease treated with trastuzumab (3). Various second-line therapeutic agents have been assessed suggesting an improved survival outcome when compared to best supportive therapy (BSC) alone.

1.2 Role of Ramucirumab in Gastric Cancer

Vascular endothelial growth factor receptor 2 (VEGFR-2) signaling in tumor vascular endothelial cells is now recognized as a pivotal and rate-limiting step in tumor angiogenesis. Most human tumors produce a high level of VEGF to trigger production of vasculature necessary to sustain tumor growth. In animal models of gastricadenocarcinoma,VEGFR-2 inhibition has reduced tumor growth and vascularity(4). Ramucirumab is a fully human monoclonal antibody (IgG1) that inhibits VEGFR-2 and has shown an overall survival benefit compared to placebo in phase III study (5). Furthermore, the combination of ramucirumab with paclitaxel significantly increases overall survival compared with placebo plus paclitaxel (9.6 months vs. 7.4 months, HR 0.807 [95% CI 0.678-0.962; p-value=0.017]) in a phase III study (6). Based on these results, ramucirumab as monotherapy or in combination with paclitaxel, was approved by the US FDA and it is now considered the standard second-line treatment for metastatic gastric and GEJ cancer (5, 6).

1.3 Trifluridine/tipiracil

Trifluridine/tipiracil(Taiho Pharmaceutical, Tokyo, Japan) is a novel oral nucleoside antitumor agent that comprised trifluridine (FTD) and tipiracil hydrochloride (TPI) at a molar ratio of 1:0.5 (7). Previous phase I studies have defined the recommended dose schedule for trifluridine/tipiracilas a 28-day cycle, with treatment on days 1-5 and 8-12, and the maximum tolerated dosage was initially defined as 25 mg/m2 twice a day (7, 8). Subsequent phase 1 study in advanced solid tumors utilized a higher dose of 35 mg/m2 reported grade IV neutropenia as a dose-limiting toxicity (DLT) in the 35 mg/m2 bid schedule (9). This dose, 35 mg/m2, was subsequently used in metastatic colorectal cancer trials and now considered the standard dose of trifluridine/tipiracil(10).

The safety and efficacy of trifluridine/tipiracil in metastatic gastric cancer was evaluated in an open-label, single-arm, multicenter phase II study in Japan (EPOC1201) (11). In this study, 29 patie trifluridine/tipiracil nts with refractory advanced gastric cancer were included and received 35 mg/m^2 dose of trifluridine/tipiracil, taken orally twice per day after meals, during a 28-day schedule with treatment on days 1–5 and 8–12. All patients had received fluoropyrimidine and platinum agents, while 18 patients (62.1%) had received taxanes and 11 patients (37.9%) had received irinotecan. Disease-control rate (DCR) was observed in 19/29 patients (65.5%) with 1 partial response (PR) and 18 stable disease (SD). After a median follow-up of 17.1 months, the median OS was 8.7 months and median PFS was 2.9 months in this heavily pretreated population. The results of this study led to the conduction of the phase III TAGS study(12). This study was a double-blind, global, phase III study, that randomly assigned 507 patients with advanced refractory metastatic gastric and GEJ cancers to receive either trifluridine/tipiracil (n=337) or placebo (n=170). All patients received platinum and either irinotecan and/or taxanes, and all but one receiving fluoropyrimidine. Median OS was 5.7 months in trifluridine/tipiracil group vs. 3.6 months in the placebo group (HR=0.69; CI 0.56 to 0.85, p= 0.0003). Median progression-free survival was 2 months in the trifluridine/tipiracil group vs. 1.8 months in the placebo group (HR= 0.57; CI 0.47 to 0.7, p<0.0001). Grade 3 or higher adverse events occurred in 266 of 335 (79.4%) treated patients who received trifluridine/tipiracil and 97 of 168 (57.7%) treated patients who received placebo. Grade 3/4 hematological laboratory abnormalities of experienced by patients treated with trifluridine/tipiracil included neutropenia (38.1%), leucopenia (21.0%), anemia (18.6%) and lymphocytopenia (18.9%). Of the 38.1% of patients who experienced grade 3/4 neutropenia when treated with trifluridine/tipiracil, six (1.8%) experienced febrile neutropenia (grade 3 or higher). No new safety signals were observed.

1.4 Combining ramucirumab and trifluridine/tipiracil

VEGF inhibition has been shown to enhance the antitumor effect of trifluridine/tipiracil in preclinical colorectal cancer xenograft model by increasing the phosphorylated trifluridine levels (13). This preclinical data was further confirmed in a phase 1/2 study showing the safety and promising efficacy of the combination of VEGF inhibitor (bevacizumab) with trifluridine/tipiracil in patients with refractory colorectal cancer (C-TASK-FORCE) (14). Moreover, the combination of trifluridine/tipiracil with bevacizumab was recently compared to standard chemotherapy with capecitabine and bevacizumab for patients with untreated metastatic colorectal cancer, who are not suitable for intensive therapy (TASCO1 trial)(15). The combination of trifluridine/tipiracil plus bevacizumab showed a potential superior efficacy with median PFS of 9.23 months compared to 7.82 months in the standard chemotherapy arm.

Paclitaxel therapy remains challenging in regards of maintenance of dose intensity given the risk of neuropathy, which is further compounded by prior exposure to platinum-based therapy in first-line. This has led to a less optimal sequencing approach by delaying use of ramucirumab to later lines with or without paclitaxel. Trifluridine/tipiracil one the other hand, was found to be tolerated in very refractory patients with gastric cancers. Furthermore, it is an appealing option given its oral route of administration.

As such, we propose a randomized phase 2 trial evaluating the efficacy of ramucirumab with trifluridine/tipiracil vs. ramucirumab with paclitaxel/in patients with metastatic

refractory gastric/GEJ adenocarcinoma.

2.0 Goals

2.1 Primary

2.11 To compare, in a non-inferiority fashion, the progression-free survival (PFS) in patients with metastatic refractory gastric/GEJ adenocarcinoma receiving the combination of ramucirumab with trifluridine/tipiracil vs. paclitaxel and ramucirumab.

2.2 Secondary

2.21 To assess overall survival (OS) in this patient population for each regimen.

2.22 Assess changes in patient quality of life (QOL) as measured by the linear analogue self-assessment (LASA) questionnaire for each regimen.

2.23 To determine the safety of the combination of ramucirumab with trifluridine/tipiracil in this patient population.

3.0 Patient Eligibility

NOTE: Waivers to eligibility criteria are not allowed per ACCRU policy

3.1 Registration – Inclusion Criteria

3.11 Age ≥ 18 years.

3.12 Histological or cytological confirmation of adenocarcinoma of the stomach or gastroesophageal junction.

3.13 Have locally advanced unresectable or metastatic disease that has progressed ≤ 180 days since last treatment.

3.14 One or more measurable or nonmeasurable evaluable lesions per RECIST as defined in Section 11.0.

3.15 Planned for second line treatment defined by failing or were intolerant to previous standard chemotherapies containing one or more of the following agents:

- fluoropyrimidine (IV 5-FU or capecitabine) and platinum (cisplatin or oxaliplatin);
- Trastuzumab in case of HER2-positive disease.

NOTE: For the patients whose disease recurred ≤168 days from the last dose of adjuvant anticancer chemotherapy, that adjuvant anticancer chemotherapy is

counted as 1 prior chemotherapy line.

3.16 ECOG Performance Status (PS) 0 or 1. (Form is available on the ACCRU web site)

3.17 Ability to swallow oral medications.

3.18 The following laboratory values obtained ≤7 days prior to registration.

- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥100,000/mm^3
- Hemoglobin ≥ 9.0 g/dL
- Total bilirubin ≤1.5 x upper limit of normal (ULN)
- Aspartate transaminase (AST) and alanine transaminase (ALT) ≤3 x ULN (≤ 5.0 x UNL, if with liver metastasis).
- Coagulation: Adequate coagulation function as defined by International Normalized Ratio (INR) ≤ 1.5 x ULN, and a partial thromboplastin time (PTT) ≤ 5 seconds above the ULN (unless receiving anticoagulation therapy).
  Note: Patients receiving warfarin must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to first dose of protocol therapy.
  Note: Patients on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin (LMWH).
  Exception: For heparin and LMWH there should be no active bleeding (that is, no bleeding within 14 days prior to first dose of protocol therapy) or pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices).
- Urinary protein is ≤1+ on dipstick or routine urinalysis (UA; if urine dipstick or routine analysis is ≥2+, a 24-hour urine collection for protein must demonstrate ≤ 1000 mg of protein in 24 hours to allow participation in this protocol).
- Creatinine ≤1.5 times the ULN or creatinine clearance (measured via 24-hour urine collection) ≥50 mL/minute (that is, if serum creatinine is ≥ 1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed).

Cockcroft-Gault Equation:

Creatinine clearance for males = $\dfrac{\textbf{(140 - age)(weight in kg)}}{\textbf{(72)(serum creatinine in mg/dL)}}$

Creatinine clearance for females = $\dfrac{\textbf{(140 - age)(weight in kg)(0.85)}}{\textbf{(72)(serum creatinine in mg/dL)}}$

3.19 Negative pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.19a Ability to complete questionnaire(s) by themselves or with assistance.

