Phase II study of ramucirumab with trastuzumab, fluoropyrimidine, and platinum in patients with metastatic HER2-positive gastroesophageal junction and gastric cancer

PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a single arm Phase II study of ramucirumab in combination with capecitabine/5-FU and a platinum and trastuzumab in patients with HER2-positive Stage IV gastric or gastroesophageal junction (GEJ) adenocarcinoma. The goal of the study is to determine the efficacy of the drug combination as measured by 6 month progression free survival (PFS). Eligible patients must be older than 18 years of age and must have histologically proven HER2-positive gastric or GEJ cancer (immunohistochemistry 3+ or FISH≥2.0).

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary:

To determine the efficacy of ramucirumab in combination with capecitabine/5-FU and oxaliplatin/cisplatin and trastuzumab in patients with HER2-positive Stage IV gastric or GEJ adenocarcinoma as measured by 6 month PFS.

Secondary:

To establish the safety of ramucirumab in combination with capecitabine/5-FU, oxaliplatin/cisplatin and trastuzumab in patients with HER2-positive Stage IV gastric or GEJ adenocarcinoma.

To establish response rate of ramucirumab with trastuzumab in patients with HER2-positive Stage IV gastric or GEJ adenocarcinoma.

To observe other measures of efficacy of ramucirumab in combination with capecitabine/5-FU, oxaliplatin/cisplatin and trastuzumab, including response rate, median PFS, overall and 1-year survival in patients with HER2-positive Stage IV gastric or GEJ adenocarcinoma.

Exploratory Objectives

To explore molecular tumor characteristics associated with resistance and/or sensitivity to ramucirumab, trastuzumab and capecitabine/cisplatin using next-generation sequencing of available archival tumor specimens.

To explore changes in ^{89}Zr-trastuzumab PET after trastuzumab and ramucirumab treatment.

To utilize cell-free tumor DNA (cfDNA) from blood specimens collected during the course of treatment to explore mechanism of primary and acquired resistance to ramucirumab and trastuzumab therapy.

3.0 BACKGROUND AND RATIONALE

3.1 Background

Cancers originating in the GEJ and stomach constitute a global health problem. Gastric cancer is the fourth most common cancer and second leading cause of cancer mortality worldwide.[1] In 2015, an estimated 22,220 people will be diagnosed and 10,990 people will eventually die of their disease in

the United States.[2] Depending on tumor characteristics and stage, treatment modalities include combinations of surgery, chemotherapy, and radiation therapy.[1] Even with maximal therapy, prognosis for gastric cancer remains poor, with 5-year survival rate of 5%[2,3] and median survival of 10 to 14 months in Stage IV disease.[4-6] The poor prognosis is largely attributed to the fact that the majority of gastric cancer patients have metastatic disease at the time of presentation.[1] Palliative chemotherapy is used to control tumor growth, improve quality of life and has been shown to prolong survival in patients with Stage IV disease.[4-6] Among patients who initially respond to chemotherapy majority ultimately suffer disease progression. In addition, a significant proportion of gastric and GEJ patients have primary chemotherapy refractory disease. For these patients there is a need for development of new therapeutic options.[6]

A meta-analysis of phase II and III randomized gastric cancer trials has shown that combination chemotherapy results in substantially improved overall survival compared with single-agent chemotherapy or best supportive care.[7] Typically, a fluoropyrimidine and a platinum compound form the backbone of chemotherapy for patients with advanced gastric cancer.

3.2 Capecitabine in combination with cisplatin in gastric cancer

The REAL-2 trial was a randomized multicenter phase III study, which compared the efficacy and safety of capecitabine-based combinations and fluorouracil-based combinations in patients with advanced gastric cancer.[6] In this study, 1002 patients were randomly assigned to receive triplet therapy with epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX) or triplet therapy with epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX). The primary end point was non-inferiority in overall survival for the triplet therapies containing capecitabine as compared with fluorouracil and for those containing oxaliplatin as compared with cisplatin. Results from this study suggested that capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated gastric cancer. For the capecitabine–fluorouracil comparison the hazard ratio (HR) for death in the capecitabine group was 0.86 (95% confidence interval [CI], 0.80 to 0.99); for the oxaliplatin–cisplatin comparison the HR for the oxaliplatin group was 0.92 (95% CI, 0.80 to 1.10). Median survival times in the ECF, ECX, EOF, and EOX groups were 9.9 months, 9.9 months, 9.3 months, and 11.2 months, respectively; survival rates at 1 year were 37.7%, 40.8%, 40.4%, and 46.8%, respectively. Toxic effects of capecitabine and fluorouracil were similar. As compared with cisplatin, oxaliplatin was associated with lower incidences of grade 3 or 4 neutropenia, alopecia, renal toxicity, and thromboembolism but with slightly higher incidences of grade 3 or 4 diarrhea and neuropathy.[6]

ML 17032, another phase III randomized trial, evaluated the combination of capecitabine and cisplatin (XP) vs. the combination of fluorouracil and cisplatin (FP) as first-line treatment in patients with previously untreated advanced gastric cancer.[13] The results of this study suggest that capecitabine is as effective as fluorouracil in the treatment of patients with advanced gastroesophageal cancers. A meta-analysis of the REAL-2 and ML17032 trials suggested that OS was superior in the 654 patients treated with capecitabine-based combinations compared with the 664 patients treated with fluorouracil-based combinations.[8]

3.3 Targeting HER2: Trastuzumab

Human epidermal growth factor receptor 2 (HER2; also known as ERBB2), a member of a family of receptors associated with tumor cell proliferation, apoptosis, adhesion, migration, and differentiation is an established biomarker and key driver of tumorigenesis in gastric cancer.[9] Approximately 20-30% of gastric and GEJ adenocarcinomas harbor HER2 overexpression.[9,10]

Trastuzumab is a humanized monoclonal antibody (IgG1 isotype) directed against the extracellular region of HER2 that induces antibody-dependent cellular cytotoxicity, inhibits HER2-mediated signaling, and prevents cleavage of the extracellular domain of HER2.[11] The ToGA study is the first randomized, prospective, multicenter, phase III trial to evaluate the efficacy and safety of trastuzumab in HER2-positive gastric and GEJ adenocarcinoma in combination with cisplatin and a fluoropyrimidine.[9] In this study, 594 patients were randomly assigned to study treatment (trastuzumab plus chemotherapy, n=298; chemotherapy alone, n=296). The results of this study established the benefit of trastuzumab in combination with cisplatin and fluoropyrimidine chemotherapy. Median overall survival was 13.8 months (95% CI 12–16) in those assigned to trastuzumab plus chemotherapy compared with 11.1 months (10–13) in those assigned to chemotherapy alone (HR 0.74; 95% CI 0·60–0·91; p=0·0046). Median progression-free survival was 6.7 months (95% CI 6–8) in the trastuzumab plus chemotherapy group compared to 5.5 months (5–6) in the chemotherapy alone group (HR 0.71, 95% CI 0.59–0.85; p=0.0002). Overall tumor response rate, time to progression, and duration of response were significantly improved in the trastuzumab plus chemotherapy group compared to the chemotherapy alone group. Rates of overall grade 3 or 4 adverse events (201 [68%] vs 198 [68%]) and cardiac adverse events (17 [6%] vs 18 [6%]) did not differ between groups.[15] On the basis of these findings, trastuzumab is now considered a standard option for patients with HER2-positive advanced gastric and GEJ cancer when combined with a chemotherapy regimen consisting of a fluoropyrimidine (5-FU or capecitabine) and platinum (cisplatin or oxaliplatin).

3.4 Targeting VEGFR2: Ramucirumab

Vascular endothelial growth factor receptor (VEGFR)-2 plays a central role in tumor growth and metastasis by promoting pathologic angiogenesis.[12] Although many potential antiangiogenic targets exist, VEGF and its receptors play a central role in both physiologic and pathologic angiogenesis. VEGF is a potent pro-angiogenic factor that not only stimulates endothelial cell proliferation, migration and survival, but also increases vascular permeability.[12] Angiogenesis is required for invasive tumor growth and metastasis and constitutes an important point in the control of cancer progression. Inhibition of angiogenesis has demonstrated clinically significant improvements in outcomes in a variety of malignancies, including gastric cancer.[13,14]

Ramucirumab is a fully human immunoglobulin IgG1 monoclonal antibody that binds with high affinity to the extracellular VEGF-binding domain of VEGFR-2 that prevents ligand binding and receptor-mediated pathway activation in endothelial cells.[15] Based on the data outlined below, the U. S. Food and Drug Administration approved ramucirumab as either a single agent or in combination with paclitaxel for the treatment of patients with metastatic, gastric or GEJ adenocarcinoma with disease progression after fluoropyrimidine/platinum chemotherapy. The REGARD trial was an international, randomized, double-blind, placebo-controlled, phase 3 trial in which 355 patients with advanced gastric or GEJ adenocarcinoma and disease progression after first-line platinum-containing or fluoropyrimidine-containing chemotherapy were randomly assigned to receive best supportive care plus either ramucirumab 8 mg/kg or placebo, intravenously once every 2 weeks.[16] Median overall survival was 5.2 months (2.3–9.9) in patients in the ramucirumab group and 3.8 months (1.7–7.1) in those in the placebo group (HR 0.776, 95% CI 0.603–0.998; p=0.047). The study demonstrated that ramucirumab is the first biological treatment given as a single drug that has survival benefits in patients with advanced gastric or gastroesophageal junction adenocarcinoma progressing after first-line chemotherapy, thus validating VEGFR-2 signaling as an important therapeutic target in advanced gastric cancer.

Ramucirumab has also shown efficacy with an acceptable safety profile in combination with paclitaxel in patients with advanced gastric or GEJ cancer whose disease had progressed after prior

platinum/fluoropyrimidine-based chemotherapy in the randomized Phase 3 study, RAINBOW (N=665).[17] The primary endpoint of OS was met; median OS was 9.63 months on the ramucirumab plus paclitaxel arm compared with 7.36 months on the placebo plus paclitaxel arm (HR=0.807, 95% CI: 0.678, 0.962; p=.0169). Grade ≥3 AEs occurring in >5% of patients on the ramucirumab plus paclitaxel arm were: neutropenia (40.7% ramucirumab plus paclitaxel arm; 18.8% placebo plus paclitaxel arm), leukopenia (17.4% vs. 6.7%), hypertension (14.1% vs. 2.4%), anemia (9.2% vs. 10.3%), fatigue (7.0% vs. 4.0%), abdominal pain (5.5% vs. 3.3%), and asthenia (5.5% vs. 3.3%). Febrile neutropenia was reported in 3.1% in the ramucirumab plus paclitaxel arm and 2.4% placebo plus paclitaxel arm.

A recently completed randomized, placebo-controlled, double-blind, Phase 2 study of ramucirumab in combination with mFOLFOX-6 as first-line therapy for advanced adenocarcinoma of the esophagus, GEJ, or stomach (N=168) showed improved PFS rate at 3-months (89.0% versus 75.3%) and an improved disease control rate (DCR) (84.5% vs. 66.7%; p=.008), although did not show improved PFS or OS. A higher rate of discontinuation from study treatment for reasons other than progressive disease (PD) in the ramucirumab arm compared with the placebo arm was observed (50% vs. 19%), which led to lower study drug exposure in the experimental arm. These observations may have had a negative impact on the results of the PFS assessment of the entire study population. Overall, the safety profile for ramucirumab in this study was consistent with the known safety profile of ramucirumab. The most common Grade ≥3 AE (by consolidated AE) reported was neutropenia (26.8% ramucirumab arm vs. 36.3% placebo arm). Fatigue (18.3% in the ramucirumab arm vs. 15.0% in the placebo arm) and neuropathy (8.5% vs. 11.3%) reported at a similar frequency in each arm.[18]

3.5 Rationale for combined VEGF and HER2 targeted therapy

Trastuzumab is the standard of care for patients with metastatic HER2-positive gastric cancer. However, the response rate in first line setting is only 47% with trastuzumab in combination with chemotherapy while acquired and intrinsic resistance to trastuzumab limits its efficacy. The short duration of response in some patients led to our hypothesis that combined inhibition of multiple oncogenic pathways that drive gastric cancer growth may achieve a greater therapeutic benefit. Cellular heterogeneity, redundancy of molecular pathways and effects of the microenvironment contribute to the survival, motility and metastasis of cells in solid tumors. It is unlikely that tumors are entirely dependent on only one abnormally activated signaling pathway; consequently, treatment with an agent that interferes with a single target may be insufficient.[19]

Preclinical and clinical studies have linked VEGF expression and HER2 signaling in human cancers.[20] Co-expression of VEGF and HER2 in clinical tumor samples is associated with worse outcome in patients with advanced breast cancer.[21] Furthermore, in HER2-positive breast cancer xenografts experiments treatment with VEGF-Trap (VEGF-A, VEGF-B and placental growth factor inhibitor) alone, trastuzumab alone, or combination of VEGF-Trap and trastuzumab which resulted in synergist effect of dual HER2 and VEGF-A blockade.[20] Compared to either agent alone or to controls, treatment with the combination produced a striking and superior inhibition of tumor microvessel density as indicated by CD31 staining, cell proliferation as indicated by Ki67 staining and tumor growth ($p = 0.008$).

Combined blockade of HER2 and VEGF exerts greater growth inhibition of HER2-overexpressing gastric cancer xenografts than individual blockade.[22] Singh et al. evaluated the antitumor effects of trastuzumab; VEGF-Trap and a combination of trastuzumab and VEGF-Trap in a gastric cancer xenograft model. Although trastuzumab and VEGF-Trap each moderately inhibited tumor growth, the combination of these agents exerted greater antitumor effect compared with either agent alone.