3.19b Provide informed written consent ≤28 days prior to registration.

3.19c Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.19d Because the teratogenicity of ramucirumab is not known, the patient, if sexually active, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods)

3.2 Registration – Exclusion Criteria

3.21 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown :

- Pregnant women
- Nursing women
- Women of childbearing potential who are unwilling to employ adequate contraception

3.22 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.23 Previous treatment with trifluridine/tipiracil or ramucirumab

3.24 Previous taxane therapy ≤180 days prior to registration

3.25 Any grade 3-4 GI bleeding ≤90 days prior to registration

3.26 History of deep vein thrombosis (DVT), pulmonary embolism (PE), or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered “significant”) ≤90 days prior to registration.

3.27 Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, ≤180 days prior to registration.

3.28 Prior history of GI perforation/fistula ≤180 days of registration or risk factors for perforation.

3.29 Serious or nonhealing wound, ulcer, or bone fracture ≤ 28 days prior to registration.

3.30 Major surgery ≤28 days prior to first dose of protocol therapy, or minor surgery/subcutaneous venous access device placement ≤7 days prior to registration.

3.31 Elective or planned major surgery to be performed during the course of the clinical trial.

3.32 Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. NOTE: Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.

3.33 Uncontrolled or poorly-controlled hypertension (≥150 mmHg systolic or ≥90 mmHg diastolic for ≥4 weeks) despite standard medical management.

3.34 Immunocompromised and known to be HIV positive and currently receiving antiretroviral therapy.

NOTE: Patients known to be HIV positive, but without clinical evidence of an immunocompromised state, are eligible for this trial.

3.35 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.36 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.37 Other active malignancy ≤3 years prior to registration. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix. NOTE: If there is a history of prior malignancy, they must not be receiving other specific treatment for their cancer.

3.38 Receiving chronic antiplatelet therapy, including dipyridamole or clopidogrel, or similar agents. NOTE: Once-daily aspirin use (maximum dose 325 mg/day) is permitted.

4.0 Test Schedule

Tests and procedures Cycle= 28 days	Screening		Active Monitoring						
	≤21 days prior to registration	≤7 days prior to registration	Day 1 of each cycle (+/-3 days)[6]	Day 8 of each cycle[5,6]	Day 15 of each cycle[6]	Every 2 Cycles	Safety follow-up +30-35 days after last dose of study treatment	Clinical follow up[9](until PD, alternative therapy, or withdrawal)	At PD, withdrawal, or removal
History and exam, weight, ECOG PS	X		X				X	X	X
Height	X								
Vital signs	X		X	X	X		X		
Concomitant medication/documentation review	X								
Adverse event assessment			X		X		X[10]	X	X
Hematology: CBC/ differential		X[8]	X	X	X				X
Chemistry: SGOT (AST), alk phos, T. bili, creatinine, calcium, phos, glucose, Na, K, glucose		X[8]	X	X	X				X
Coagulation tests		X[4,8]							
Urinalysis		X[8]	X						
Tumor measurement	X[1]					X[1]		X	X
Serum Pregnancy test		X[2]	X						
Subject Medication Diary (Appendix III)[3]			X						
Mandatory Patient Questionnaire Booklet (Appendix II)[7]			X						X

1 CT or MRI of chest, abdomen, and pelvis. Same method for tumor assessment should be employed at every assessment. CT or MRI of the chest, abdomen, and pelvis to assess sites of measurable disease as per RECIST 1.1 template dated 2/16/2011. Unless clinically indicated, the same method for tumor assessment should be employed at every restaging. At baseline must be ≤21 days prior to registration; every restaging (may occur +/-14 days prior to Day 1 of the new cycle); and as clinically indicated. Re-staging will occur prior to treatment cycles 3, 5, 7 etc. If the patient is clinically stable after two years of treatment, CT or MRI of the chest, abdomen, and pelvis may be performed once every 12 weeks (every 3 cycles +/- 14 days). Upload imaging report for each scan to the supporting documentation folder in RAVE.

2 For women of childbearing potential only. Must be done ≤ 7 days prior to registration and day 1 of each cycle

3 Arm A only: The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution.

4 PT/INR/aPTT

5 For patients on Arm A, the Day 8 visits of each cycle are not required.

6 Administrative Scheduling Window: After Cycle 1, Day 1, allowance of ±3 days for subsequent study visits is permitted for scheduling considerations other than adverse event management (e.g. holidays, weekends, inclement weather).

7 Patient questionnaire will be completed at Day 1 of each cycle prior to dosing, and end of treatment (within 30 days after last dose as noted in Appendix II). Patient questionnaire booklets must be used; copies are not acceptable for this submission. The booklet order form is located on the ACCRU website under Manuals and Forms.

8 If screening tests occur ≤ 3 days prior to Cycle 1 Day 1, they do not have to be repeated prior to dosing.

9 Clinical follow up will occur every 3 months (90 days) for up to 1 year after treatment is discontinued or until PD, alternative therapy, or withdrawal.

10 Adverse events for the safety follow up visit will be recorded in the folder of the final cycle of treatment.

5.0 Stratification Factors

5.1 ECOG performance status 0 vs. 1

5.2 Age: <65 vs. ≥65

5.3 Gender: Male vs. Female

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

6.11 To register a patient, access the ACCRU web page at [redacted] go to the Application section and click on "Registration" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Instructions for the registration/randomization application are available on the above web page under the Study Resources section, "Application Training."

Prior to initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted] If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Application Training" at [redacted] click on "Registration, Installation & Entry Instructions".

6.12 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with ACCRU. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS). If the necessary documentation is not submitted in advance of attempting patient registration, the randomization will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals is required until the study has been closed through your IRB.

6.13 Prior to accepting the registration/randomization, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.14 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.

6.15 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.16 All required baseline symptoms (see Section 10.5) must be documented and graded.

6.17 Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.

6.18 Study drug is available on site.

6.19 Patient questionnaire booklet is available on site; copies are not acceptable for this submission.

6.2 Randomization Procedures

6.21 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups (17).

- trifluridine/tipiracil + ramucirumab
- paclitaxel+ ramucirumab

7.0 Protocol Treatment

7.1 Treatment Schedule - Use actual weight or estimated dry weight if fluid retention

Arm	Agent	Dose Level	Route	Day
A	trifluridine/tipiracil	35 mg/m^{2}/dose twice daily	Oral	1-5 and 8-12
A	ramucirumab	8mg/kg	IV	1 and 15

Cycle length=28 days

Arm*	Agent	Dose Level	Route	Day
B	paclitaxel	80 mg/m^2	IV	1,8,15
B	ramucirumab	8mg/kg	IV	1 and 15

Cycle length=28 days

* When given in combination, administer ramucirumab prior to administration of paclitaxel.

7.2 Patients receiving trifluridine/tipiracil can be instructed in administration techniques and granted treatment independence with nursing staff approval.

7.3 Trifluridine/tipiracil should be taken twice daily with food.

7.4 Maximum dose of trifluridine/tipiracil is 80 mg/dose based on the trifluridine component.

7.5 Both agents should always start on day 1. If one agent needs to be delayed both agents should be delayed.

7.6 Treatment by a local medical doctor (LMD) for trial treatment is not allowed.

7.7 For this protocol, the patient must return to the consenting ACCRU institution for evaluation as per the study calendar during treatment. Additional visits during treatment are not mandated by the study protocol, but are advised to optimize symptom management and provide optimal care.

7.8 Trifluridine/tipiracil dosing table for 35mg/m^2. Additional tables for patients with dose reductions can be found in section 8.1

Trifluridine/Tipiracil Dose (2x daily)	**BSA (m2)**	**Dosage in mg (2x daily)**	**Total daily dose (mg)**	**Tablets per dose**	
				15mg	**20mg**
35 mg/m^2	< 1.07	35	70	1	1
	1.07 - 1.22	40	80	0	2
	1.23 - 1.37	45	90	3	0
	1.38 - 1.52	50	100	2	1
	1.53 - 1.68	55	110	1	2
	1.69 - 1.83	60	120	0	3

	1.84 - 1.98	65	130	3	1
	1.99 - 2.14	70	140	2	2
	2.15 - 2.29	75	150	1	3
	≥2.30	80	160	0	4

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first two cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be followed to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose Modifications for Trifluridine/Tipiracil

Dose Reduction Levels

Study medication dose reductions in case of toxicity and number of tablets for each calculated BSA are described in Table 8.1a. Patients are permitted dose reduction(s) to a minimum dose of 20 mg/m$^{2/}$dose (40 mg/m^2/day) in 5 mg/m^2 steps.

Table 8.1a Trifluridine/tipiracil Dose Modifications

Dose Level	Trifluridine/Tipiracil
0 starting dose	35 mg/m^2/ dose twice daily Days 1-5 and 8-12
-1	30 mg/m^2/ dose twice daily Days 1-5 and 8-12
-2	25 mg/m^2/ dose twice daily Days 1-5 and 8-12
-3	20 mg/m^2/ dose twice daily Days 1-5 and 8-12

Table 8.1b: Trifluridine/Tipiracil Dose Reduction Levels and Number of Tablets per Dose

Trifluridine/Tipiracil Dose (2x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose	
				15 mg	20 mg
Level 1 Dose Reduction: From 35 mg/m^2 to 30 mg/m^2					
30 mg/m^2	< 1.09	30	60	2	0
	1.09 - 1.24	35	70	1	1
	1.25 - 1.39	40	80	0	2
	1.40 - 1.54	45	90	3	0
	1.55 - 1.69	50	100	2	1
	1.70 - 1.94	55	110	1	2
	1.95 - 2.09	60	120	0	3
	2.10 - 2.28	65	130	3	1
	≥ 2.29	70	140	2	2
Level 2 Dose Reduction: From 30 mg/m^2 to 25 mg/m^2					
25 mg/m^2	< 1.10	25[a)]	50[a)]	2 (PM)[a)]	1 (AM)[a)]
	1.10 - 1.29	30	60	2	0
	1.30 - 1.49	35	70	1	1
	1.50 - 1.69	40	80	0	2
	1.70 - 1.89	45	90	3	0
	1.90 - 2.09	50	100	2	1
	2.10 - 2.29	55	110	1	2
	≥ 2.30	60	120	0	3
Level 3 Dose Reduction: From 25 mg/m^2 to 20 mg/m^2					
20 mg/m^2	< 1.14	20	40	0	1
	1.14 – 1.34	25[a)]	50[a)]	2 (PM)[a)]	1 (AM)[a)]
	1.35 – 1.59	30	60	2	0
	1.60 – 1.94	35	70	1	1
	1.95 – 2.09	40	80	0	2
	2.10 – 2.34	45	90	3	0

Trifluridine/Tipiracil Dose (2x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose	
				15 mg	20 mg
	≥ 2.35	50	100	2	1

[a)] At a total daily dose of 50 mg, patients should take 1 x 20-mg tablet in the morning and 2 x 15- mg tablets in the evening.

BSA=body surface area (calculate to 2 decimal places)

If dose modification fails to result in achieving minimal criteria to resume treatment, the Investigator should discontinue study medication.

Study medication should be discontinued if toxicities that require dose reduction recur after dose reduction to 20 mg/m^2.

Table 8.1c: Trifluridine/Tipiracil Dose Modification Criteria for Non-hematologic Toxicities

Grade[a]	Dose Hold/Resumption within a 28-day Treatment Cycle	Dose Adjustment for Next Cycle
Grade 1 or 2		
Any occurrence	Maintain treatment at the same dose level	None
Grade 3[a)] or Higher		
1st, 2nd, or 3rd occurrence	Suspend treatment until Grade 0 or 1	Reduce by 1 dose level from the previous level
4th occurrence	Discontinue treatment	Discontinue treatment

[a)]Except for Grade 3 nausea and/or vomiting controlled by aggressive antiemetic therapy or diarrhea responsive to antidiarrheal medication.

Dose Modification in Response to Hematologic Toxicities

Criteria for dose hold and resumption in response to hematologic toxicities related to myelosuppression are described in Table 8.1d and Table 8.1e respectively.

NOTE: For all patients with decreases in neutrophils and/or platelets, the next cycle of study treatment should not be started until the resumption criteria in Table 8.1e are met; these resumption criteria apply to the start of the next cycle for all patients regardless of whether or not the hold criteria were met.

Table8.1d: Trifluridine/Tipiracil Dose Hold Criteria for Hematologic Toxicities Related to Myelosuppression

Parameter	Hold Criteria	
	Conventional Units	**SI Units**
Neutrophils	<500/mm^3	<0.5 × 10^9/L
Platelets	<50,000/mm^3	<50 × 10^9/L

SI=International System

Table 8.1e: Trifluridine/Tipiracil Resumption Criteria for Hematologic ToxicitiesRelated toMyelosuppression

Parameter	Resumption Criteria[a)]	
	Conventional Units	**SI Units**
Neutrophils	≥1500/mm^3	≥1.5 × 10^9/L
Platelets	≥75,000/mm^3	≥75 × 10^9/L

[a)] These resumption criteria apply to the start of the next cycle for all patients regardless of whether or not the hold criteria were met.

SI=International System

Criteria for dose reduction in response to hematologic toxicities are as follows:

- Uncomplicated neutropenia or thrombocytopenia ≤Grade 3 do not require a reduction in dose of study medication.
- Patients who experience uncomplicated Grade 4 neutropenia or thrombocytopenia that results in a ≤1 week delay of the start of the next cycle should start the next cycle at the same dose level.
- Patients who experience uncomplicated Grade 4 neutropenia or thrombocytopenia that results in a >1 week delay of the start of the next cycle should start the next cycle at one reduced dose level as described in Table 8.1c.

In the event of febrile neutropenia:

- Interrupt dosing until toxicity resolves to Grade 1 or baseline
- When resuming dosing, decrease the dose level by 5 mg/m^2/dose from the previous dose level (as per Table 8.1c).

Overdose

There is no known antidote available in case of trifluridine/tipiracil overdose. Overdose should be managed aggressively with close monitoring and administration of prophylactic and symptomatic therapies to prevent or correct potential side effects.

8.2 Dose Modifications for ramucirumab

Ramucirumab 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. 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 8.2 a Modified dose of ramucirumab

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

Table 8.2b Dosing level of ramucirumab for treatment related adverse events

Toxicity Grade	Worse Interval Toxicity	Day of Treatment
1	Maintain dose level	Continue treatment per protocol schedule
2	Maintain dose level	Hold until resolved to grade1 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

8.2. 1 Management of Hypertension

Interrupt ramucirumab for severe hypertension until controlled with medical management. Permanently discontinue ramucirumab for severe hypertension that

cannot be controlled with antihypertensive therapy. Patients with grade 4 hypertension must not receive further treatment with ramucirumab.

8.2. 2 Management of proteinuria

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

8.2.3 Venous Thromboembolic Events

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.

Grade 3 and 4 arterial thromboembolic events, or any PE/DVT occurring or worsening during anticoagulant therapy, require permanent discontinuation of ramucirumab therapy. Any venous or arterial event leading to discontinuation of ramucirumab therapy will be considered serious and should be reported via the serious adverse event (SAE) mechanism.

8.2.4 Conditions for permanent discontinuation of ramucirumab

Listed below are clinical conditions in which ramucirumab 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 Related 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

8.3 Dose Modifications for paclitaxel

Prior to the first dose of paclitaxel in a given cycle, the absolute neutrophilic count (ANC) must be ≥ 1.5 x 10^9/L and the platelet count must be ≥ 100 x 10^9/L. If the spoke parameters are not met, and in the opinion of the investigator the myelosuppression is most likely result paclitaxel therapy, the dose of paclitaxel should be reduced according to the following criteria as delineated in the table:

Table 8.3a: Paclitaxel Dose Modifications due to Hematologic AEs

Lab Value	Investigator Action
ANC≥ 1.5 x 10^9/L **AND** platelets ≥ 100 x 10^9/L	Continue treatment at full (current) dose.
ANC 1.0- 1.5 x10^9/L **OR** platelets 75-100x10^9/L	Consider treatment at *next lower dose level or more (at discretion of investigator)**. Paclitaxel does not need to be held.
ANC<1.0 x 10^9/L **OR** platelets <75 x 10^9/L	Hold paclitaxel for that week. recommence treatment *at the next lower dose level or more* at next scheduled visit if ANC and platelet count have recovered (ANC≥ 1.0 x 10^9/L and platelets≥ 75 x10^9/L)**
* or maintain full (current dose) ** Neupogen/G-CSF may be used at discretion of the investigator.	

The paclitaxel dose should be reduced by one or more dose levels if the dose is held more than once during a 4 week cycle.

For patients who experience grade 3 non-hematologic adverse event (except alopecia), and in the opinion of the investigator the event is most likely a result of paclitaxel therapy, the dose of paclitaxel should be held until the adverse event has improved to grade 2, and then reduced by one or more dose levels for subsequent doses of paclitaxel.

Table 8.3b: Paclitaxel Dose Modifications due to Non-hematologic AEs

Dose Level*	Dose
Full dose	80 mg/ m^2
Modification Level-1	70 mg/ m^2
Modification Level-2	60 mg/ m^2
Modification Level-3	40 mg/ m^2**
* If the dose of paclitaxel is reduced because of potentially-related AEs, subsequent dose increases are not permitted. * if paclitaxel dose is required to be reduced below 40 mg/m2, or if any life-threatening paclitaxel-related events occur, paclitaxel should be permanently discontinued.	