Immunohistochemistry analyses indicated that the reduction in tumor growth was associated with decreased proliferation and increased apoptosis of tumor cells and decreased tumor vascular density. As indicated in Figure 1, the combined treatment resulted in fewer proliferating tumor cells, more apoptotic cells and reduced tumor vascular density compared with treatment with trastuzumab or VEGF-Trap alone, indicating that trastuzumab and VEGF-Trap had additive inhibitory effects on the tumor growth and angiogenesis of the gastric cancer xenografts.

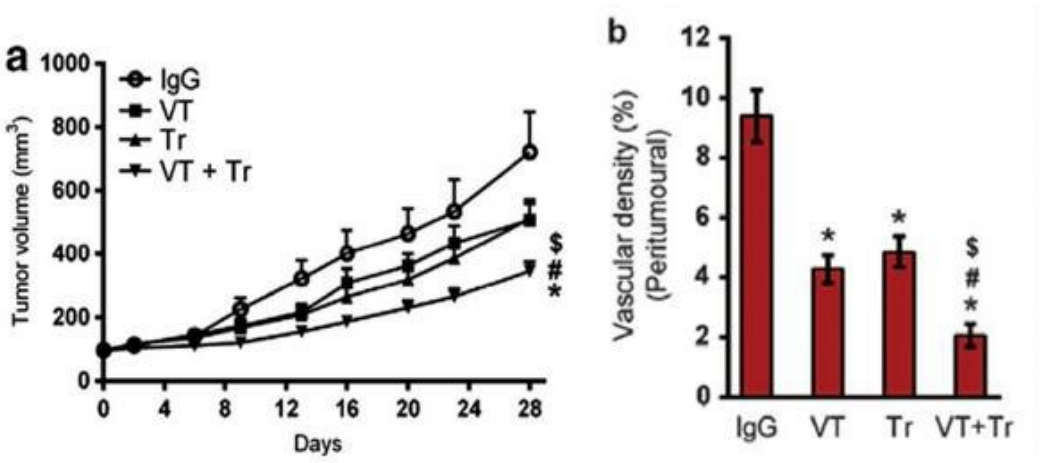

Figure 1. The combined inhibition of HER2 and VEGF reduces tumor growth more efficiently than single-agent inhibition. (a) Mice bearing NCI-N87Luc+tumors were divided into four groups and treated with an isotype-control antibody, VEGF-Trap (VT), trastuzumab (Tr) or a combination of VEGF-Trap and trastuzumab (VT+Tr) for 28 days. (b) The effect of treatment on vascular density. The scale bar represents 100 μm (n=7; *P<0.05 versus isotype control; *P<0.05 versus vascular endothelial growth factor (VEGF)-Trap (VT); *P<0.05 versus trastuzumab (Tr)). IgG, immunoglobulin G.

3.6 Clinical data to support VEGF and HER2 targeted therapy in HER2-positive gastric cancer. A recent multicenter phase II trial, led by investigators at Dana Farber, explored the combination of capecitabine/oxaliplatin with both bevacizumab (anti-VEGF A ligand monoclonal antibody) and trastuzumab in patients with stage IV HER2-positive gastric and GEJ adenocarcinoma. This study enrolled 35 patients and demonstrated that combination of capecitabine/oxaliplatin with bevacizumab and trastuzumab is safe and results superior efficacy compared to historical control of capecitabine/fluoropyrimidine and trastuzumab in HER2-positive gastric cancer. Patients received a loading dose of trastuzumab 4mg/kg, day 1. One week later, patients received bevacizumab 7.5mg/kg/d1, trastuzumab 6mg/kg/d1, oxaliplatin 130mg/m^2/d1 and then q21d. Capecitabine-14 of 21 days was decreased from 1700mg/m^2/d to 1200mg/m^2/d after 4 of the first 5 patients developed Grade 3 diarrhea. Primary endpoint was RR by RECIST 1.1, scored by independent Harvard Tumor Imaging Metrics Core. Safety for 30 patients (enrolled after CAP dose change): 16 patients required dose modification: capecitabine dose modification in 2 patients; oxaliplatin dose modification in 14 patients; bevacizumab dose modification in 2 patients; none of the patients required trastuzumab dose reduction. Combination of chemotherapy with HER2 and VEGF inhibitors was well-tolerated overall with low rate of grade 3 or 4 toxicities. Patients with grade 3-4 adverse events: peripheral neuropathy in 3 patients; bleeding in 3 patients; thromboembolic event in 2 patients; hypertriglyceridemia in 2 patients; low ANC in 2 patients; hypertension in 1 patients; low platelets in 1 patient; diarrhea in 1 patient. One patient died of cardiac arrest after 3 years on treatment

In this trial, combination of chemotherapy with trastuzumab resulted in unprecedented response rate of 81% (95% CI, 0.59 - 0.88) by blinded review, median PFS 13.9 months (95%CI, 8.5 - 22.33); with

75% of patients progression free at 6 months, median OS 26.92 months (95%CI, 11.31 - 36.36) (Figure 2)[23].

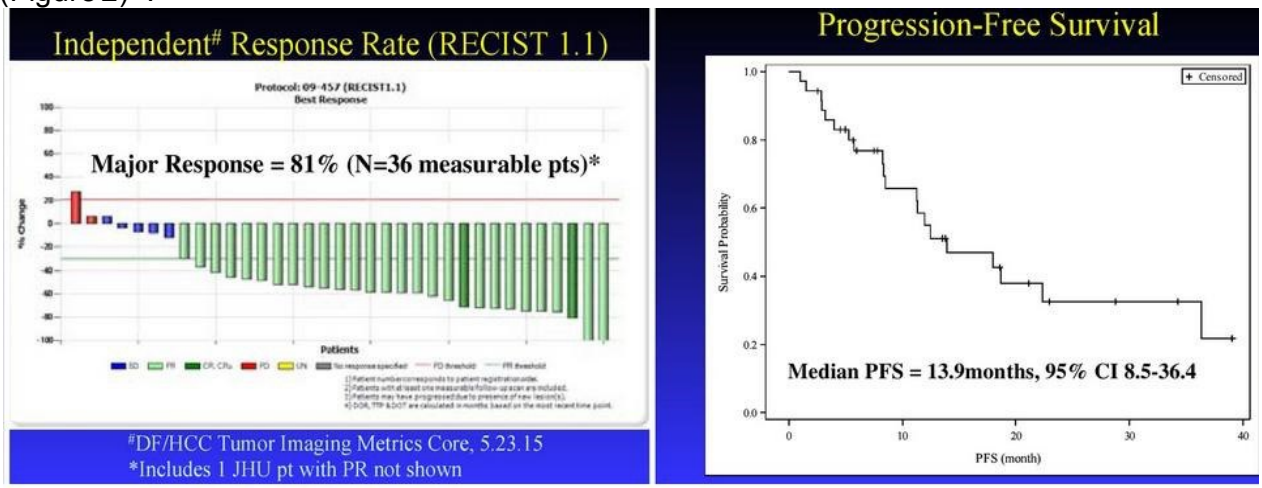

Figure 2 Waterfall plot of best response (left) and PFS with trastuzumab, bevacizumab, and capecitabine/oxaliplatin therapy.

While these data suggest an important role of angiogenesis in the progression of HER2-positive gastric cancer, a first line trial exploring chemotherapy in combination with bevacizumab failed to meet its primary endpoints, therefore bevacizumab is not available for treatment of gastric cancer. Ramucirumab is approved by the U. S. Food and Drug Administration for patients with gastric and GEJ adenocarcinoma and is thus available to study in combination with trastuzumab. Our trial will be the first trial to explore first line combination fluoropyrimidine/platinum with ramucirumab and trastuzumab in HER2-positive gastric and GEJ cancer.

3.7 Rationale for Correlative Studies

3.7.1 ^{89}Zr-trastuzumab PETs as pharmacodynamic biomarker

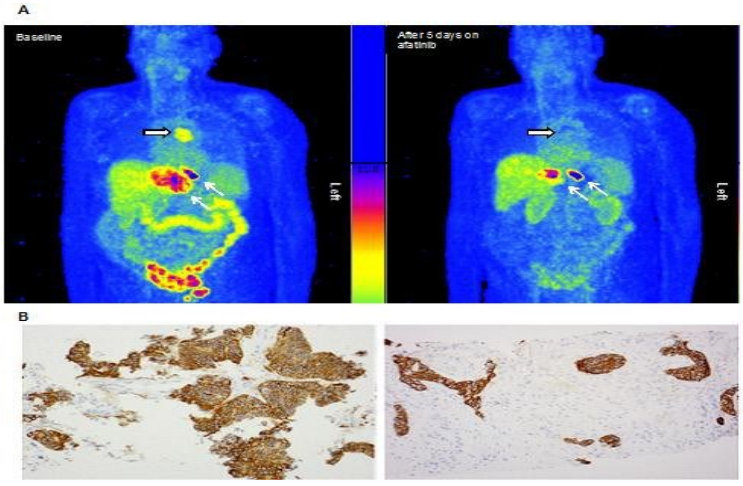

Figure 3 A ^{89}Zr-trastuzumab PET of a patient with heavily pretreated EG cancer before and 5 days after single agent afatinib therapy. B. Corresponding pre and post afatinib liver biopsy showing persistent high HER2 immunohistochemistry expression (IHC 3+) in Segment 2 liver lesion with persistently high SUV uptake post afatinib indicated in Table 1.

Table 1	Primary	M1	M2	M3
ERBB2 CNV	16.5	8.9	9.2	2.5
^{89}Zr-PET SUV				
Baseline	21	9	16	0
Post afatinib	24	7	16	0

Our group in collaboration with Drs. Lewis and Weber implemented functional imaging with ^{89}Zr-trastuzumab PET to characterize the extent of response heterogeneity to HER2 directed therapy between primary tumor and metastases in HER2-positive gastric and GEJ cancer. ^{89}Zr-trastuzumab is well-tolerated with ideal imaging interval of 5 days post injection. **Figure 3** shows ^{89}Zr-Trastuzumab PET images of a patient with heavily pretreated HER2 + GEJ cancer which demonstrate the selective and high accumulation of ^{89}Zr-

trastuzumab in posterior-esophageal lymph nodes and liver metastasis with very low background of uptake in normal organs. **Table 1** shows the estimated ^{89}Zr-trastuzumab PET SUVs and corresponding HER2 copy number variation (CNV) in primary tumor and metastases obtained during rapid autopsy of a patient treated with afatinib (**Figure 3**), where high ^{89}Zr SUV value correlates with HER2 copy number. Heterogeneity in response is noted with dramatic decrease in lymph node uptake after 5 days of afatinib (EGFR/HER2 TKI) and persistently high uptake noted in liver lesions and primary esophageal mass. Post-afatinib liver biopsy showed persistently high HER2 expression (IHC3+ **Figure 3**).The patient had radiographic tumor response on 8 week CT, reduction in liver and lymph node metastasis. At the time of therapy failure, the disease progressed in liver and primary tumor (sites of persistently high ^{89}Zr-trastuzumab PET), while posterior esophageal mass had durable complete regression.

^{89}Zr-trastuzumab PET has a potential advantage over single site biopsies as it can non-invasively assess variation in level of HER2 and target engagement in both the primary tumor and all sites of metastases simultaneously.[24-26] Our preliminary data in 20 patients imaged thus far at MSK demonstrates that ^{89}Zr-trastuzumab PET is feasible and provides exceptional image quality in HER2-positive gastric cancer patients with ideal imaging interval of 5 days post radiotracer injection. Thus far, by imaging HER2-positive gastric cancer patients with ^{89}Zr-trastuzumab PET (IRB 13-165 co-PI Janjigian) we have been able to demonstrate 1) the differences in degree of HER2 inhibition between afatinib vs afatinib + trastuzumab therapy and 2) variability in ERBB2 (HER2) amplification between primary tumor and sites of metastasis. The lead-in cycle with ramucirumab + trastuzumab will provide key pilot data on activity on targeted therapy without chemotherapy in first line HER2-positive gastric and GEJ cancer. In select patients, baseline and early assessment ^{89}Zr-trastuzumab-PET will be performed under IRB 13-165 with CT/MRI scan performed after the initial 3 weeks (1 cycle).

3.7.2 Next Generation Sequencing in Esophagogastric cancer

Investigators at Broad/DFCI and MSKCC recently led a comprehensive molecular and genomic characterization of gastric cancer, evaluating the mutations, copy-number, gene expression and DNA methylation across 295 cases through The Cancer Genome Atlas.[27] While therapeutic development for gastric cancer has largely viewed the disease as a single entity, our unbiased informatics approach integrating somatic genomic alterations, methylation and gene expression led us to redefine the disease into four distinct subclasses. 1) Tumors with Epstein-Barr virus (EBV) infection showed profound hypermethylation, and had a novel finding of 80% of tumors harboring a *PIK3CA* mutation. 2) Microsatellite unstable (MSI) harbored DNA hypermethylation (distinct from that of EBV tumors) and had elevated somatic mutation rates with highly recurrent mutations of *PIK3CA* (42%) and ERBB3 (26%) with 12% of tumor having alterations of both genes. 3) Tumors with chromosomal instability (CIN) showed marked aneuploidy. While lacking common mutations of *PIK3CA/ERBB3* they harbored recurrent amplifications of receptor tyrosine kinases, most notably HER2 (24%). 4) Tumors lacking aneuploidy and elevated rates of mutation or hypermethylation were termed genomically stable (GS), largely those of the diffuse histologic subtype. We identified that 30% of these tumors harbored novel alterations of the Rho signaling pathway, somatic mutations of *RHOA* or fusion genes involving RHO GTPase activating proteins. This classification structure creates a foundation to develop rational therapeutics for distinct groups of patients. At MSK next generation sequencing and gene copy number analysis is routinely performed on all advanced gastric tumors using next generation using the MSK-IMPACT ™ assay (Integrated Mutation Profiling of Actionable Cancer Targets), an on-site 410 cancer-associated gene bait capture, next generation sequencing assay.