When laboratory parameters indicate that the dose of paclitaxel should be delayed, the infusion of paclitaxel scheduled for that day is not given. The infusion is considered "missed", and is not made up at another time. The next paclitaxel infusion would be according to the protocol specified administration schedule. Laboratory parameters should be evaluated prior to the next scheduled dose of paclitaxel and actions taken according to the protocol parameters.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetic's may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (ASCO), Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update.[18]

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all adverse events to the sponsor as described within the protocol. Refer to the adverse event and serious adverse event sections of the protocol for detailed information.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms
Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

For the purposes of this Clinical Trial, other experiences with the TAIHO Investigational Medicinal Product(s) IMP shown below should also be reported to TAIHO:

A) Drug exposure during pregnancy and lactation, or paternal drug exposure
B) Experience In patients below 18 years of age (depending on Inclusion criteria)
C) Lack of drug effect
D) Unintended beneficial effect
E) Any suspected transmission of an infectious agent by a medicinal product
F) Product quality complaints associated with possible safety issue(s)
G) Drug or food interaction
H) Overdose
I) Medication error
J) Misuse
K) Occupational exposure

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:
[redacted]

a. Adverse event monitoring and reporting is a routine part of every clinical trial.

b. Identify the grade and severity of the event using the CTCAE version 5.0.

c. Determine whether the event is expected or unexpected (see Section 10.2).

d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

f. Determine if other reporting is required (see Section 10.5).

g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).
NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

10.31 **AEs Experienced Utilizing Investigational Agent(s) and Commercial Agent(s) on <u>SEPARATE</u> Arms**

- An AE that occurs on an arm using an investigational agent /intervention under an IND/IDE must be assessed in accordance with the guidelines in the appropriate **IND/IDE** Reporting Table in Section 10.4.

- An AE that occurs on an arm using a commercial agent on a separate treatment arm must be assessed as specified in the protocol**. Refer to Commercial** Reporting Table in Section 10.4.

10.32 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the <u>SAME</u> (Combination)Arm**

When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting**. These AEs should be assessed as specified in the appropriate **IND/IDE** reporting guidelines in Section 10.4

10.321 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**

    - Death attributable to a CTCAE term.

    - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

    - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

    - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

    - Death due to progressive disease that cannot be attributed to a CTCAE term associated with Grade 5 should be reported as **Grade 5 "Disease**

progression" under the system organ class (SOC) of General Disorders and Administration Site Conditions. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.322 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:

    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])

    - Myelodysplastic syndrome (MDS)

    - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.323 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.324 Pregnancy

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn

infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting [redacted] he potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

Drug Exposure During Pregnancy and Lactation, or Paternal Drug Exposure Reports

The Institution will report Exposure During Pregnancy and Lactation, or Paternal Drug Exposure on any Clinical Trial Subject while participating in the Clinical Trial, and following exposure to a TAIHO IMP, to TAIHO (as specified below) using copies of the ACCRU SAE Report Form and within two weeks of first becoming aware of the pregnancy or exposure. If the partner of a Clinical Trial Subject becomes pregnant, the Institution may collect information about the pregnancy and birth if the partner agrees.

The Clinical Trial Subject will also be followed by the Institution to determine the outcome of the pregnancy (including any premature termination of the pregnancy). Information on the status of the mother and child will be forwarded to TAIHO. The Institution must provide final outcome of pregnancy to TAIHO. If any SAE(s) is observed in Clinical Trail Subject or fetus/child, then SAE(s) must also be reported to TAIHO following SAE Reporting guidelines.

Routing of Drug Exposure During Pregnancy and Lactation, or Paternal Drug Exposure Reports

Such reports and Information as outlined above, Including Investigator causality assessments against all concerned TAIHO IMP(s) and English translations where reporting Is from a non-English speaking country, shall be sent:

by e-mail to: [redacted]

Requesting Follow up information:

The institution will provide TAIHO with details of whom TAIHO shall address requests for follow up Information on SAE and pregnancy cases reported from this Clinical Trial, and further agree to update such contact details as necessary.

10.4 Expedited Adverse Event Reporting Requirements for IND/IDE Agents

Late Phase 2 and Phase 3 Studies: Expedited Reporting via the **ACCRU Adverse Event Expedited Report Form** for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour; 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Special Instructions:

For patients on Arm A:

1) Submit SAE's using the MedWatch form 3500A. ([redacted] or found on the ACCRU web site) along with the MedWatch Fax Cover Sheet (found on the ACCRU web site) to the ACCRU SAE Coordinator via fax [redacted]

2) The ACCRU SAE Coordinator will forward the report to [redacted] (primary method) or by facsimile to PV CONTACT NUMBER : [redacted]

3) The ACCRU SAE Coordinator will forward the report to Eli Lilly [redacted]

4) The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

For patients on Arm B:

1) Submit MedWatch form 3500A ([redacted] or found on the ACCRU web site) along with the MedWatch Fax Cover Sheet (found on the ACCRU web site) to the ACCRU SAE Coordinator via fax [redacted]

2) The ACCRU SAE Coordinator will forward the report to Eli Lilly [redacted]

3) The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Baseline and Adverse Events Evaluations

The following pre-treatment symptoms/conditions are to be graded at baseline and adverse events are to be graded at each evaluation using CTCAE v5.0 grading.

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Gastrointestinal disorders	Nausea	X	X
Gastrointestinal disorders	Vomiting	X	X
Blood and lymphatic system disorders	Anemia	X	X
Investigations	Neutrophil count decreased	X	X
Investigations	Platelet count decreased	X	X

Nervous system disorders	Peripheral sensory neuropathy	X	X
Nervous system disorders	Peripheral motor neuropathy	X	X
Skin and subcutaneous tissue disorders	Alopecia	X	X
Vascular disorders	Hypertension	X	X
Renal and urinary disorders	Proteinuria	X	X

10.53 Submit via appropriate Academic and Community Cancer Research United (ACCRU) Case Report Forms the following AEs experienced by a patient and not specified in Section 10.5:

10.531 Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.532 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure

10.533 Grade 5 AEs (Deaths)

10.5331 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5332 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.54 Late occurring adverse events are any adverse events that occur during Clinical Follow-Up and Survival Follow-Up reporting periods. These are reported in compliance with Section 4.0 and Section 18.0.

10.55 Reconciliation: Reconciliation shall be performed quarterly as an exchange of Line Listings or other means in English. On a quarterly basis, the institution shall provide to TAIHO a line listing or other means of cumulative SAE received to date. At the end of the Clinical Trial a global reconciliation shall be performed. Please reference contact information when sending this reconciliation. All serious adverse events via a MedWatch Form need to be sent to the FDA and to Taiho Oncology, Inc., via [redacted]

If requested by Institution, TAIHO shall provide the Institution with the final version of this DSUR report within 15 calendar days after submission to health agencies and ethics committees.

10.56 Quarterly Report: Research Coordinating Center will provide Taiho and Eli Lilly with accrual and a toxicity report on a quarterly basis.

10.57 IND Annual Reports: All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Taiho and Eli Lilly. Copies of such reports should be faxed or emailed.

11.0 Treatment Evaluation Using RECIST Guideline

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measurable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (16) . Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations: For the purposes of this study, patients should be reevaluated every 8 weeks.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: '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 patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.

- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered ‘negative.’ New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

  b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

    i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

    ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

    iii If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 11.44).

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

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by

CT/MRI/PET-CT must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all target lesions.

  b. Each target lymph node must have reduction in short axis to <1.0 cm.

- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all non-target lesions.

  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	**Non-Target Lesions & Non-Target Lymph Nodes**	**New Sites of Disease**	**Overall Objective Status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the ACCRU protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

For Patients with Non-Measurable Disease Only:

Non-Target Lesions & Non-Target Lymph Nodes	***New Sites of Disease***	***Overall Objective Status***
CR	*No*	*CR*
Non-CR/Non-PD	*No*	*Non-CR/Non-PD*
*Not All Evaluated**	*No*	*Not Evaluated (NE)*
Unequivocal PD	*Yes or No*	*PD*
Any	*Yes*	*PD*

*See Section 11.431

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical

conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

12.1 Disease Characteristics: Unresectable vs. Metastatic

12.2 Primary tumor location: Gastric vs. GEJ

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or SD will continue treatment per protocol for a maximum of 36 cycles.

13.2 Patients who develop PD while receiving therapy will go to survival follow up.

13.3 Patients who complete treatment per protocol, go off treatment for unacceptable adverse events, other complicating disease, or other reasons will go to clinical follow up per Section 18.0. Clinical follow up is every 90 days (3 months) for up to 1 year after treatment is discontinued, until PD, alternative therapy, or withdrawal.

13.4 Survival follow up is every 90 days (3 months) for 3 years after registration. If patient is still alive 3 years after registration, no further follow up is required.

13.5 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the survival follow up phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Survival follow-up will be required per Section 18.0 of the protocol.

- If the patient never received treatment, on-study material and the off treatment form must be submitted. No further data submission is necessary.

13.6 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the survival follow up phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Survival follow up will be required per Section 18.0 of the protocol.

13.7 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the Off Treatment Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

None.

15.0 Drug Information

IND exempt

15.1 Trifluridine Tipiracil (, Lonsurf®)

15.11 **Background**: FTD/TPI is an orally available combination drug of an antineoplastic thymidine-based nucleoside analogue, 1M trifluridine (FTD), and 0.5 M tipiracil hydrochloride (TPI). FTD is incorporated into deoxyribonucleic acid (DNA) of tumor cells following phosphorylation. TPI inhibits degradation of FTD by thymidine phosphorylase (TPase).

15.12 **Formulation**: Trifluridine/tipiracil contains trifluridine (FTD) and tipiracil (TPI as active ingredients with a molar ratio of 1:0.5. Trifluridine/tipiracildrug products are immediate-released film coated tablets, with two strengths of 15 mg and 20 mg (expressed as FTD). The inactive ingredients of the Trifluridine/tipiracil 15 mg and 20 mg tablets are lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, red ferric oxide (only 20 mg tablet), and magnesium stearate.

- (Trifluridine/tipiracil) tablet (15 mg) contains 15 mg trifluridine and 6.14 mg tipiracil as active ingredients. The appearance is white round, biconvex film-coated tablets.
- (Trifluridine/tipiracil) tablet (20 mg) contains 20 mg trifluridine and 8.19 mg tipiracil as active ingredients. The appearance is pale red round, biconvex film-coated tablets.

15.13 **Preparation and storage**: Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F). If stored outside of original bottle, discard after 30 days.

15.14 **Administration:** The recommended dosage of LONSURF is 35 mg/m2 up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle

15.15 **Pharmacokinetic information**:
Protein Binding: Trifluridine: >96% (primarily to albumin); Tipiracil: <8%
Absorption: Trifluridine: 57%; Tipiracil: 27%

Metabolism: Trifluridine and tipiracil are not metabolized by cytochrome P450 (CYP) enzymes. Trifluridine is mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, 5-(trifluoromethyl) uracil (FTY)

Half-life elimination: Trifluridine: 2.1 hours (at steady state); Tipiracil: 2.4 hours (at steady state)
Time to peak, plasma: Trifluridine: 2.2-2.4 hours (following multiple doses); tipiracil: 3.1-3.3 hours (following multiple doses)
Excretion: Trifluridine: Urine (55% [as inactive metabolite FTY and trifluridine glucuronide isomers]; 1.5% [as unchanged drug]; feces (<3% [as unchanged drug]); expired air (<3%)
Tipiracil: Urine (27% [6-HMU and 29% as unchanged drug]); feces (50% [as tipiracil and 6-HMU])
Hepatic Impairment: No dose adjustment is recommended for the starting dose in patients with mild hepatic impairment. FTD/TPI is not recommended for use in patients with baseline moderate or severe hepatic impairment (National Cancer Institute Criteria Group C and D defined by total bilirubin >1.5 × ULN).
Renal Impairment: No dose adjustments of FTD/TPI are required for patients with mild or moderate renal impairment, and these patients may receive the recommended dose (i.e., 35 mg/m^2 BID based on BSA).
For patients with severe renal impairment, it is recommended to start treatment with 20mg/m2 twice daily and to reduce the dose to 15mg/m2 twice daily in case of toxicities. Patients with end-stage renal disease (CrCl< 15mL/min) were not enrolled and have not been studied.

15.16 **Potential Drug Interactions**: Caution is required when using drugs that are human thymidine kinase substrates, e.g., stavudine, zidovudine, telbivudine. Such drugs, if used concomitantly with Trifluridine/tipiracil, may theoretically compete with the effector of Trifluridine/tipiracil, i.e., FTD, for activation via thymidine kinases. Therefore, when using antiviral drugs that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral agent, and consider switching to an alternative antiviral agent that is not a human thymidine kinase substrate such as: lamivudine, zalcitabine, didanosine, abacavir, etc.

15.17 **Known potential toxicities**:
Very common known potential toxicities, >/= 10%:
Central nervous system: Fatigue
Gastrointestinal: Nausea, decreased appetite, diarrhea, vomiting, abdominal pain
Hematologic and oncologic:: Anemia, , neutropenia, thrombocytopenia, febrile neutropenia
Infection: Infection
Neuromuscular & skeletal: Asthenia
Miscellaneous: Fever

Less common known potential toxicities, >/=1% - <10%:
Cardiovascular: Pulmonary embolism
Dermatologic: Alopecia
Gastrointestinal: Stomatitis, dysgeusia

Uncommon known potential toxicities, <1% (Limited to important or life-threatening):
Blood and lymphatic: Pancytopenia
Gastrointestinal: Ileus, acute pancreatitis,

Infections: Infections,urinary tract infection, fatal sepsis/septic shock

15.18 **Drug procurement:** Trifluridine/tipiracil will be provided free of charge by Taiho Oncology. Refer to Taiho Reorder drug supply form found on ACCRU website l for drug procurement instructions.

Drug destruction: Trifluridine/tipiracil will be destroyed by the site according to their SOPs. Destruction logs should be made available to Taiho at the end of the study. See section 8 of pharmacy manual.

15.19 **Nursing Guidelines:**

15.191 Instruct patients that agent should be taken within 1 hour after completion of morning and evening meal.

15.192 Patients may experience fatigue. Instruct patients in energy conserving lifestyle.

15.193 GI side effects are common, including nausea, decreased appetite, diarrhea, vomiting, and abdominal pain.

15.194 Cytopenias are common. Monitor CBC w/diff and instruct patients to report any signs or symptoms of infection and/or unusual bruising or bleeding to the study team.

15.195 Rarely Pulmonary embolism has been reported with this agent. Instruct patient to report any shortness of breath or chest pain to study team and/or seek out emergency medical attention.

15.196 Although uncommon, warn patients of the possibility of alopecia.

15.2 **Ramucirumab (Cyramza®, IMC-1121B, LY3009806)**

15.21 **Background:**

Ramucirumab is a recombinant human monoclonal antibody of the immunoglobulin G subclass 1 (IgG1) subclass that specifically binds VEGF Receptor 2 and blocks binding of VEGF-A, VEGF-C, and VEGF-D. As a result, ramucirumab inhibits ligand-stimulated activation of VEGF Receptor 2 and its downstream signaling components, including p44/p42 mitogen-activated protein kinases, neutralizing ligand-induced proliferation and migration of human endothelial cells.

15.22 **Formulation:**

Ramucirumab is an anti-VEGF Receptor 2 recombinant human monoclonal antibody of the IgG1 subclass. Ramucirumab DP is a sterile, preservative-free solution for infusion of ramucirumab formulated in an aqueous solution at a concentration of 10 mg/mL ((100 mg/10 mL and 500 mg/50-mL vial). The buffer contains 10 mM histidine, 75 mM sodium chloride, 133 mM glycine, and 0.01% polysorbate 80.

Ramucirumab is a clear to slightly opalescent and colorless to slightly yellow liquid without visible particles. The pH is 6.0. The osmolality is 285 mmol/kg.

All excipients used for the manufacture of ramucirumab DP are of pharmacopeial grade. No animal-derived components are known to be used in the manufacture

of ramucirumab DP excipients.

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15.23 **Preparation and Storage:**

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

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

3. Calculate the dose and volume of ramucirumab needed to prepare the infusion solution. Vials contain either 100 mg or 500 mg as a 10 mg/mL solution of ramucirumab. Dilute ramucirumab as required to achieve a final volume of 250 mL. Only use sterile sodium chloride (0.9%) solution for injection as a diluent.
In case of prefilled I.V. infusion container usage:
Based on the calculated volume of ramucirumab, remove the corresponding volume of sterile sodium chloride (0.9%) solution for injection from the prefilled 250 mL I.V. container. Aseptically transfer the calculated volume of ramucirumab to the I.V. container. The final total volume in the container should be 250 mL. The container should be gently inverted to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medications.
In case of empty I.V. infusion container usage:
Aseptically transfer the calculated volume of ramucirumab into an empty I.V. container. Add a sufficient quantity of sterile sodium chloride (0.9%) solution for injection to the container to make the total volume 250 mL. The container should be gently inverted to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medication.

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

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

Refer to each study protocol for specific instructions.

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. DO NOT FREEZE OR SHAKE the vial.

DO NOT FREEZE OR SHAKE the prepared ramucirumab infusion solution. 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]).

15.24 **Administration:**
Administer via infusion pump through a separate infusion line. Use of a protein sparing 0.22 micron filter is recommended. Infuse over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be administered over 30 minutes. A separate infusion line must be used for the infusion and the line must be flushed with sterile sodium chloride (0.9%) solution for injection at the end of the infusion. If first-Infusion Is well tolerated (Ie.e. 60 minutes) subsequent Infusions may be reduced to 30-minutes (as determined by physician)

Premedication is recommended with a histamine H1 antagonist (eg, diphenhydramine) I.V. prior to administration of ramucirumab.
If a patient experiences a Grade 1 or 2 IRR, premedication must be given for all subsequent infusions. If a patient has a second Grade 1 or 2 IRR, administer dexamethasone (or equivalent); then, for subsequent infusions, premedicate with the following or equivalent medications: diphenhydramine hydrochloride I.V., acetaminophen, and dexamethasone.
As with other monoclonal antibodies, infusion-related reactions (IRRs) were reported in clinical trials with ramucirumab. The majority of events occurred during or following a first or second ramucirumab infusion. Monitor patients during the infusion for signs of hypersensitivity reactions with resuscitation equipment readily available. Symptoms included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension.