Using available archival tumor samples from patients treated on the trial, we will profile genomic alterations in key cancer-associated genes found to drive resistance in esophagogastric cancer

using the IMPACT assay. In brief, DNA from each patient is sheared, and then both tumor DNA and normal DNA is end-repaired and ligated to adapters, minimally amplified with bar-coded primers, and the exons corresponding to the genes of interest are captured using Agilent SureSelect beads.[28,29] We have validated the robustness of this assay using DNA derived from formalin-fixed, paraffin embedded (FFPE) tumor tissue. While TCGA is an international collaboration using previously untreated frozen primary tumor specimens comprehensive molecular profiling is increasingly embraced in routine clinical practice on 'less than perfect' archival paraffin embedded samples.[28,29] A recent comparison with the TCGA results performed by our group compared to MSK cohort of esophagogastric cancer patients revealed an over-representation of the CIN subtype (65% vs. 50% in TCGA) in gastric cancer patients in United States using chemotherapy treated, metastatic tumor specimens.[30] According to The Cancer Genome Atlas analysis of the four distinct molecular gastric cancer subtypes[27], HER2-positive tumors are characterized by chromosomal instability (CIN), marked aneuploidy, and dependency on receptor tyrosine kinase signaling. It is therefore possible that recurrent amplification in key tyrosine kinases (such as EGFR[22], HER3[31], HER4 and MET) contribute to drug resistance. In-depth analysis of tumor samples from patients enrolled in HER2-positive trials using next generation sequencing platforms may help identify gene signatures (beyond HER2 IHC or FISH) predictive of resistance to HER2 directed agents.

3.7.3 Cell-Free DNA (cfDNA)

Preliminary data obtained in collaboration with MSKCC Laboratory Medicine Core (E. Peerschke and A. Samoila) demonstrates that cf DNA collection is feasible and results in adequate DNA yield from peripheral blood collection of patient with metastatic HER-2 positive GE junction adenocarcinoma. Results from collection of sample from 6 patients treated in Dr. Janjigian's clinic, as summarized in the table below. Cell-free DNA (cfDNA) will be obtained from plasma samples collected at baseline, at week 3, every 9 weeks and at the time of treatment discontinuation. cfDNA will be subject to molecular profiling to identify ERBB2 amplifications and other gene operations related to protocol therapy response and resistance.

		cfDNA results		
EG Cancer Patient	Tube ID	Conc (pg/µl)	Elution volume (µl)	Total yield (ng)
1	MJ_901	716	60	43.0
2	AF_203	158.4	60	9.5
3	SF_152	248	60	14.9
4	EH_317	754	60	45.2
5	AD_129	1434	60	86.0
6	EV_233	450	60	27.0

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This will be a single arm study of ramucirumab 8mg/kg administered intravenously on days 1 and 8 + trastuzumab (8 mg/kg loading dose; 6 mg/kg maintenance) administered intravenously every 21 days. CT/MRI scan will be performed after the initial 3 weeks (1 cycle) to determine response to

ramucirumab with trastuzumab, and every 9 weeks thereafter. On subsequent cycles for all patients capecitabine 850mg/m^2 will be added, taken orally twice a day for fourteen days (days 1 through 14) followed by a 7 day rest period, in addition to cisplatin 80mg/m^2 administered as an IV infusion every 21 days. Each cycle consists of 21 days. As an alternative fluoropyrimidine, 5-fluorouracil may be considered for patients who cannot be administered capecitabine for any specific reason. 5-fluorouracil (5-FU) 800mg/m^2/day will be administered on Day 1-Day 5 of every 21 days. Oxaliplatin may also be considered for patients who cannot be administered cisplatin for any specific reason. Oxaliplatin 130 mg/m^2/day will be administered on Day 1 beginning with cycle 2. If the patient is not a good candidate for induction chemotherapy, capecitabine/5-FU and cisplatin/oxaliplatin can be added during cycle 1 of treatment. Treatment will be administered on an outpatient basis. In an effort to prevent adverse events, all patients will be premedicated per institutional guidelines prior to treatment. All other antiemetics and supportive agents may be administered at the discretion of the primary oncologist. Treatment will be performed on the scheduled day ± 7 days to allow for clinic closure, holidays, and patient's preference. Adverse events and clinical monitoring will take place during weekly physician visits for 6 weeks (2 cycles) followed by visits every three weeks thereafter. In case of discontinuation of capecitabine/5-FU and/or cisplatin/oxaliplatin due to cumulative toxicity, administration of ramucirumab 8mg/kg IV infusion on days 1 and 8 + trastuzumab 6mg/kg every 21 days will be continued.

All patients must be able to provide informed consent prior to enrollment.

See Section 10 for treatment table.

4.2 Intervention

Up to 37 patients will be enrolled on this clinical trial. Patients will receive ramucirumab 8mg/kg intravenously on days 1 and 8 + trastuzumab 8mg/kg administered as an IV infusion on cycle 1 day 1. Patients must have evaluable or measurable disease and will undergo a computerized tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis <28 days prior to start of therapy, at three weeks, and every nine weeks thereafter (every 3 cycles), with a scheduling window of up to one to fourteen (1-14) days. CT scans occurring every 9 weeks will coincide with the 6 month CT scan, and if necessary, an additional scan will be done at 6 months. After cycle 1, capecitabine 850mg/m^2 taken orally twice a day for fourteen days followed by a one week rest period, and cisplatin 80mg/m^2 IV every 21 days will be administered in addition to ramucirumab 8mg/kg intravenously day 1 and 8 with trastuzumab 6mg/kg intravenously every three weeks. As an alternative fluoropyrimidine, 5-fluorouracil may be considered for patients who cannot be administered capecitabine for any specific reason. 5-fluorouracil (5-FU) 800mg/m^2/day will be administered on Day 1-Day 5 of every 21 days. Oxaliplatin may also be considered for patients who cannot be administered cisplatin for any specific reason. Oxaliplatin 130 mg/m^2/day will be administered on Day 1 beginning with cycle 2. The same imaging modality performed at baseline (CT or MRI) will be repeated at subsequent imaging. Intrapatient dose reduction will be allowed depending on the type and severity of toxicity encountered provided that criteria for patient withdrawal from study treatment have not been met. Once treatment is dose reduced, the patient should not go back to the starting dose. Therapy will be administered in the outpatient setting, with each cycle consisting of 21 days of continuous therapy. The cycle start date will coincide with the physician visit date.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Table 5.1 **Treatment Regimens/Dosing Schedule**

Drug	Dose	Time for Administration (21 day cycle)

Ramucirumab[a]	8mg/kg IV	Administered over approximately 60 min, D1,D8
Trastuzumab	8mg/kg 6mg/kg	Administered IV every 21 days
Capecitabine[b,c]	850mg/m^2	Administered orally twice daily on D1- D14
Cisplatin[d]	80mg/m^2	Administered IV on Day 1, up to maximum of 6 cycles
5-Fluorouracil[e]	800mg/m^2/day	Administered IV on Day 1 to Day 5 of every 21 days
Oxaliplatin[f]	130mg/m^2	Administered IV on Day 1 after cycle 1, for up to up to maximum of 8 cycles

a. Ramucirumab/trastuzumab will be administered until disease progression or other withdrawal criteria are met. Capecitabine/5-FU and cisplatin/oxaliplatin will be initiated after cycle 1. After 1 year, at the investigator's discretion, capecitabine/5-FU treatment can be discontinued. Cisplatin will be administered up to a maximum 6 cycles (oxaliplatin will be administered up to 8 cycles), in the absence of disease progression or until other withdrawal criteria are met.
b. Capecitabine should be taken within 30 minutes after a meal. Total daily dose of capecitabine administered will be 1700 mg/m2. Patients who are unable to take capecitabine on the morning of Day 1 can start their capecitabine on the evening of Day 1, in which case the final dose of capecitabine for that cycle will be administered on the morning of Day 15.
c. Premedication per institutional guidelines is required prior to infusion of ramucirumab.
d. Maintenance of satisfactory GFR and adequate hydration pre- and post-cisplatin administration should be performed per local clinical practices.
e. As an alternative fluoropyrimidine, 5-FU, may be considered for eligible patients who cannot be administered capecitabine for any specific reason (such as malabsorption, difficulty swallowing, or other conditions that could affect intake of oral capecitabine medication). This decision should be made prior to randomization by the investigator, switching from capecitabine to 5-FU, or vice versa, will not be allowed during the study. 5-FU will be administered at 800 mg/m^2/day continuous IV infusion on Day 1-Day 5 every 21-day cycle, after completion of the cisplatin infusion.
f. As an alternative oxaliplatin, may be considered for eligible patients who cannot be administered cisplatin for any specific reason. This decision should be made prior to randomization by the investigator, switching from cisplatin to oxaliplatin, or vice versa, will not be allowed during the study. Oxaliplatin will be administered at 130 mg/m^2 continuous IV infusion on Day 1 every 21 day cycle, after completion of the first cycle. Patients may receive reduced dose of oxaliplatin at 20% or 30% dose reduction at treating physician discretion

5.1.1. Premedication Prior to Administration of Ramucirumab

Premedication per institutional guidelines is required prior to infusion of ramucirumab. Additional premedication may be provided at investigator discretion.

5.1.2. Hydration Schedule for Cisplatin

Maintenance of satisfactory GFR and adequate hydration pre- and post-cisplatin administration should be performed per local clinical practices. Cisplatin administration and hydration will be done per institutional guidelines. It is recommended that a urinary output of 100 mL/h is maintained

before, during and after cisplatin administration. If clinically not contraindicated, patients should be advised to drink 3 liters id water or other acceptable fluid over a period of 24 hours before and after administration of cisplatin. The suggested hydration schedule is provided in table 5.1.2.1.

Table 5.1.2.1 Hydration Schedule for Cisplatin Administration

Time	Supportive care and Hydration	Duration
T0[a] + 1h	Antiemetics	15-30min
1h 30min	Prehydration (1L 0.9% saline)	60 min
2h 30min	200mL Mannitol 20%	30min
3h	Cisplatin 80mg/m^2 in500 mL 0.9% saline	60-120min
4-5h	Post hydration (1L 0.9% saline) + 20mmol KCl + 1g $MgSO_4$	2h

Abbreviations: I.V. = intravenously; po = orally
[a] Relative to the start of administration of ramucirumab

5.1.3. Antiemetic Schedule for Cisplatin

Antiemetic schedule will be done per institutional guidelines. Recommended antiemetic schedule for at-home medication after administration of cisplatin: aprepitant 80 mg PO once daily for 2 days, dexamethasone 4 mg PO (or equivalent) once daily for 3 days, ondansetron 8 mg PO twice daily for 1 day (or equivalent), metoclopramide 10 to 20 mg PO 3 times daily if required. If aprepitant is not given then the dose of dexamethasone should be doubled.

5.2. Preparation and Administration of Ramucirumab

Ramucirumab will be provided by Lilly. Patients will receive ramucirumab by I.V. infusion over approximately 60 minutes at 8 mg/kg on Day 1 and Day 8 every 21 days in the absence of disease progression or until other withdrawal criteria are met. The first dose of ramucirumab is dependent upon the patient's baseline body weight in kilograms. Ramucirumab infusion will be prepared and administered in accordance to institutional guidelines.

5.3. Preparation and Administration of Trastuzumab

Trastuzumab will be administered on every 3 week dosing schedule, with initial loading dose of 8 mg/kg as a 90 minute infusion, followed by trastuzumab 6 mg/kg every 3 weeks, administered as a 30 minute infusion if the initial loading dose was well tolerated. Trastuzumab infusion will be prepared and administered in accordance to institutional guidelines.

5.4. Preparation and Administration of Cisplatin

Investigators should consult the manufacturer's instructions for cisplatin for complete prescribing information and follow institutional procedures for the administration of cisplatin. Cisplatin will be administered as an I.V. infusion of 80 mg/m^2 over approximately 60 to 120 minutes on Day 1 every 21-day cycles, up to a maximum of 6 cycles in the absence of disease progression or until other withdrawal criteria are met. Cisplatin will be administered after the completion of the ramucirumab infusion.

5.5 Preparation and Administration of Oxaliplatin

Investigators should consult the manufacturer's instructions for Oxaliplatin for complete prescribing information and follow institutional procedures for the administration of Oxaliplatin.

Oxaliplatin may be administered instead, at a dose of 130 mg/m^2/day as an I.V. over approximately 2 hours on Day 1 every 21-day cycles, up to a maximum of 8 cycles in the absence of disease

progression or until other withdrawl criteria are met. Oxaliplatin will be administered after the completion of the pembrlizumab infusion.

Oxaliplatin will continue until progression of disease, intolerable toxicity, or other withdrawal criteria are observed. After 1 year, at the treating physician's discretion, oxaliplatin treatment can be discontinued.

5.6. Administration of Capecitabine

Investigators should consult the manufacturer's instructions for capecitabine for complete prescribing information and follow institutional procedures for the administration of capecitabine. Capecitabine will be orally self-administered at 850 mg/m^2 twice daily on Day 1 through Day 14, followed by a 7-day non-dosing interval in each 21-day cycle in the absence of disease progression or until other withdrawal criteria are met. Patients who are unable to take capecitabine on the morning of Day 1 can start their capecitabine on the evening of Day 1 in which case the final dose of capecitabine for that cycle will be administered on the morning of Day 15. Capecitabine should be taken within 30 minutes after a meal. Capecitabine will continue until PD, intolerable toxicity, or other withdrawal criteria are observed. After 1 year, at the investigator's discretion, capecitabine treatment can be discontinued.

5.7 Preparation and Administration of 5-Fluorouracil

Investigators should consult the manufacturer's instructions for 5-FU for complete prescribing information and follow institutional procedures for the administration of 5-FU.

Only for patients unable to take oral medications (because of certain circumstances such as malabsorption, difficulty swallowing, or other conditions that could affect intake of oral capecitabine medication), 5-FU may be administered instead, at a dose of 800 mg/m^2/day as a continuous infusion over 5 days (Day 1 to Day 5 of each cycle), every 21 days. This decision should be made prior to registration by the treating physician; switching from capecitabine to 5-FU, or vice versa, will not be allowed during the study. 5-FU will be administered after completion of the cisplatin infusion.

5-FU will continue until progression of disease, intolerable toxicity, or other withdrawal criteria are observed. After 1 year, at the treating physician's discretion, 5-FU treatment can be discontinued.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Patients must have pathologically or cytologically MSKCC confirmed diagnosis of gastric or GEJ adenocarcinoma.
- Patients must have Stage IV gastric or GEJ adenocarcinoma with HER2 overexpression and/or amplification as determined by next generation sequencing assay, immunohistochemistry (IHC 3+) or fluorescent in situ hybridization (FISH+ is defined as HER2:CEP17 ratio ≥ 2.0). MSKCC confirmation of HER2 status is not mandatory prior to enrollment and treatment on study. For patients with outside HER2 testing, if sufficient tissue is available HER2 testing will be repeated at MSKCC for purpose of analysis and will not impact the patient's eligibility.
- Available archival tumor tissue should be submitted to MSKCC for IMPACT analysis, but will not be required prior to registration. Note: if tissue is depleted, patient will still be eligible after discussion with the PI.

- Patients must have disease that can be evaluated radiographically. This may be measurable disease or non-measurable disease per RECIST 1.1.
- Patients may have received no prior chemotherapy for Stage IV disease. Patients may have received prior adjuvant therapy (chemotherapy and/or chemoradiation) if more than 6 months have elapsed between the end of adjuvant therapy and registration.
- Age of 18 years or older.
- ECOG performance status 0-1.
- Peripheral neuropathy ≤ grade 1
- Patients who have adequate hepatic function as defined by a total bilirubin ≤1.5 mg/dL (25.65 µmol/L) (except patients with Gilbert's disease), and aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 times ULN or ≤ 5.0 times the ULN in the setting of liver metastases.
- Patients who have adequate hematologic function, as evidenced by absolute neutrophil count (ANC) ≥1500/µL, hemoglobin ≥9 g/dL (5.58 mmol/L), and platelets ≥100,000/µL.
- Patients who have adequate renal function as defined by a serum creatinine ≤1.5 x ULN, or creatinine clearance (measured via 24-hour urine collection) ≥40 mL/minute (that is, if serum creatinine is >1.5 x ULN, a 24-hour urine collection to calculate creatinine clearance must be performed).
- Patients whose urinary protein is ≤1+ on dipstick or routine urinalysis (UA) If 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).
- The patient must have adequate coagulation function as defined by International Normalized Ratio (INR) ≤ 1.5, and a partial thromboplastin time (PTT) ≤ 5 seconds above the ULN (unless receiving anticoagulation therapy). Patients receiving warfarin must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to first dose of protocol therapy.
- Patients, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods).
- Female patients of childbearing potential must have a negative serum pregnancy test within 7 days of study entry.

6.2 Subject Exclusion Criteria

- Patients who have uncontrolled or poorly-controlled hypertension (>139 mmHg systolic or >89 mmHg diastolic for >4 weeks) despite standard medical management.
- Patients receiving any concurrent anticancer therapy or investigational agents with the intention of treating gastric/GEJ cancer. Previously received trastuzumab as part of a regimen in the metastatic setting with evidence of progression. ^{89}Zr-trastuzumab use as imaging agent for ^{89}Zr-trastuzumab PET permitted.
- Patients having:
  - 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. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.
- Active or clinically significant cardiac disease including:

  - Congestive heart failure – New York Heart Association (NYHA) > Class II.
  - Active coronary artery disease.
  - Left ventricular function <50%.
  - Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
  - Unstable angina (anginal symptoms at rest), new-onset angina within 3 months before randomization, or myocardial infarction within 6 months before randomization.
  - Patients who have experienced any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to first dose of protocol therapy.
  - Patients who are receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-infalmmatory drugs (NSAIDs, cinluding ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin (maximum dose 325 mg/day) is permitted.
- Evidence or history of bleeding diathesis or coagulopathy.
- Patients who have experienced any Grade 3-4 GI bleeding within 3 months prior to first dose of protocol therapy.
- Unwillingness to give written informed consent, unwillingness to participate, or inability to comply with the protocol for the duration of the study.
- Patients with prior trastuzumab treatment.
- Patients with known active brain or central nervous system metastases, including leptomeningeal disease. Patients with treated and asymptomatic brain metastases may be eligible after discussion with PI.
- Patients who are pregnant or breast-feeding.
- Patients with a serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to enrollment.
- The patient has undergone major surgery within 28 days prior to first dose of protocol therapy
- Patients who have elective or planned major surgery to be performed during the course of the clinical trial. Minor surgery/subcutaneous venous access device placement within 7 days prior to first dose of protocol therapy is permitted.
- Patients may not have had radiation within 28 days prior to first dose. weeks of registration.
- Patients may not have any other medical condition or reason, in that investigator's opinion, makes the patient unstable to participate in a clinical trial.
- The patient has a 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‖) during the 3 months prior to first dose of protocol therapy.
- Patients may not have a prior history of GI perforation/fistula (within 6 months of first dose of protocol therapy) or risk factors of perforation.

7.0 RECRUITMENT PLAN

Patients that are eligible will be identified for enrollment from MSKCC clinical practice and clinic lists. No additional measures, e.g. advertisement, payment to patients, will be

employed to recruit patients. Patients will be accrued to this study without regard for gender or minority status.

Inclusion of women and minorities

The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation with regards to race or gender.

Our institutional demographics for accrual of patients on esophageal, gastric and GE junction cancer trials reflect the national incidence of this disease: 10-15% of our patients have been women; African-American males comprise 3-5% of patients treated on protocol. Given that our protocol accrual closely reflects the national incidence of this disease, no specific strategy will be undertaken to recruit women or persons of color on this trial. None of the eligibility requirements (section 6) will make it difficult for diverse populations to participate in this trial.

This protocol does not include children because the number of children with esophageal, gastric and GE junction cancer is very small and because the majority are already accessed by a nation-wide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

8.0 PRETREATMENT EVALUATION

Pretreatment evaluation will be performed within 2 weeks of study entry and will include:

- History, concomitant medications, and toxicity assessment.
- Physical exam, vital signs, and performance status.
- Serum pregnancy test for women of childbearing potential (WOCBP)
  In addition, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g. late or missed period) at any time during study participation.
- Routine urinalysis
- Laboratory evaluation including complete blood count, magnesium and comprehensive chemistry panel (includes BUN, creatinine, ALT, AST, albumin, glucose, total protein, calcium, bilirubin, bicarbonate, sodium, chloride, potassium, alkaline phosphatase), and INR&APTT
- Research blood tests for cfDNA analysis.

The following must be obtained within one month prior to starting protocol therapy:

- CT/MRI scan of chest, abdomen, and pelvis <4 weeks prior to start of study treatment.
- Electrocardiogram
- Assessment of Left Ventricular Ejection Fraction (LVEF) as measured by echocardiography (ECHO) with speckle tracking. If an ECHO cannot be performed, a multi-gated acquisition scan (MUGA) scan can be performed. If possible, the same method of measurement is recommended throughout the study.

To be completed any time prior to starting therapy:

- Histological confirmation of gastric or GEJ adenocarcinoma at MSKCC prior to study enrollment.
- Patients with outside biopsies who do not have enough tissue for correlative studies will still be considered eligible. MSKCC confirmation of HER2 status is not mandatory prior to enrollment and treatment but should be confirmed.
- Available archival tumor tissue should be submitted to MSKCC for future correlative analysis, but will not be required prior registration. Note: if tissue is depleted, patient will still be eligible after discussion with the PI.

9.0 TREATMENT/INTERVENTION PLAN

Treatment will be administered on an outpatient basis. Ramucirumab 8mg/kg will be administered intravenously on day 1 and day 8 + trastuzumab 8mg/kg administered as an IV infusion on cycle 1 day 1. CT/MRI scan will be performed after the initial three weeks (cycle 1) to determine response, and every 9 weeks thereafter. CT scans occurring every 9 weeks will coincide with the 6 month CT scan, and if necessary, an additional scan will be done at 6 months for assessment of PFS at 6 months. On subsequent cycles, capecitabine 850mg/m^2 will be added for all patients, taken orally twice a day for fourteen days followed by a one week rest period, in addition to cisplatin 80mg/m^2 administered as an IV infusion every (3 weeks) 21 days, ramucirumab 8mg/kg IV on day 1 and day 8 + trastuzumab 6mg/kg every 3 weeks. As an alternative fluoropyrimidine, 5-fluorouracil may be considered for patients who cannot be administered capecitabine for any specific reason. 5-fluorouracil (5-FU) 800mg/m^2/day will be administered on Day 1-Day 5 of every 21 days. Oxaliplatin may also be considered for patients who cannot be administered cisplatin for any specific reason. Oxaliplatin 130 mg/m^2/day will be administered on Day 1 beginning with cycle 2. If the patient is not a good candidate for induction chemotherapy, capecitabine/5-FU and cisplatin/oxaliplatin can be added during cycle 1 of treatment. Each cycle consists of 21 days. In an effort to prevent adverse events, all patients will be premedicated per institutional guidelines prior to treatment. All other anti-emetics and supportive agents may be administered at the discretion of the primary oncologist. Treatment will be performed on the scheduled day ± 7 days. Adverse events and clinical monitoring will take place during weekly physician visits for 6 weeks followed by every two weeks visits thereafter. In case of discontinuation of capecitabine and/or cisplatin due to cumulative toxicity, administration of ramucirumab 8mg/kg IV infusion day 1 and day 8 + trastuzumab 6mg/kg every three weeks will be continued.

Grade 1 and 2 toxicities will be managed with medical therapy specific to the particular adverse reaction. Intrapatient dose reduction will be allowed depending on the type and severity of toxicity encountered provided that criteria for patient withdrawal from study treatment have not been met. Evaluation in person will be made when there is concern for a drug-related toxicity irrespective of grade.

9.1 Collection of blood of cell-free DNA (cfDNA)

Cell-free DNA (cfDNA) be obtained from plasma samples collected at baseline, week 3, every 9 weeks, and at the time of treatment discontinuation

Approximately 20 ml of whole blood per visit (baseline, every 9 weeks, and treatment discontinuation) will be collected at ambient temperature into 2x 10mL cell free DNA BCT tubes for plasma isolation.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Procedure	Screen[a, p]	Cycle 1 (21 days)[p]			Cycle 2[g, p]			Cycle 3-[p] subsequent cycles			EOT[c, p]	F/U[d, p]
		D 1	D8	D15	D 1	D8	D15	D1	D8	D15		
Medical Hx/Demographics	X	X	X	X	X	X	X	X			X	X
Serum Pregnancy Test	X											
Tumor biopsy samples and blood collection for biomarkers[e]	X											
Physical exam[b]	X	X[f]	X	X	X	X	X	X			X	X
Performance status	X	X[f]	X	X	X	X	X	X			X	X
Toxicities/AE assessment[h]	X	Reported from screening throughout all subsequent cycles.									X	X
Hematology[b]	X	X[f]	X	X	X	X	X	X			X	
Chemistry[b]	X	X[f]	X	X	X	X	X	X			X	
INR&APTT	X											
Urinalysis[b]	X	X[f]		X	X		X	X			X	
Research Test: cfDNA[q]	X			X				X Every 9 weeks (3 cycles)			X	
MRI/CT assessment[i]	X			X				Every 9 weeks (3 cycles) after initial CT			X	X
Concomitant medications[j]	X	All medications taken during the study will be documented										X
12-lead ECG	X	X[f]										
ECHO/ MUGA[o]	X						X	Every 12 weeks (4 cycles) [o]				
^{89}Zr- trastuzumab PET[n]	X			X								
Ramucirumab[k]		X	X		X	X		X[g]	X			
Trastuzumab[l]		X			X			X[g]				
Capecitabine/5-FU+ cisplatin/oxaliplatin[m]					X			X[g]				
Capecitabine compliance					X	X		X				

ECG = electrocardiogram; ECHO = echocardiogram; EOT = end of treatment; FU = follow-up; LVEF = left ventricular ejection fraction; h = hour(s); hx = history; MUGA = multiple gated acquisition scan

Radiological imaging studies <28 days prior to start of study treatment, other screening evaluation within 2 weeks prior to start of study treatment.