15.25 **Pharmacokinetic Information:**
Distribution: 5.4 L
Half-life elimination: 14 days
Excretion: 0.015 L/hour

15.26 **Potential drug interactions:**
No drug-drug interactions were observed between ramucirumab and paclitaxel, docetaxel and ramucirumab, or ramucirumab and irinotecan.

15.27 **Known potential adverse events:**
Most common known potential adverse events ≥5%:
Gastrointestinal: abdominal pain, diarrhea
Metabolism & Nutrition: hypokalemia, hyponatremia
Nervous System: Headache
Vascular: Hypertension
Common known potential adverse events 1% - <5%:
Dermatologic: Rash
Gastrointestinal: Intestinal obstruction
Hematologic & oncologic: Neutropenia
Respiratory: Epistaxis
Vascular: Arterial thromboembolic events
Rare known potential adverse events<1% (Limited to important or life-threatening): Proteinuria, infusion-related reactions and GI perforations

15.28 **Drug Procurement:** Ramucirumab will be supplied by Eli Lilly.

Each participating ACCRU treating location will be responsible for monitoring the supply of Ramucirumab. Sites will order Ramucirumab from Eli Lilly using the drug supply reorder form. Once your site is activated you will receive a site specific order form. All orders should be sent to [redacted]

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.281 Temperature excursions that occur at the site should be reported by the site. To report a temperature excursion email Eli Lilly at [redacted] and request the most recent temperature excursion form. Emailing instructions once the form has been completed will be found on the form itself.

15.29 **Nursing Guidelines:**

15.291 Special administration guidelines exist for both tubing and the IV container. Please refer to section 15.24 for these guidelines.

15.292 Administer over 60 minutes. However longer infusion rates may be required to not exceed an infusion rate of greater than 25 mg/min or in patients with prior infusion reactions.

15.293 Infusion reactions may happen during or after the administration of ramucirumab and may be severe. It is recommended that patient be pre-medicated with a histamine H1 antagonist (diphenhydramine). Refer to the protocol for management of infusion related reactions. Patients who experience reaction must be premedicated for subsequent cycles with diphenhydramine, acetaminophen, and dexamethasone.

15.294 Nausea and vomiting have occurred. Administer antiemetics and assess for their effectiveness.

15.295 Myalgia and arthralgia have been reported. Administer analgesics as necessary and assess for their effectiveness.

15.296 Because this agent blocks VEGF, serious bleeding and/or thrombotic events may occur. Patients should be instructed to report any unusual bleeding to the study team immediately. Likewise patients should be instructed in the warning signs for PE/DVT.

15.297 Epistaxis may occur. Instruct patient to report any prolonged epistaxis to the study team. Intervention may be necessary.

15.298 Diarrhea is common. Administer anti-diarrheals as necessary and assess for their effectiveness.

15.299 Headache is also common. Administer analgesics as necessary and assess for their effectiveness.

15.3 Paclitaxel (Taxol)

15.31 **Background**: Antineoplastic Agent, Antimicrotubular, Taxane derivative. Paclitaxel promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly, interfering with the late G_2 mitotic phase, and inhibiting cell replication. In addition, the drug can distort mitotic spindles, resulting in the breakage of chromosomes. Paclitaxel may also suppress cell proliferation and modulate immune response.

15.32 **Formulation**: Commercially available for injection 6 mg/mL (5 mL, 16.7 mL, 25 mL, and 50 mL) [contains alcohol and purified Cremophor EL (polyoxyethylated castor oil)].

15.33 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature and protect from light. Dilute in 250-1000 mL D_5W or 0.9% NaCL to a concentration of 0.3 – 1.2 mg/mL. Chemotherapy dispensing devices (e.g., Chemo Dispensing Pin) should not be used to withdraw paclitaxel from the vial.

Paclitaxel should be dispensed in either glass or non-PVC containers (e.g., Excel/PAB). Use nonpolyvinyl (non-PVC) tubing (e.g., polyethylene) to minimize leaching.

15.34 **Administration:** Refer to package insert for IV administration. When administered as sequential infusions, taxane derivatives should be administered before platinum derivatives (cisplatin, carboplatin) to limit myelosuppression and to enhance efficacy. Infuse through a 0.22 micron in-line filter and nonsorbing administration set.

15.35 **Pharmacokinetic information**:
Distribution: $V_{d:}$ Widely distributed into body fluids and tissues; affected by dose and duration of infusion
V_{dss}: 1- to 6-hour infusion: 67.1 L/m^2
V_{dss}: 24-hour infusion: 227-688 L/m^2
Metabolism: Hepatic via CYP2C8 and 3A4; forms metabolites (primarily 6α-hydroxypaclitaxel).
Half-life elimination: 1- to 6-hour infusion: Mean (beta): 6.4 hours,
3-hour infusion: Mean (terminal): 13.1-20.2 hours
24-hour infusion: Mean (terminal): 15.7-52.7 hours
Excretion: Feces (~70%, 5% as unchanged drug); Urine (14%)
Clearance: Mean: Total body: After 1- and 6-hour infusions: 5.8-16.3 L/hour/m^2; after 24-hour infusions: 14.2-17.2 L/hour/m^2

15.36 **Potential Drug Interactions**:
Cytochrome P450 Effect: Substrate (major) of CYP2C8, CYP3A4;
Induces CYP3A4 (weak).

Increased Effect/Toxicity: CYP2C8 inhibitors may increase the levels/effects of paclitaxel. Refer to the package insert or LexiComp[1] for example inhibitors.
Decreased Effect: CYP2C8 inducers may decrease the levels/effects of paclitaxel. Refer to the package insert or LexiComp[1] for example inducers.
Herb/Nutraceutical Interactions: Avoid black cohosh, dong quai in estrogen-dependent tumors. Avoid valerian, St John's wort (may decrease paclitaxel levels), kava kava, gotu kola (may increase CNS depression).

15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information. Percentages reported with single-agent therapy. **U.S. Boxed Warning**: Bone marrow suppression is the dose-limiting toxicity; do not administer if baseline absolute neutrophil count (ANC) is <1500 cells/mm^3 (1000 cells/mm^3 for patients with AIDS-related KS); reduce future doses by 20% for severe neutropenia. **U.S. Boxed Warning**: Severe hypersensitivity reactions have been reported.

Common known potential adverse events, > 10%:
Cardiovascular: Flushing, ECG abnormal, edema, hypotension.
Dermatologic: Alopecia, rash.
Gastrointestinal: Nausea/vomiting, diarrhea, mucositis, stomatitis, abdominal pain (with intraperitoneal paclitaxel)
Hematologic: Neutropenia, leukopenia, anemia, thrombocytopenia, bleeding.
Hepatic: Alkaline phosphatase increased, AST increased.
Local: Injection site reaction (Erythema, tenderness, skin discoloration, swelling).
Neuromuscular & skeletal: Peripheral neuropathy, arthralgia, myalgia, weakness.
Renal: Creatinine increased.
Miscellaneous: Hypersensitivity reaction, infection.

Less common known potential adverse events, 1% - 10%:
Cardiovascular: Bradycardia, tachycardia, hypertension, rhythm abnormalities, syncope, venous thrombosis.
Dermatologic: Nail changes.
Hematologic: Febrile neutropenia.
Hepatic: Bilirubin increased.
Respiratory: Dyspnea.

Rare known potential adverse events, <1% (Limited to important or life-threatening):
Anaphylaxis, ataxia, atrial fibrillation, AV block, back pain, cardiac conduction abnormalities, cellulitis, CHF, chills, conjunctivitis, dehydration, enterocolitis, extravasation recall, hepatic encephalopathy, hepatic necrosis, induration, intestinal obstruction, intestinal perforation, interstitial pneumonia, ischemic colitis, lacrimation increased, maculopapular rash, malaise, MI, necrotic changes and ulceration following extravasation, neuroencephalopathy, neutropenic enterocolitis, ototoxicity, pancreatitis, paralytic ileus, phlebitis, pruritus, pulmonary

embolism, pulmonary fibrosis, radiation recall, radiation pneumonitis, pruritus, renal insufficiency, seizure, skin exfoliation, skin fibrosis, skin necrosis, Stevens-Johnson syndrome, supraventricular tachycardia, toxic epidermal necrolysis, ventricular tachycardia (asymptomatic), visual disturbances.

15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.39 **Nursing Guidelines:**

15.391 Premedicate with steroids, antihistamines, and H2 blockers as per institutional guidelines.

15.392 Mix the infusion bag well. Thorough admixture of this drug often prevents a hypersensitivity reaction. An inline filter of <0.22 micron must be used distal to the infusion pump. Filter may need to be changed if infusion is to be prolonged >12 hours. Inspect solution for excessive particulate matter, if present do not use.

15.393 Caution patients that the alcohol contained in the infusion may cause impairment in operating heavy equipment or in driving a vehicle and to assess their ability before trying either. Advise avoidance of any alcohol or depressants such as sedatives and opiates if not necessary.