a Radiological imaging studies and electrocardiogram <28 days prior to start of study treatment, other screening evaluation within 2 weeks prior to start of study treatment.

b Physical exam (vital signs [BP, heart rate, temperature], weight, and a review of body systems), chemistry, and urinalysis on intended days 1 and 15 of each cycle prior to chemotherapy or ≤ 72 h prior to dosing. If chemotherapy is delayed then the physical exam must be repeated weekly until retreatment or ≤ 72 h prior to dosing. Hematology and physical exam will be done weekly for the first 6 weeks and on the intended days 1 and days 15 of each cycle prior to the chemotherapy or ≤ 72 h prior to dosing thereafter.

c Within 14 days of tumor progression or study treatment discontinuation. If permanent discontinuation of the study drug falls on a scheduled visit, examinations as defined for EOT should be performed instead of the examinations of the scheduled visit. If patient is unable to come in to see MD, a nurse phone call to evaluate toxicities can be substituted.

d Assessment by treating medical oncologist as clinically indicated. For those patients no longer followed by MSKCC MD, a nurse will make a follow up phone call every 3 months to assess patient's vital status.

e A sample of archival tumor biopsy, or other available tumor biopsy and one time research blood sample should be submitted for biomarker analysis during screening. Patients should be consented for protocol #12-245. Tumor biopsy samples may also be submitted for biomarker analysis at any other time during the course of the clinical study.

f Physical exam, laboratory assessments and urinalysis are not required if screening assessments were done within 72 hours of first dose. ECG is not required if screening ECG was done within 7 days of first dose.

g In cycle 2 procedures will be performed identical to cycle 1. Radiologic tumor assessment will be performed after the initial three weeks to determine response and every 9 weeks thereafter.

h AE monitoring should continue for at least 4 weeks following the last dose of study treatment. AEs that occur within 30 days following the last study treatment will be followed until resolution.

i The baseline and subsequent scans to assess response must be performed using identical technique. Radiological imaging studies to evaluate tumor status will be performed after the initial three weeks (1 cycle) to determine response and every 9 weeks thereafter while on study regardless of treatment delays. CT scans occurring every 9 weeks will coincide with the 6 month CT scan, and if necessary, an additional scan will be done at 6 months. For subjects who have entered the survival follow-up period and have not yet experienced PD, every effort should be made to follow-up for tumor evaluation (by CT or MRI) until progression of their malignancy every 9 weeks, or until a new anticancer treatment is started. Window of +/- 7 days during the first cycle, and +/-14 days for all subsequent cycles for radiological imaging studies. Patient may have CT or MRI scan on an earlier or later date than allowed by the window of +/-14 days, if clinically indicated at the investigator's discretion.

j All medication given within 2 weeks prior to the start of study treatment.

k Ramucirumab 8mg/kg administered intravenously on day 1 and day 8.

l Trastuzumab 8mg/kg administered as an IV infusion on cycle 1 day 1, followed by infusion of 6mg/kg every 3 weeks

m CT/MRI will be performed after the initial three weeks to determine response and every 9 weeks thereafter. On subsequent cycles capecitabine 850mg/m^2 will be added, taken orally twice a day for fourteen days followed by a one week rest period, in addition to cisplatin 80mg/m^2 administered as an IV infusion every three weeks. Capecitabine may be skipped if clinically indicated. Only for patients unable to take oral medications (because of certain circumstances, such as malabsorption, difficulty swallowing, or other conditions that could affect intake of oral capecitabine medication), 5-FU (800 mg/m^2/day continuous infusion on Day 1 to Day 5 of Cycle 2 and on) may be considered. The decision to treat with capecitabine or 5-FU needs to be made prior to randomization by the investigator. Switching between 5-FU and capecitabine is not allowed.

n Some patients will have ^{89}Zr-trastuzumab PET at baseline and week 3 (any time between days 15 and 21) only if deemed appropriate by investigator. Patients will have to sign a written informed consent for 13-165. Patient participation to this procedure is voluntary.

o Baseline ECHO/MUGA must be obtained within one month prior to starting protocol therapy. ECHO with

speckle tracking will be the preferred modality for LVEF assessment. When possible, the same method used to measure LVEF at baseline (either ECHO or MUGA) should be used throughout the study. Repeat LVEF assessments will be performed after 6 and 12 weeks of initiating protocol therapy, and thereafter every 12 weeks (4 cycles). Window of +/-14 days for ECHO/MUGA.

p To avoid violations and deviations from the protocol, blood tests, CT/MRI scans, and physician visits (including physical exam, vitals, blood pressure, weight, performance status, and concomitant medications) may vary by up to one to fourteen (1-14) days to allow flexibility of scheduling.

q Cell-free DNA (cfDNA) will be obtained from plasma samples collected at baseline, at week 3, every 9 weeks and at the time of treatment discontinuation, as the same time as the MRI/CT evaluations. Research tests may vary by up to one to fourteen (1-14 days).

11.0 TOXICITIES/SIDE EFFECTS

The investigator should withdraw a patient from **ramucirumab** for any of the following reasons:

- **Arterial thromboembolic event** (ATE): Any Grade 3-4 ATE occurring or worsening during anticoagulation therapy, require permanent discontinuation of ramucirumab therapy. Any ATE leading to discontinuation of ramucirumab therapy will be considered serious and should be reported via the serious adverse event (SAE) mechanism.
- **Venous thromboembolic event** (VTE): A Grade 3 or 4 VTE occurring or worsening during anticoagulation therapy, that is considered by the investigator to be life-threatening, or symptomatic and not adequately treated by anticoagulation therapy. Any VTE leading to the discontinuation of ramucirumab therapy will be considered serious and should be reported via the serious adverse event (SAE) mechanism.
- **Severe bleeding**: Grade 3-4 bleeding due to any reason
- **Hypertension** that cannot be medically controlled with antihypertensive therapy in patients with hypertensive crisis or hypertensive encephalopathy; patients with grade 4 hypertension must not receive further treatment with ramucirumab
- **Infusion-related reaction**: Grade 3-4 IRR must not receive further treatment with ramucirumab.
- **Gastrointestinal perforation or fistulae**: Any clinically apparent GI perforation or fistulae;
- **Impaired wound healing**: Discontinue ramucirumab if wound is not fully healed within 42 days of withholding ramucirumab;
- **New occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis;**
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS);** all cases of RPLS must be reported via the SAE mechanism
- **Urine protein:** The patient will have ramucirumab permanently discontinued if the protein level is >3 g/24 hours, if there is a third occurrence of >2 g/24 hours, or if the protein level does not return to <2g/24 hours within 2 weeks.
- **Any Grade 4 (life-threatening) nonhematologic toxicity** considered by the investigator to be possibly, probably or definitely related to ramucirumab;
- **Dose modifications**: >2 dose reductions.
- **Hepatic encephalopathy**: Any patient who experiences signs of hepatic encephalopathy or other serious signs of liver impairment such as hepatorenal syndrome must be permanently discontinued from ramucirumab therapy.

Patients who are permanently discontinued from ramucirumab will continue to be in the study, and should continue to receive the other study agent(s) in the absence of disease progression, in accordance with this protocol.

11.1.1. General Dose-Modification Guidelines for Ramucirumab

- Treatment for the first cycle should only commence if all the inclusion criteria are met. For subsequent cycles, dose delay/modification is permitted as described in section specific for ramucirumab, trastuzumab, capecitabine, and cisplatin.
- Ramucirumab dose modifications are not required for hematologic laboratory abnormalities unless associated with clinical symptoms. As an initial step, the dose of chemotherapy should be reduced first before any dose reductions for ramucirumab are considered.
- All study treatment will be discontinued in case of disease progression.
- Dose modifications are permanent; no dose escalations allowed after dose reduction.
- Control hypertension prior to initiating treatment with ramucirumab.
- Temporarily suspend ramucirumab for severe hypertension until medically controlled.
- Ensure any wound is fully healed prior to commencing or continuing ramucirumab.
- Ramucirumab/trastuzumab therapy should continue as scheduled if there is a delay or discontinuation of capecitabine and/or cisplatin. When the subsequent cycle of chemotherapy is initiated, administration of ramucirumab, trastuzumab and chemotherapy will be resynchronized according to the study design described in this protocol (that is, the cycle will begin at Day 1 for ramucirumab, trastuzumab and chemotherapy).
- Doses of ramucirumab omitted are not replaced or restored; instead, the patient should resume the planned treatment cycles.
- In the case of ramucirumab-related toxicity, ramucirumab will be delayed for one week and administered on Day 8 of the treatment cycle provided that ramucirumab-related toxicities have resolved to Grade <2 or baseline.
- If a toxicity related to ramucirumab does not resolve in the same treatment cycle, the administration of ramucirumab can be delayed up to 42 days. If the toxicity does not resolve within 42 days, ramucirumab will be discontinued unless it is determined by the treating investigator that the patient might benefit from continuation of ramucirumab.
- If there is a delay or modification in administration of ramucirumab due to toxicity, treatment with other study agent(s) should continue as scheduled. If clinically appropriate, the investigator can delay all treatment components up to a maximum of 7 days to allow synchronized administration of all agents.
- 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 treating physician.

11.1.2. Dose-Modification Guidelines for Ramucirumab for Specific Adverse Events

The sections below provide dose-modification guidelines for ramucirumab for specific AEs related to administration of ramucirumab. Refer to Section 11.0 for criteria for discontinuation of ramucirumab.

Toxicity		**Grade**	**Dose adjustment for Ramucirumab**
Reversible, non-life-threatening toxicity (for example, fatigue/anorexia/fever/laboratory abnormalities[a]) For hypertension, see below.	First instance	3/4	8 mg/kg (full dose) on recovery to Grade ≤1 within the same cycle without interruption
	Second instance	3/4	6 mg/kg (first dose reduction) for next dose on recovery to Grade ≤1

	Subsequent instances	3/4	Discontinue (if a third dose reduction is needed)
Infusion-related reactions		1-2	If clinically indicated, stop the infusion temporarily and then reduce the infusion rate of ramucirumab by 50%
		≥3	Discontinue
Hypertension controlled with medications		1	8 mg/kg (full dose) without interruption
	Resolution to Grade <2 within 3 weeks	2/3	Delay ramucirumab administration. Administer 8 mg/kg (full dose) once hypertension is controlled with medications and is Grade <2 within 3 weeks.
	Resolution to Grade <2 within 3 to 6 weeks	2/3	Delay ramucirumab administration. Administer ramucirumab at 6 mg/kg if hypertension is Grade <2 by the fourth week. Discontinue ramucirumab if blood pressure does not improve to Grade <2 by the sixth week (42 days) despite medical management of hypertension.
Uncontrolled hypertension, hypertensive crisis, hypertensive encephalopathy		4	Discontinue
Congestive heart failure		3/4	Discontinue
Proteinuria (urinalysis <2+)[a]			Administer baseline or full previous dose of ramucirumab without interruption
Proteinuria (urinalysis 2+)[a]			Administer baseline or full previous dose of ramucirumab without interruption. Perform a 24-hour urine collection within 3 days prior to the next ramucirumab dose administration. If the 24-hour collection shows proteinuria <2g/24 hours administer unchanged dose of

			ramucirumab. If ≥2g/24 hours then follow dose adjustment based on 24-hour collection (below)
Proteinuria (urinalysis >2+) [a]			Delay ramucirumab administration. Perform a 24-hour urine collection within 3 days prior to the next ramucirumab dose administration. If the 24-hour collection shows proteinuria <2g/24 hours administer unchanged dose of ramucirumab. If ≥2g/24 hours then follow dose adjustment based on 24-hour collection (below)
Proteinuria based on 24-hour urine collection ≥2g/24 hours[b]	First instance		6 mg/kg once urinary protein returns to <2g/24 hours
	Second instance		5 mg/kg once urinary protein returns to <2g/24 hours
	Third instance		Discontinue (if a third dose reduction is needed)
Proteinuria based on 24-hour urine collection >3g/24 hours[b] or in the setting of nephrotic syndrome			Discontinue
Arterial thromboembolic events, venous thromboembolic events, or bleeding		3/4	Discontinue
Gastrointestinal perforation or fistulae		Any	Discontinue
RPLS			Discontinue
Liver injury/liver failure		Any	Discontinue

Abbreviations: RPLS = Reversible Posterior Leukoencephalopathy Syndrome
[a] Dose modifications are not required for hematologic laboratory abnormalities unless associated with clinical symptoms. As an initial step, the dose of chemotherapy should be reduced first before any dose reductions for ramucirumab are considered.
[b] Urinalysis test for proteinuria should be performed on day 1 and day 15 for the first 2 cycles, then on the first day of each cycle thereafter. If both urinalysis and 24-hour tests are performed, the results of 24-hour collection should be used for clinical decision-making.

11.1.2.1. Treatment Guidelines for Specific Adverse Events Related to Ramucirumab
Adverse events of concern, which may or may not be associated with ramucirumab therapy, may include IRRs, hypertension, arterial or venous thromboembolic events, bleeding (hemorrhagic)

events, GI perforation, proteinuria, congestive heart failure (CHF), surgery and impaired wound healing, liver injury/liver failure, reversible posterior leukoencephalopathy syndrome (RPLS).

11.1.3. Infusion-Related Reactions

Any treatment-related infusion-related reactions are defined according to the NCI-CTCAE Version 4.0 definition (General disorders and administration site conditions). Symptoms occurring during or following infusion of investigational therapy may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome (Immune system disorders). In the setting of symptoms occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE term "infusion-related reaction" and any additional terms (including those not listed here) that best describe the event. Consistent with usual medical practice, the patient should be clinically monitored and selected parenteral medications may be utilized for Grade 2 allergic/hypersensitivity reaction as detailed below. Clinical and laboratory monitoring will be performed per institutional guidelines.

Grade 1 IRR

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

Grade 2 IRR

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

For a second Grade 1 or 2 IRR, administer dexamethasone 8-20 mg I.V. (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally, and dexamethasone 8-20 mg I.V. (or equivalent).

Grade 3 or Grade 4 IRR

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride I.V. (or equivalent, per institutional guidelines), dexamethasone I.V. (or equivalent, per institutional guidelines), bronchodilators for bronchospasm, and other medications/treatment as medically indicated.
- Give epinephrine or bronchodilators as indicated.
- Hospital admission for observation may be indicated.
- Patients who have a Grade 3 or 4 IRR will not receive further ramucirumab treatment, but will continue to be followed on the protocol.

11.1.4. Hypertension

The following are general treatment guidelines for hypertension (an expected AE in patients receiving ramucirumab) that develops during the study. Routine clinical and laboratory monitoring is highly recommended in patients who develop *de novo* hypertension or experience a

deterioration in previous hypertension. Control hypertension prior to initiating treatment with ramucirumab. Monitor blood pressure prior to every administration of ramucirumab or more frequently as indicated during treatment.

Grade 1 hypertension

- Continue ramucirumab therapy at baseline or previous dose. Initiate or continue antihypertensive therapy if clinically indicated.

Grade 2 or Grade 3 hypertension

- If the hypertension is not associated with symptoms, continue ramucirumab therapy and initiate or continue antihypertensive therapy.
- If the hypertension is associated with symptoms, hold ramucirumab therapy and initiate or continue antihypertensive therapy until symptoms resolve to Grade <2 (systolic BP <140 mm Hg or diastolic BP <90 mm Hg)
- If ramucirumab administration is interrupted due to hypertension or related symptoms, review blood pressure once a week for 3 weeks, and if less than Grade 2 administer previous dose of ramucirumab
- Patient should be referred for cardiology evaluation for further hypertension management if grade ≥2 hypertension.

If blood pressure improves to Grade <2 by the fourth week, reduce ramucirumab dose to 6 mg/kg on Day 1 and Day 8.

- If blood pressure improves to Grade <2 by the sixth week, reduce ramucirumab dose to 5 mg/kg on Day 1 and Day 8.
- If blood pressure does not improve to Grade <2 by the sixth week (42 days) discontinue ramucirumab.

Grade 4 or refractory hypertension

- Patients with Grade 4 hypertension (life-threatening consequences, for example, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis; or urgent intervention indicated) or patients whose hypertension is poorly controlled (>160 mm Hg systolic or >100 mm Hg diastolic for >6 weeks [>42 days]) despite appropriate oral medication (for example, 2 or more oral agents at maximum tolerated dose) will be discontinued from ramucirumab.

11.1.5 Thromboembolic Events

Investigators should perform all testing required to fully characterize arterial or venous thromboembolic/vascular events. The incidence and type of thrombotic/vascular events will be collected and reported.

Ramucirumab therapy should be discontinued in the event of any Grade 3 or 4 arterial thromboembolic event or any Grade 3 or 4 venous thromboembolic event that is considered by the investigator to be life-threatening, or symptomatic and not adequately treated by anticoagulation therapy. At the investigator's discretion, ramucirumab therapy may be continued in the setting of an incidentally diagnosed, asymptomatic deep vein thrombosis or pulmonary embolism or following a symptomatic deep vein thrombosis or pulmonary embolism when symptoms have resolved with the institution of anticoagulation therapy. Ramucirumab should also be discontinued in the setting of a deep vein thrombosis or pulmonary embolism that occurs or intensifies while the patient is receiving therapeutic anticoagulation therapy.

11.1.6 Bleeding (Hemorrhagic) Events

Serious hemorrhagic AEs have been reported from clinical studies investigating ramucirumab. Hemorrhagic complications are associated with some malignancies (e.g. variceal bleeding from portal hypertension in hepatocellular carcinoma, lower GI hemorrhage from bowel metastases in ovarian carcinoma) although the rate of these complications varies considerably. As detailed in the ramucirumab IB, the incidences of hemorrhagic events to date, significant background incidence of bleeding in some malignancies, and use of concomitant antiplatelet therapy in some of the reported cases precludes any definitive association between bleeding and ramucirumab though ongoing surveillance and identification (and exclusion) of patients with high bleeding risk remain essential and are detailed in the inclusion/exclusion criteria. Discontinue ramucirumab in the event of a Grade 3 or 4 bleeding (hemorrhagic) event.

11.1.7 Proteinuria

If, while on ramucirumab therapy, a patient has proteinuria ≥2+ per routine urinalysis test, a 24-hour urine collection will be conducted. If the protein level is <2 g/24 hours, the patient will continue on ramucirumab therapy at the same dose without interruption. If urinalysis shows 2+, administer full previous dose of ramucirumab without interruption. Perform a 24-hour urine collection within 3 days prior to next ramucirumab dose administration. If the 24-hour collection shows proteinuria <2g/24 hours administer unchanged dose of ramucirumab. If the protein level is ≥2 g/24 hours, perform a 24-hour urine collection prior to the next planned dose of ramucirumab. Ramucirumab treatment will resume at a reduced dose level (6 mg/kg) once the protein level returns to <2 g/24 hours. The patient will be discontinued from ramucirumab treatment if the protein level is >3 g/24 hours, if there is a second occurrence of proteinuria ≥2 g/24 hours, or if the protein level does not return to <2 g/24 hours within 42 days of interruption ramucirumab.

11.1.8 Gastrointestinal Perforation

Patients with unresected (or recurrent) primary tumors, mesenteric or peritoneal disease who participate in this clinical study may be at increased risk for GI perforation due to the nature of the disease (metastatic gastric cancer).

An infrequent incidence of GI perforations has been associated with some antiangiogenic therapeutic agents, more specifically in the context of colorectal cancer (treated with combination regimens including anti-VEGF antibodies and cytotoxic chemotherapy) and in advanced ovarian cancer. These events may be associated with extensive abdominal/peritoneal disease burden. Gastrointestinal perforation has been reported from clinical studies investigating ramucirumab. The incidences of these events to date and presence of significant comorbidities and risk factors preclude any definitive association with ramucirumab, although ongoing surveillance remains essential. More information about GI perforation may be found in the IB. Patients with a history of GI perforation within 6 months prior to randomization are excluded from participation. Ramucirumab should be permanently discontinued in the event of a GI perforation.

11.1.9 Surgery and Impaired Wound Healing

Surgery and impaired wound healing have been observed with some antiangiogenic agents. Ramucirumab will not be administered to patients who have undergone major surgery within 28 days prior to randomization or have undergone central venous access device placement within 7 days prior to first dose of study treatment, except if the procedure is minimally invasive (for example, introduction of PICC line) and the investigator does not anticipate any significant bleeding.

11.1.10 Liver Injury/Liver Failure

Liver failure or other significant liver injury events, such as hepatic encephalopathy, have been observed in patients receiving ramucirumab. Patients with the following conditions should not be enrolled in clinical trials with ramucirumab: 1) cirrhosis at a level of Child-Pugh Class B (or worse) *or*

2) cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. "Clinically meaningful ascites" is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis. Ramucirumab should be discontinued in the event of any new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis.

11.1.11 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Reversible posterior leukoencephalopathy syndrome is a clinical and radiologic syndrome typically consisting of reversible cortical neurological dysfunction and brain-imaging findings of subcortical edema involving the posterior circulation, particularly the occipital lobes. . The symptoms of RPLS most often include generalized seizures, headache, delirium, and cortical blindness, although these may vary significantly and occasionally include focal neurological deficits. Magnetic resonance imaging (MRI) represents the most reliable method for diagnosis. Clinical symptoms and MRI abnormalities usually recover within days to weeks with proper management, although permanent neurologic dysfunction has been reported. Across the ramucirumab clinical program, 2 blinded cases of RPLS have been reported. Both cases occurred in the ongoing double-blind, randomized, placebo-controlled Phase 3 Study evaluating FOLFIRI in combination with ramucirumab versus FOLFIRI in combination with placebo for patients with metastatic colorectal cancer.

Reversible posterior leukoencephalopathy syndrome should be identified and treated promptly in order to minimize potential for permanent neurological damage. Treatment encompasses careful control of BP, withdrawal of potentially causative medication, and administration of anti-convulsant agents to those experiencing seizures. If the diagnosis of RPLS is confirmed or if clinically indicated, ramucirumab should be permanently discontinued.

11.2 Trastuzumab
Principal adverse effects include cardiac dysfunction, infusion related reactions, potentiation of chemotherapy related hematologic side effects. A complete listing of toxicities can be found in the trastuzumab package insert.

11.2.1Trastuzumab Dose Delays or Modifications
There will be no dose modifications of trastuzumab. Trastuzumab dose delays are permitted for Grade 3/4 clinical toxicity or at investigator discretion. Dose delays are not required for laboratory abnormalities unless associated with clinical symptoms. Omitted doses of trastuzumab are not

Replaced or restored; instead, the patient should resume the planned treatment cycles. Patients who develop signs and symptoms of CHF should have trastuzumab held and should receive treatment for CHF. Patients with an asymptomatic absolute decrease in LVEF of $\geq$16 percentage points or an absolute decrease in LVEF of 10 to 15 percentage points to below the lower limit of normal should have trastuzumab held as outlined below.

11.2.2 Congestive Heart Failure and other Cardiac Dysfunction

All patients must have a baseline evaluation of cardiac function including a measurement of LVEF by ECHO (with speckle tracking) prior to entry into the study. If an ECHO cannot be performed or is technically limited, a MUGA scan can alternatively be performed. Patients with an LVEF </=40% may still be eligible after consultation with cardiology and study investigator. Patients with decreased LVEF should be optimized on medical therapy with ACE inhibitors, β-blockers, diuretics, and cardiac glycosides, as needed per management of cardiac changes below. These patients should be monitored for heart failure after cisplatin infusion as well. All patients will undergo regular cardiac monitoring throughout the study, including at baseline, 6 and 12 weeks after initiation of trastuzumab

therapy, and every 12 weeks (4 cycles) thereafter. During the course of trastuzumab therapy, patients should be monitored for signs and symptoms of CHF (i.e., dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain). Patients who develop signs or symptoms of CHF will be further evaluated with a repeat LVEF assessment using the same method selected at baseline (either ECHO or MUGA) if possible.

Management of Symptomatic Cardiac Changes

Patients who develop signs and symptoms of CHF should have trastuzumab held and should receive treatment for CHF as recommended by the American Heart Association (AHA)/American College of Cardiology (ACC)(e.g., ACE inhibitors, angiotensin-II receptor blockers, β-blockers, diuretics, and cardiac glycosides, as needed) with referral to cardiology for consultation.

If the symptoms of CHF resolve with treatment, and/or cardiac function improves to baseline, reinitiation of trastuzumab can be considered at the discretion of the investigator, after discussion with the patient concerning the risks and benefits of continued therapy and in consultation with a cardiologist. If the patient is benefiting clinically from trastuzumab, the benefit of continued treatment may outweigh the risk of cardiac dysfunction or heart failure. If trastuzumab is restarted, continued surveillance with noninvasive measures of LVEF (MUGA or ECHO) will resume as regularly scheduled. Additional LVEF assessments prior to the next regularly scheduled LVEF measurement may be performed at the investigator's discretion.

Management of Asymptomatic Decreases in LVEF

Trastuzumab can be continued in patients experiencing an asymptomatic absolute decrease in LVEF of <16 percentage points from baseline, when the ejection fraction remains within the imaging center's range of normal limits. Repeat measures of LVEF should be obtained using the methodology selected at baseline if possible. Close follow-up of such patients is recommended. Patients with an asymptomatic absolute decrease in LVEF of ≥16 percentage points or an absolute decrease in LVEF of 10 to 15 percentage points to below the lower limit of normal should have trastuzumab held. Referral to cardiology should be considered for evaluation and management of left ventricular systolic dysfunction with adherence to ACC/AHA guidelines. In light of the variability inherent in the assessment of ejection fraction, consideration should be given to repeating the study within 4-7 days to confirm an observed decline. Repeat measures of LVEF should be obtained using the same methodology selected at baseline if possible, but at the discretion of the investigator or consulting cardiologist. If trastuzumab has been held for an asymptomatic decline in LVEF, a repeat measure of LVEF will be obtained within 1 month to evaluate for recovery of LVEF. If LVEF does not improve after repeat assessment within 1 month, the patient should be monitored with monthly or as clinically indicated ECHOs/MUGAs until LVEF is improved.

If cardiac function improves and LVEF no longer meets "hold" criteria as defined above, trastuzumab may be restarted. If trastuzumab is restarted, continued surveillance with noninvasive measures of LVEF (MUGA or ECHO), using the optimal methodology as determined by the investigator or consulting cardiologist, will resume per the standard schedule. Additional LVEF

Assessments prior to the next regularly scheduled LVEF measurement may be performed at the investigator's discretion. If the patient is benefiting clinically from trastuzumab, the benefit of continued treatment may outweigh the risk of cardiac dysfunction even in the setting of an asymptomatic LVEF decline, and reinitiating of trastuzumab can be considered at the discretion of the investigator after consultation with a cardiologist and discussion with the patient concerning the risks and benefits of

continued therapy.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease or CHF. Patients with symptomatic CHF, unstable angina pectoris, or symptomatic or poorly controlled cardiac arrhythmia should not be enrolled in clinical trials with ramucirumab. Ramucirumab should be discontinued in the event of any Grade 3 or 4 events consistent with CHF.