15.394 Assess the patient frequently for the first 30 minutes. Taxol® hypersensitivity reactions, which may include chest pain, back pain, flushing, diaphoresis, dyspnea, pruritus, hypotension, hypertension, bronchospasm and/or urticaria, usually occur early in the infusion. Have the anaphylaxis tray available.

15.395 If a reaction occurs, stop the infusion immediately. Epinephrine, IV fluids, diphenhydramine, and methylprednisolone may be used as per MD's order.

15.396 Approximately 60% of patients experience peripheral sensory neuropathy (numbness, tingling, burning pain, fine motor skills impairment, paresthesias, distal sensory loss). Patients receiving higher doses at shorter infusion times are at greater risk. Most cases have been reported at doses >170 mg/m^2/day and with cumulative doses over multiple courses of therapy. The nerve damage may take months to resolve. Nonsteroidal anti-inflammatory agents and opiates have not been effective in treating neuropathic pain. Consult MD about trying tricyclic antidepressants or possibly Neurontin.

15.397 Increased risk of cardiotoxicity when given in combination with doxorubicin, with a sharp increase in risk of CHF once cumulative dose of doxorubicin is > 380 mg/m^2. At this point taxol should be continued as a single agent only. Monitor for sign/symptoms of CHF.

Instruct patient to report any swelling in the hands, arms, feet, or legs, and any chest pain.

15.398 Mucositis can usually be managed with a salt and soda mouthwash (1 tsp. Salt, 1 tsp. Soda and 1 quart boiled water) or try OTC oral Lysine or Vitamin E.

15.399a Narcotics and nonsteroidal anti-inflammatory drugs may be used to manage the myalgias.

15.399b Monitor CBC closely. Neutropenia is most severe in patients who have had previous chemotherapy. Instruct patient to report signs or symptoms of infection, unusual bruising or bleeding to the health care team.

15.399c There is an increased risk of neutropenia and stomatitis when given prior to doxorubicin. Therefore Taxol should always be given after doxorubicin administration.

15.399d Monitor IV site closely and establish patency before administration. Paclitaxel is an irritant, however rarely rash, radiation recall, and ulceration have occurred with infiltration of drug.

15.399e Monitor liver function tests

15.399f Inform patient about total alopecia.

15.399g If given on the same day as a platinum agent, paclitaxel should be administered first to limit myelosuppression and enhance efficacy of agent.

16.0 Statistical Considerations and Methodology

16.1 Overview

This randomized phase II trial is designed to assess the non-inferiority of trifluridine/tipiracil + ramucirumab (treatment arm) compared to paclitaxel + ramucirumab (control arm) in patients with previously treated advanced gastric or gastroesophageal junction adenocarcinoma. Patients will be randomized at a ratio of 1:1 between the treatment and control arms. An interim analysis for futility is incorporated for early stopping.

Assumptions used to inform this trial were made using data from the RAINBOW study. In RAINBOW, patients were randomized to receive either ramucirumab plus paclitaxel or placebo plus paclitaxel. Patients who received ramucirumab plus paclitaxel experienced a median PFS of 4.4 months.

The null hypothesis for this trial is that the treatment arm does not show a non-inferior PFS outcome compared to the control arm. The alternative hypothesis is that the

treatment arm shows a non-inferior PFS outcome compared to the control arm. A hazard ratio of 1.19 will be used as the non-inferiority margin.

Evaluable Population: The Evaluable Population comprises all patients who are eligible, consented, randomized, and received any protocol treatment.

Safety Population: The Safety Population comprises all patients who received any protocol treatment.

16.2 Statistical Design

16.21 Primary Endpoint

The primary endpoint for this study is progression-free survival (PFS). Progression free survival is defined as the time interval between randomization date and the date of disease progression or death (referred to as an "event"), whichever occurs first. Disease progression will be determined based on RECIST 1.1 criteria. Patients who do not experience an event will be censored at the last disease assessment date.

16.22 Secondary Endpoints

Secondary endpoints for this study will include overall survival (OS), a quality of life (QOL) measurement, and adverse event rates.

16.23 Power and Sample Size

The median PFS for this patient population receiving paclitaxel + ramucirumab (control arm) is approximately 4.4 months. A hazard ratio of 1.19 (the non-inferiority margin) is equivalent to observing a median PFS of 3.7 months or less in the treatment arm, given that we expect the control arm to experience a median PFS of 4.4 months.

The trial has a single interim analysis for futility planned for the end of 2024. The Rho family spending function with parameter 1.5 will be used for the futility boundary. The futility boundary will be considered non-binding.

Additionally, we believe the true median PFS of the treatment arm is 5.5 months (equivalent to a hazard ratio of 0.8, given a median PFS of 4.4 months in the control arm). With these assumptions, 97 events are required to achieve a one-sided alpha of 0.15 and 80% power. Total target sample size for the study will be 116 patients (58 per arm). Additionally, we assume a dropout rate of 5% throughout the duration of the trial.

EAST software was used to determine sample size and the corresponding decision rule.

16.24 Operating Characteristics

The table below includes the operating characteristics according to the design outlined above. The proportion of times that the study would conclude non-inferiority of the treatment arm at the final analysis are tabulated by true median PFS times and equivalent hazard ratios for PFS by treatment groups.

Table 16.24 Summary of Operating Characteristics

True median progression-free survival (months)[1]		True Hazard Ratio	% of times the study will be stopped for futility at the interim analysis[2,3]	% of times the treatment arm is deemed non-inferior at the final analysis[2]
Paclitaxel + Ramucirumab (Control)	TAS-102 + Ramucirumab (Treatment)			
4.4	3.7	1.19	47.6%	14.1%
4.4	4.0	1.1	36.4%	24.4%
4.4	4.4	1.0	25.0%	40.7%
4.4	5.0	0.88	13.7%	64.0%
4.4	5.5	0.80	7.6%	79.4%

[1] Although we use the median PFS to illustrate each scenario, the hypothesis testing is based on the entire survival curve.

[2] Percentages are based on 50,000 replicates in a simulation study performed using EAST software

[3] Assuming the interim analysis is conducted when 50% of the projected number of events have occurred.

16.25 Accrual Time and Study Duration

The anticipated accrual rate is 4 patients per month. Therefore, the accrual period for this trial is expected to be around 29 months. The final analysis can begin as soon as the 97th PFS event has occurred; approximately 32 months after the study begins, under the alternative hypothesis.

16.3 Analysis Plan

The analysis for this trial will take place at planned time points (see 16.25 and 16.31). Decision to perform such analyses will be made by the Statistician and Study Chair, in accord with ACCRU Standard Operating Procedures, availability of data for secondary endpoints, and the level of data maturity.

16.31 Interim Analysis

The interim analysis for futility will be performed at the end of 2024. The data will be frozen for this analysis on December 16, 2024. The specific hazard ratio and critical Z-values for declaring futility at the interim are specified in the decision rule table below (see 16.33), assuming the interim is conducted when 50% of the projected number of events have occurred. Our decision boundary will be adjusted based on the number of events observed at the time of analysis. The trial will continue accrual while the interim analysis is being conducted.

16.32 Primary Endpoint Analysis

The primary analysis can begin when 97 events have occurred, across both arms combined. The formal test statistic for the analysis will be a Z-statistic generated using the log-hazard ratio (treatment arm / control arm), between arms from a stratified Cox regression model. If $\delta = \ln(HR)$, and $\delta_0 = \ln(1.19)$, then $Z = (\delta - \delta_0) / SE(\delta)$. Stratification factors are listed in section 5.0.

Based on the analysis occurring at 100% of expected events, the critical Z-value to reject the null hypothesis (and thus conclude that non-inferiority is attained) is $Z < -1.036$. Hazard ratio (HR) of TAS102 + ramucirumab vs. paclitaxel + ramucirumab, as well as the upper bound of a one-sided 85% confidence interval of the HR will be calculated. The decision rule above is approximately correspondent to a hazard ratio of < 0. 963 or the upper bound of the one-sided 85% confidence interval < 1.19 in order to reject the null hypothesis of inferiority. The Z statistic will be used for decision making.

The median progression free survival of each arm, corresponding 95% confidence intervals, and hazard ratio comparing the treatment arm to the control arm will be reported.

16.33 Decision Rules

Analysis time point	Number of events[1]	Critical Z-value		Hazard Ratio	
		Futility	Non-Inferiority	Futility	Non-Inferiority
50%[2]	49	≥ 0.074	N/A	≥ 1.215	N/A
100%	97	≥ -1.036	< -1.036	≥ 0.963	< 0.963

[1] *Documentation of progression or death*

[2] *The decision boundary will be determined at timing of interim analysis*

16.34 Over Accrual

If more than the target number of patients are accrued, the additional patients will be used in the decision-making process. They will also be included in final point estimates and confidence intervals.

16.35 Secondary Endpoint Analysis

16.351 Overall Survival (OS)

Overall survival is defined as the time from study entry to death from any cause. Median OS will be estimated using the Kaplan-Meier method. Patients who do not experience death while on study will be censored at the last known date alive. The median OS and corresponding 95% confidence interval will be reported by arm.