11.2.3 Infusion-Related Reactions

Any treatment-related infusion-related reactions are defined according to the NCI-CTCAE Version 4.0 definition (General disorders and administration site conditions). Symptoms occurring during or following infusion of investigational therapy may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome (Immune system disorders). In the setting of symptoms occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE term "infusion-related reaction" and any additional terms (including those not listed here) that best describe the event. Consistent with usual medical practice, the patient should be clinically monitored and selected parenteral medications may be utilized for Grade 2 allergic/hypersensitivity reaction as detailed below. Clinical and laboratory monitoring will be performed per institutional guidelines.

Grade 1 IRR

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

Grade 2 IRR

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

For a second Grade 1 or 2 IRR, administer dexamethasone 8-20 mg I.V. (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally, and dexamethasone 8-20 mg I.V. (or equivalent).

11.3. General Dose-Modification Guidelines for Chemotherapy

- Treatment for the first cycle should only commence if all the inclusion criteria are met and patient has been enrolled. For subsequent cycles, dose delay/modification is permitted as described in sections specific for ramucirumab, trastuzumab, capecitabine, 5-FU and cisplatin. All study treatment will be discontinued in case of disease progression.
- Cisplatin and 5-FU dose modifications are permanent; no dose escalations allowed after dose reduction. Any patient who has had 2 dose reductions (50% of original dose) and who experiences a toxicity that would cause a third dose reduction must be discontinued from the study drug that is causing the toxicity.

- The dose of capecitabine should be determined at the start of each treatment cycle. Based on investigator's discretion, full dose of capecitabine can be re-administered after 1 dose reduction (25% dose reduction). Re-escalation is not allowed after the second dose reduction. The maximum number of dose reductions for capecitabine is 3 (75% of the original dose).
- Doses of any study drug omitted for toxicity are not replaced or restored; instead, the patient should resume the planned treatment cycles. Supportive care (for example, colony-stimulating factors, blood and blood products, etc. can be administered in accordance with the latest ASCO or other equivalent guidelines.
- Dose modification, for non-serious and non-life-threatening toxicities like alopecia, altered taste or nail changes may not be required and the final decision is left to the discretion of the treating investigator.
- In situations where concomitant toxicities of varying severity exist, dose modification will be tailored for the toxicity with highest CTCAE grading.
- If there is a delay or modification in administration of study drug(s) due to toxicity, treatment with the other study agent(s) should also be held. If clinically appropriate, the investigator can delay all treatment components up to a maximum of 7 days to allow synchronized administration of all agents.

If a toxicity related to any component of chemotherapy does not resolve in the same treatment cycle, the administration of that component can be delayed up to 42 days. If the toxicity does not resolve within 42 days, that component will be discontinued unless it is determined by the treating investigator that the patient might benefit from continuation of the component.

11.4 Capecitabine, 5-FU, Cisplatin, and Oxaliplatin Dose Delays and Modifications

Trastuzumab dose interruptions are not required for laboratory abnormalities unless associated with clinical symptoms in which case trastuzumab may be held per investigator discretion. For hematologic laboratory abnormalities as an initial step, the dose of capecitabine/5-FU or cisplatin/oxaliplatin should be reduced first before any dose reductions for ramucirumab are considered. Capecitabine/5-FU or cisplatin/oxaliplatin will be held for grade 3 or 4 non-hematologic toxicity (with the exception of grade 3 electrolyte abnormalities) or for not meeting treatment parameters as described in the tables below on the day of treatment. If the toxicity has resolved and the patient meets treatment parameters but experienced interval toxicity, then for the purposes of determining dose reductions, the grade of toxicity should be that seen despite maximal medical management (i.e. intensive loperamide or tincture of opium for diarrhea). If multiple toxicities are seen the dose administered for a particular drug should be based on the most severe toxicity noted. In general, when multiple toxicities are experienced that can result in the dose reduction of multiple drugs, reducing multiple drugs at one time is the preferred approach. Treatment may resume when the toxicity has resolved to $\leq$ grade 2, except as indicated below.

Generally, during the first six cycles of therapy when treatment is held for chemotherapy related toxicity, all drugs (cisplatin or oxalplatin and capecitabine or 5-FU, Pembrolizumab/Trastuzumab) will be held for coordinated scheduling. Re-evaluation visit should occur in no more than 7 days. For an elevated creatinine or for ototoxicity, cisplatin or oxaliplatin alone may be held at investigator discretion and the patient may continue with capecitabine or 5-FU without treatment delay. If capecitabine or 5-FU is held for more than 4 weeks for toxicity, patients will be taken off study, unless there is a clinical benefit. If there is a clinical benefit, patients may be retreated at a lower dose after resolution of toxicity to $\leq$ NCI- CTCAE v4.0 grade 2, except as indicated below. Cisplatin or oxaliplatin and capecitabine or 5-FU may each be dose attenuated, either in combination, or individually. For all toxicities, appropriate clinical judgment should be applied to manage the symptoms.

Tables **11.4.1, 11.4.2**, **11.4.3, 11.4.4, 11.4.5 11.4.6 ,11.4.7, 11.4.8, and 11.4.9** address specific chemotherapy dose delays and modifications instructions. Colony stimulating factors: Patients should not routinely receive prophylactic colony stimulating factors (e.g., G-CSF, GM-CSF) during cycle 1. Subsequent use will be at the discretion of the treating physician.

Table 11.4.1 Capecitabine dose levels

Starting dose 0	Capecitabine 850 mg/m^2 orally twice daily
Dose Level -1	Capecitabine 640 mg/m^2 orally twice daily
Dose Level -2	Capecitabine 425 mg/m^2 orally twice daily

Table 11.4.2 Cisplatin dose levels

Starting dose 0	Cisplatin 80 mg/m^2
Dose Level -1	Cisplatin 60 mg/m^2
Dose Level -2	Cisplatin 40 mg/m^2

Table 11.4.3 Dose-modification guidelines for cisplatin or oxaliplatin and capecitabine for thrombocytopenia, neutropenia, febrile neutropenia, and infection[a].

ANC Count (x 10^9/L)	**Platelet Count (x 10^9/L)**	**Dose adjustment for cisplatin and capecitabine**
≥1.5 and	≥100	Maintain dose level without interruption
1.0 and/or	<75	Wait for counts to recover[b]; if within 42 days of interruption, ANC ≥1.0 x 10^9/L and platelets ≥75 x 10^9/L, reduce by 1 dose level if permissible[c].
<1.0 and	Fever ≥38.5°C (101°F) or infection of any duration	Reduce by 1 level on recovery of ANC ≥1.0 x 10^9/L

Abbreviations: ANC = Absolute Neutrophil Count.

a. No chemotherapy should be administered if ANC <1.0 x 10^9/L and platelet count <75 x 10^9/L
b. If unscheduled laboratory assessments during a treatment cycle show that the neutrophil count drops <1.0 x 10^9/L or that the platelet count drops <75 x 10^9/L, treatment with capecitabine should be interrupted
c. Dose reductions of capecitabine for ANC <1.5 x 10^9/L but ≥1.0 x 10^9/L may be determined at the discretion of the investigator or institutional guidelines. In such situations, if administration of chemotherapy is prohibited, then capecitabine must be held until the ANC recovers to ≥1.5 x 10^9/L

Table 11.4.4 Oxaliplatin dose levels

Starting dose 0	Oxaliplatin 130 mg/m^2
Dose Level -1	Oxaliplatin 90 mg/m^2*
Dose Level -2	Discontinued

*Or 104 mg/m^2 at discretion of treating physician

Table 11.4.5 Dose-modification guidelines for nonhematologic adverse events thought to be related to capecitabine[a]

Toxicity CTCAE Grades	During a Course of Therapy	Dose adjustment for next dose (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
- First appearance	Interrupt until resolved to Grade 0-1 or pretreatment baseline	75%
- Second appearance		50%
- Third appearance	Discontinue treatment permanently	Not applicable
Grade 3		
- First appearance	Interrupt until resolved to Grade 0-1 or pretreatment baseline	75%
- Second appearance		50%
- Third appearance	Discontinue treatment permanently	Not applicable
Grade 4		
- First appearance	Discontinue treatment permanently OR If the investigator deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0-1 or pretreatment baseline	Not applicable OR 50%
- Second appearance	Discontinue treatment permanently	Not applicable

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; SmPC = Summary of Product Characteristics; USPI = United States Package Insert

a. Adapted from Xeloda USPI and SmPC

Table 11.4.6 Dose-modification guidelines for cisplatin or oxaliplatin for reduced glomerular filtration rate

Creatinine clearance requirement	Dose adjustment for cisplatin
>60 mL/min prior to Day 1 of Cycle 1-6	Maintain dose level
51-59 mL/min prior to Day 1 of Cycle 2-6	Reduce 1 dose level, if permissible
41-50 mL/min prior to Day 1 of Cycle 2-6	Reduce 2 dose levels, if permissible
≤40 mL/min prior to Day 1 of Cycle 2-6	Stop cisplatin or oxaliplatin permanently

Table 11.4.7 Dose-modification guidelines for cisplatin or oxaliplatin related for nonrenal and nonhematologic adverse events

Toxicity	Grade	Dose adjustment for cisplatin
Nausea/vomiting/diarrhea (either on its own or in	≥3	Reduce 1 dose level, if permissible, on recovery to

combination)		Grade 1 or below
Ototoxicity	≥2	Discontinue
Neurotoxicity	0-1	No dose adjustment required
Neurotoxicity	2	Reduce 2 dose levels, if permissible, on recovery to Grade 1 or below
Neurotoxicity	>3	Discontinue
Any other toxicity thought to be due to cisplatin	4	Discontinue

For toxicities not listed in table 11.4.4, appropriate clinical judgment should be applied to manage any symptoms arising out of these AEs. For any AE which is Grade ≥3 or if the AE is considered clinically significant by the treating investigator, temporarily stop administering cisplatin to allow for recovery of the toxicity to Grade 1 or baseline, for a maximum period of 42 days. Once the toxicity recovers, reduce the dose of cisplatin by 1 dose level, if permissible. If the toxicity does not recover within the 42-day period, permanently discontinue cisplatin. Discontinue cisplatin if a third dose reduction is required.

Table 11.4.8 Dose modification guidelines for 5-FU related to nonhematologic adverse events

Toxicity	Grade	Dose adjustment for 5-FU
Diarrhea/stomatitis	3	Reduce 1 dose level, if permissible, on recovery to Grade 1 or below
Diarrhea/stomatitis	4	Reduce 2 dose levels, if permissible, on recovery to Grade 1 or below
Cardiac toxicity (related to 5-FU)	≥2	Discontinue
Skin toxicities	≥3	Reduce 2 dose levels, if permissible, on recovery to Grade 1 or below

Table 11.4.9 5-FU dose levels

Starting dose 0	5-FU 800 mg/m^2 /day, Day 1-Day 5
Dose Level -1	5-FU 600 mg/m^2 /day, Day 1-Day 5
Dose Level -2	5-FU 400 mg/m^2 /day, Day 1-Day 5

11.5 Supportive Care

Patients should receive full supportive care measures per local institutional practice including but not limited to antidiarrhea gents, antiemetic agents, analgesics appetite stimulants and granulocyte growth factors as judged necessary by their treating physician. Additional palliative radiation therapy during the study is allowed if clinical indicated after consultation with Principal Investigator.

11.5.1 Therapy for Diarrhea

In the event of diarrhea, the following supportive measures are strongly recommended as outline below.

Upon the patient experience the first episode of loose stool, the patient should be given initial dose of loperamide, 2 capsules (4mg) by mouth, then 1 capsule (2mg) by month every 2 hours or 2 capsules every 4 hours overnight at least 12 hours after the first liquid stool and up to 12 hours after the last liquid stool. If diarrhea is not controlled with loperamide, consider capecitabine dose reduction and/or additional Lomotil (diphenoxylate hydrochloride and atropine sulfate) tablets. Patients should have access to loperamide and Lomotil for home use prior to the start of each cycle.

11.5.2 Therapy for Hand-Foot Syndrome

Patients should receive full supportive care measures per local institutional practice, prophylactic use of emollients and moisturizes to prevent hand-foot syndrome (HFS) is recommended. Immediate institution of supportive measures for symptomatic relief for patients with grade 1 or above hand foot syndrome is recommended. Treatment with pyridoxine (B6) at dose of 100 to 150mg per day is permitted.

Use of creams

- Non-urea based creams may be applied liberally.
- Keratolytic creams (e.g. urea-based creams, salicylic acid 6%) may be used sparingly and only to affected (hyperkeratotic) areas.
- Alpha hydroxyl acids (AHA) based creams may be applied liberally 2 times a day. Approximately 5% to 8% provides gentle chemical exfoliation.
- Topical analgesics (e.g. lidocaine 2%) are to be considered for pain control.
- Topical corticosteroids like clobetasol 0.05% should be considered for subjects with Grade 2 or 3 HFS. Avoid systemic steroids.

Tender areas should be protected as follows:

- Use socks/gloves to cover moisturizing creams
- Wear well-padded footwear
- Use insole cushions or inserts (e.g. silicon, gel)
- Foot soaks with tepid water and Epson salts

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

All patients who receive at least one dose of ramucirumab and began trastuzumab therapy will be evaluable for toxicity and response. Patients who did not begin ramucirumab therapy will not be evaluated for toxicity or response and will be replaced by a new patient.