16.352 Quality of Life

Patient reported quality of life (QOL) outcomes will be collected using the Linear Analog Self-Assessment (LASA) Questionnaire. Data will be collected each cycle. Mean values of the first question (regarding overall QOL) at each cycle will be plotted, and stratified by arm. Additional analyses using data collected from the LASA questionnaire may be performed. The mean change from baseline to 6 months post-randomization of the first question (regarding overall QOL), along with the corresponding 95% confidence interval, will be reported by arm.

16.353 Adverse Events / Toxicities

All patients who have initiated treatment will be considered evaluable for adverse event analyses. Adverse events will be summarized by frequency and severity using CTCAE v 5.0. They will be reviewed to determine overall adverse event patterns, and will be closely monitored throughout the study. The proportion of patients who experience a grade 3+ adverse event at least possibly related to treatment will be reported by arm.

16.4 Data & Safety Monitoring

16.41 Review

The study chair(s) and the study statistician will review the study at least twice per year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice per year, based on reports provided by the MCCC Statistical Office.

16.42 Adverse Event Stopping Rule(s)

The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The

study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time, in either arm, we observe events considered to be at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy the following:

If at any time 10 of the initial 20 treated patients or 50 % or more of all patients (when accrual is greater than 20 patients) have experienced a grade 4+ toxicity at least possible related to treatment, enrollment will be suspended so that adverse event data can be examined and a trial recommendation will be formulated and presented to Mayo DSMB.

We note that we will review Grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.43 CT.gov Reporting

Expected durations and timelines for certain events (e.g. accrual) and endpoints for CT.gov reporting purposes can be found in sections 16.25, 16.311, and 16.32.

17.0 Pathology Considerations/Tissue Biospecimens

None.

18.0 Records and Data Collection Procedures

All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. Access the RAVE RDE system through the iMedidata portal at [redacted] All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions [redacted]

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after registration
On-Study	
On-Study: Prior Surgery[1]	
On-Study: Prior Systemic Therapy[1]	
On-Study: Prior Radiation[1]	

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Adverse Event: Baseline	
RECIST Measurements: Baseline[1]	
Measurements (Non-Measurable Disease Only): Baseline[1]	
Supporting Documentation: Baseline[2]	
Patient Status: Baseline	
Notice of New Primary[1]	
OP and Path Reports (see Section 17.0)[2]	
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Patient Questionnaire Booklet-PRO/QOL: Linear Analogue Self Assessment (LASA)	≤ 2 weeks after registration - Patient questionnaire booklet must be used; copies are not acceptable for this submission.
PRO/QOL : Booklet Compliance Form[1]	≤ 2 weeks after registration - This form must be completed only if the Linear Analogue Self Assessment (LASA) contains absolutely NO patient provided assessment information.
ACCRU Deviation Form[1]	Submit only if applicable during ***all*** **phases** of the study (initial, active and observation)

1. Submit only if applicable.
2. Upload via the Supporting Documentation: Baseline form. Required items to be uploaded include: imaging report and pathology report.

Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Clinical Follow Up
Treatment (Intervention)	X	X	
Treatment (Intervention): Dose Modifications, Omissions and Delays[1]	X		
Adverse Events: Solicited	X	X	
Adverse Events: Other[1]	X	X	
Adverse Events: Late			X
RECIST Measurements[1,2]	X	X	X
Measurements (Non-Measurable Disease Only)[1]	X	X	X
Supporting Documentation[1,2]	X	X	X
Patient Status: Treatment (Intervention)	X	X	
Patient Medication Diary[1,6]	X		
Patient Status: Clinical Follow-Up/Observation			X
Notice of New Primary[1]	X	X	X

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Clinical Follow Up
Consent Withdrawal (choose appropriate form)[1] • Consent Withdrawal: Clinical Follow-Up Only • Consent Withdrawal: All Follow-Up	X	X	X
Off Treatment		X	
ACCRU Deviation[1]	X	X	X
Lost to Follow-up[3]			X
Patient Questionnaire Booklet-PRO/QOL: Linear Analogue Self Assessment (LASA)[4]	X	X	
PRO/QOL : Booklet Compliance Form [1,5]	X	X	

1. Submit only if applicable.
2. Upload imaging for all scans to support RECIST measurements in the supporting documentation folder.
3. Patients are eligible to be confirmed lost to follow-up after 2 years of unsuccessful contact with the patient.
4. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
5. This form must be completed **only** if the Linear Analogue Self Assessment (LASA) contains absolutely **NO** patient provided assessment information.
6. This form is to be completed by the patient and uploaded to RAVE in the Treatment (Intervention) folder for each cycle. Arm A patients only.

Follow-up Material(s)

CRF	**Event Monitoring Phase[1]**				
	q. 3 months until PD or subsequent therapy	At PD or subsequent therapy	After PD or subsequent therapy q. 3 mos.	Death	New Primary
Patient Status: Survival and Disease Status Follow-Up/Event Monitoring	X[2]	X[2]	X	X	
Adverse Events: Late[3]	X	X	X	X	
Supporting Documentation[3]	X	X	X	X	
Notice of New Primary[3]					X
Consent Withdrawal (choose appropriate form)[3] •					

CRF	Event Monitoring Phase[1]				
	q. 3 months until PD or subsequent therapy	At PD or subsequent therapy	After PD or subsequent therapy q. 3 mos.	Death	New Primary
• Consent Withdrawal: Clinical Follow-Up Only • Consent Withdrawal: All Follow-Up					
Lost to Follow-Up[3]					
ACCRU Deviation Form[3]	X[3]	X[3]	X[3]	X[3]	

1. If a patient is still alive 3 years after registration, no further follow-up is required.
2. Upload a copy of documentation of response or progression in RAVE on the Supporting Documentation Form.
3. Submit only if applicable.

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded:

19.3 Other budget concerns:

19.31 Ramucirumab will be provided free of charge by Eli Lilly.

19.32 Trifluridine/tipiracil will be provided free of charge by Taiho.

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Appendix I: ACCRU-GI-1810 SUBJECT INFORMATION SHEET
Subject Completed Quality of Life Booklet
(Each Cycle and End of Treatment)

You will be given booklets to complete for this study. This booklet contains some questions about your 'quality-of-life' as a subject receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete a questionnaire booklet for this study. This booklet must be completed prior to dosing at each cycle and at the end of treatment (within 30 days after your last dose).

2. This booklet contains the following questionnaire:
    a. Linear Analogue Self Assessment (LASA)

3. Directions on how to complete each set of questions are written on the top of the page.

4. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

5. Please complete the booklet and return it to your study staff. It is very important that you return the booklet to us.

Thank you for taking the time to help us.

Appendix II: ACCRU-GI-1810 LINEAR ANALOGUE SELF ASSESSMENT

Subject Name: _____ Date: _____
Subject Number: _____

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

How would you describe:

1. your overall Quality of Life?

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

2. your overall mental (intellectual) well being?

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

3. your overall physical well being?

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

4. your overall emotional well being?

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

5. your level of social activity?

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

6. your overall spiritual well being?

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

7. the frequency of your pain?

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

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

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

9. your level of fatigue, on the average?

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

10. your level of support from friends and family?

0	1	2	3	4	5	6	7	8	9	10
No support										Highest level of support

11. your financial concerns?

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

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

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

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Appendix III: ACCRU-GI-1810 SUBJECT MEDICATION DIARY

Name:	Patient ID Number:
Cycle:	

ORAL MEDICATION DIARY
Patient Instructions

- Please bring your Medication Diary and any empty or unused medication container(s) with you to every appointment
- Please use an ink pen when completing the Medication Diary as these will be retained in our research record.
- Please contact your physician and study coordinator any time you go into the hospital. Your physician can advise if you should stop taking your medication or continue it.
- To correct an error or mistake, please make a single line through that entry and write your initials and date next to the error or mistake.
- Please record each dose as soon as you take it and fill in the date as directed.
- Please indicate on the calendar below every day that you take your study medication by placing the dose taken on the line under the date.
- If you miss a dose, place a "0" under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- If you accidentally take more than you are instructed to, contact your doctor or the emergency room immediately.
- If you miss a dose, do not make up the dose or double up the next dose.
- Your dose may be held due to side effects, be sure to record a 0 on those days your medication is held. Once you restart the medication, record the dose again.

Example:

	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Date	1/1/2019	1/2/2019	1/3/2019	1/4/2019	1/5/2019	1/6/2019	1/7/2019
AM dose time	7:00 AM						
PM dose time	8:00 PM						
AM dosage in mg							
PM dosage in mg							

ACCRU-GI-1810 Subject Medication Diary – TAS-102

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date							
AM dose time							
PM dose time							
AM dosage in mg							
PM dosage in mg							

	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Date							
AM dose time							
PM dose time							
AM dosage in mg							
PM dosage in mg							

	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Date							
AM dose time							
PM dose time							
AM dosage in mg							
PM dosage in mg							

	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Date							
AM dose time							
PM dose time							
AM dosage in mg							
PM dosage in mg							

Date:_____ Participants Signature_____

Area Below Only To Be Completed only by Coordinator

Week	1	2	3	4	Discrepancy (Yes or No)
Date of Pill Count					
Number of Pills Returned					
Study Coordinator Initials					