The primary endpoint of the study is the efficacy of the combination of ramucirumab and trastuzumab in addition to cisplatin and capecitabine in terms of progression free survival (PFS) at 6 months.

Secondary endpoints include toxicity, overall survival, response to ramucirumab and trastuzumab after the first cycle, best overall RECIST 1.1 response (CR+PR) to capecitabine/5-FU,

cisplatin/oxaliplatin, ramucirumab and trastuzumab, overall clinical benefit defined as stable disease (SD), complete response rate (CR), or partial response (PR) safety and tolerability. The type, frequency, severity, timing, and relationship of each adverse event will be determined as per the NCI Common Toxicity Criteria, version 4.0. Toxicity during cycle 1 and subsequent cycles will be reported.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient develops progressive disease on combination of ramucirumab and trastuzumab with cisplatin and capecitabine he/she will be taken off study unless the investigator judges it to be of clinical benefit for the patient to continue on trial therapy. If at any time the patient develops unacceptable toxicity that fails to resolve after a maximum treatment delay of 9 weeks, he/she will be removed from study. Before being removed from the study, patients will be scanned to assess the response. If the off study scan shows progression of disease then the patient will be considered as a non responder, while a CR or PR will be considered as response.

A patient will be withdrawn from the study treatment in the following circumstances:

- The patient is no longer able to participate in the study (e.g., AE, surgery, concomitant diagnoses, concomitant therapies or administrative reasons); in such a case the Investigator's reason for a patient's removal must be recorded in CRDB.
- Patient withdrawal of consent or election to discontinue participation in the trial
- Significant deviation from the protocol or eligibility criteria; such events will be considered protocol violations and the patients will be removed from study.
- Non-compliance with study or follow-up procedures.
- Drug related AE(s) have not resolved after 4 weeks of treatment interruption. An exception could be considered upon discussion with Principal Investigator for patients who derive obvious clinical benefit according to the investigator's judgment. The dose reduction scheme provided should be followed in this case.
- Repeated episodes of drug related toxicity despite dose reduction as indicated in Section 11.
- Documented progressive disease

As soon as a patient is withdrawn from the study treatment, the End of Treatment (EOT) visit has to be performed within 1-14 days after off treatment date. Every effort should be made to follow-up patients in case an adverse event is still ongoing at the time of withdrawal. Patients who show a clinical benefit (i.e., with either an objective tumor response or the absence of disease progression), may continue to receive additional treatment courses. Patients with radiologically documented progressive disease should be removed from the study unless the investigator judges it to be of clinical benefit for the patient to continue on trial therapy.

14.0 BIOSTATISTICS

The phase III ToGA study established the benefit of trastuzumab in combination with cisplatin and fluoropyrimidine (CF) chemotherapy in HER2-positive metastatic gastric/GEJ adenocarcinoma. The trastuzumab/CF cohort from the ToGA will be used as historic control for this study. In ToGa patients assigned to receive trastuzumab + CF had a significant improvement in progression free survival (5.5 mos vs 6.7 mos, HR 0.71 [0.59-0.85], p=0.0002), overall survival (13.8 mo vs 11.1 mo, HR 0.74 [0.6-0.91], p = 0.0046). Approximately 55% of the capecitabine/cisplatin/trastuzumab-treated

patients were progression free at 6 months. The hypothesis is that addition of ramucirumab to fluoropyrimidine and platinum and trastuzumab will improve outcome in previously untreated patients with HER2 GE junction gastric cancer.

The primary endpoint is PFS, as measured from the start of the ramucirumab and trastuzumab to the date of either documentation of disease progression on chemotherapy with trastuzumab and ramucirumab or death. CT/MRI scan performed after the initial 3 weeks (1 cycle). With subsequent cycle for all patients capecitabine and cisplatin will be administered together with ramucirumab and trastuzumab. We will define progression of disease to chemotherapy with trastuzumab and ramucirumab per RECIST 1.1 criteria. Patients with measurable disease and with evaluable radiographically but non-measurable disease will be eligible for study entry. As per

RECIST 1.1 criteria, any evidence of progression in non-measurable lesions, measurable lesions, or the development of new lesions, would qualify as disease progression. Using an exact single stage binomial design, we will accrue 37 Stage IV gastric and GE junction adenocarcinoma patients to differentiate between 6-month PFS of 55% and 75% with type I of 5% and power of 80%. If 26 or more patients are progression free at 6 months, capecitabine/5-FU/cisplatin/oxaliplatintrastuzumab +ramucirumab will be considered worthy of further investigation. Patients who come off study before 6 months without documented progression will be considered as events for the primary endpoint of 6 months PFS. Patients who come off study before 3 week CT scan will be considered inevaluable for primary endpoint and will be replaced. We anticipate enrollment to be 1-2 patients/ month with completion of accrual in approximately 36 months. Patients that come off study due to toxicity before 6 months without documented progression will continue to be scanned to obtain 6 months assessment of progression. Patients that were lost to follow up or withdrew consent before 6 months without documented progression will be counted as events for the primary endpoint; however this is expected to be a rare occurrence.

Patients who completed at least one cycle of trastuzumab + ramucirumab will be considered evaluable.

Secondary endpoints include response to ramucirumab and trastuzumab after the first cycle, best RECIST 1.1 response rate (CR+PR) and overall clinical benefit (SD+CR+PR) which will be estimated using binomial proportions along with exact 95% confidence intervals; survival endpoint will be measured from the start of treatment to death or last follow-up; overall survival, median PFS, overall and 1-year survival in patients with HER2-positive Stage IV gastric or GEJ adenocarcinoma will be estimated using the Kaplan-Meier method. Toxicity will be summarized using descriptive statistics.

An exploratory analysis of correlative biomarkers will be performed. Presence of genomic alterations (categorized as binary) in archival tumor samples will be correlated with overall clinical benefit to protocol therapy using Fisher's exact test. In select patients, changes in ^{89}Zr-trastuzumab PET between baseline and Week 3 will be correlated with tumor response by CT using Wilcoxon rank sum test. We will also examine an optimal cut point for the change in SUV between baseline and Week 3 that best separates between responders and non-responders using the method of maximally selected chi square statistics of Miller and Siegmund.[16]

Generalized estimating equations (GEE) will be used to look at associations between response and cfDNA while Cox regression with time dependent covariate will be used to associate survival with cfDNA.

Previous clinical trial has reported the frequency of adverse events attributable to treatment with capecitabine, oxaliplatin, bevacizumab and trastuzumab.[23] A similar frequency of adverse events will be considered attributable to ramucirumab and trastuzumab used in this trial and therefore acceptable. In order to reduce patient risk, the study design includes early termination of the trial in the event of excessive grade 4+ neutropenia, grade 3+ diarrhea despite adequate antidiarrheal management (loperamide and diphenoxylate/atropine) or grade 3+ neuropathy. In addition, the safety analysis will assess the toxicity rates that may arise related to ramucirumab-related persistent grade 3+ hypertension despite adequate medical management. Furthermore, presence of grade 3+ events which in the clinical judgment of the principal investigator are felt to be serious, unexpected, and a side effect likely due to with ramucirumab and trastuzumab, will give evidence to reduce the dose as well. Adverse events (possibly, probably, or definitely) related to the study treatment during all treatment cycles will count towards the excessive toxicity boundaries below. The stopping rules are derived using repeated significance testing are given in the table below.

Toxicity	# of toxicities needed to stop the study	Toxicity rate	Probability boundary is crossed
Gr 4+ Neutropenia	5 within the first 10 patients 7 within the first 20 patients 11 within 37 patients	.19	.11
		.45	.98
Gr 3+ Diarrhea	4 within the first 10 patients 6 within the first 20 patients 8 within 37 patients	.12	.08
		.35	.97
Gr 3+ Neuropathy	2 within the first 10 patients 3 within the first 20 patients 5 within 37 patients	.05	.13
		.25	.98
Gr 3+ persistent hypertension	2 within the first 10 patients 3 within the first 20 patients 4 within 37 patients	.04	.1
		.2	.96

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in the section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

16.0 DATA MANAGEMENT ISSUES

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at MSKCC were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled –Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials‖ which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Clinical Research Administration. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb2.mskcc.org/irb/index.htm

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center‘s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

MSK‘s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (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

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 „Reporting of Serious Adverse Events", the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data required to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event

- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form.
  - If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:

The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND office.

17.2.1

Any SAE will be reported within 24 hours of becoming aware of the event to the Eli Lilly Global Product Safety Fax Number for all Cyramza (ramucirumab) Studyies at 866-644-1697 or 317-453-3402.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)

4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2015. CA Cancer J Clin 65:5-29, 2015
2. van Hagen P, Hulshof MC, van Lanschot JJ, et al: Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 366:2074-84, 2012
3. Cunningham D, Allum WH, Stenning SP, et al: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. New England Journal of Medicine 355:11-20, 2006
4. Roth AD, Fazio N, Stupp R, et al: Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: A randomized phase II trial of the Swiss group for clinical cancer research. Journal of Clinical Oncology 25:3217-3223, 2007
5. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al: Phase III Study of Docetaxel and Cisplatin Plus Fluorouracil Compared With Cisplatin and Fluorouracil As First-Line Therapy for Advanced Gastric Cancer: A Report of the V325 Study Group, 2006, pp 4991-4997
6. Cunningham D, Starling N, Rao S, et al: Capecitabine and oxaliplatin for advanced esophagogastric cancer. New England Journal of Medicine 358:36-46, 2008
7. Wagner AD, Grothe W, Haerting J, et al: Chemotherapy in advanced gastric cancer: A systematic review and meta-analysis based on aggregate data. Journal of Clinical Oncology 24:2903-2909, 2006
8. Okines AFC, Norman AR, McCloud P, et al: Meta-analysis of the REAL-2 and ML17032 trials: Evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Annals of Oncology 20:1529-1534, 2009
9. Bang YJ, Van Cutsem E, Feyereislova A, et al: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet, 2010
10. Tafe LJ, Janjigian YY, Zaidinski M, et al: Human epidermal growth factor receptor 2 testing in gastroesophageal cancer: correlation between immunohistochemistry and fluorescence in situ hybridization. Arch Pathol Lab Med 135:1460-5, 2011
11. Hudis CA: Trastuzumab--mechanism of action and use in clinical practice. N Engl J Med 357:39-51, 2007
12. Folkman J: Role of angiogenesis in tumor growth and metastasis. Semin Oncol 29:15-8, 2002

13. Erber R, Thurnher A, Katsen AD, et al: Combined inhibition of VEGF- and PDGF-signaling enforces tumor vessel regression by interfering with pericyte-mediated endothelial cell survival mechanisms. The FASEB Journal, 2003
14. Fischer C, Jonckx B, Mazzone M, et al: Anti-PlGF Inhibits Growth of VEGF(R)-Inhibitor-Resistant Tumors without Affecting Healthy Vessels. Cell 131:463-475, 2007
15. Fuchs CS, Tomasek J, Yong CJ, et al: Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. The Lancet 383:31-39
16. Fuchs CS, Tomasek J, Yong CJ, et al: Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. The Lancet, 2013
17. Wilke H, Muro K, Van Cutsem E, et al: Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. The Lancet Oncology 15:1224-1235
18. Yoon H, Bendell J, Braiteh F, et al: Ramucirumab (RAM) plus FOLFOX as front-line therapy (Rx) for advanced gastric or esophageal adenocarcinoma (GE-AC): Randomized, double-blind, multicenter phase 2 trial., 2014 ASCO Annual Meeting J Clin Oncol 32:5s, 2014 (suppl; abstr 4004)
19. Gomez-Martin C, Plaza JC, Pazo-Cid R, et al: Level of HER2 Gene Amplification Predicts Response and Overall Survival in HER2-Positive Advanced Gastric Cancer Treated With Trastuzumab. Journal of Clinical Oncology 31:4445-4452, 2013
20. Comprehensive molecular portraits of human breast tumours. Nature 490:61-70, 2012
21. Satoh T, Xu R-H, Chung HC, et al: Lapatinib Plus Paclitaxel Versus Paclitaxel Alone in the Second-Line Treatment of HER2-Amplified Advanced Gastric Cancer in Asian Populations: TyTAN—A Randomized, Phase III Study. Journal of Clinical Oncology, 2014
22. Kim J, Fox C, Peng S, et al: Preexisting oncogenic events impact trastuzumab sensitivity in ERBB2-amplified gastroesophageal adenocarcinoma. The Journal of Clinical Investigation 124:5145-5158, 2014
23. Enzinger P, Abrams T, Cha J, et al: Multicenter phase 2: Capecitabine (CAP) + oxaliplatin (OX) + bevacizumab (BEV) + trastuzumab (TRAS) for patients (pts) with metastatic esophagogastric cancer (MEGCA). J Clin Oncol 33, 2015 (suppl; abstr 4038), 2015
24. Leyland-Jones B, Colomer R, Trudeau ME, et al: Intensive Loading Dose of Trastuzumab Achieves Higher-Than-Steadyâ€–State Serum Concentrations and Is Well Tolerated. Journal of Clinical Oncology 28:960-966
25. Oude Munnink TH, Dijkers EC, Netters SJ, et al: Trastuzumab Pharmacokinetics Influenced by Extent Human Epidermal Growth Factor Receptor 2-Positive Tumor Load. J Clin Oncol 28:e355-356, 2010
26. Janjigian YY, Viola-Villegas N, Holland JP, et al: Monitoring Afatinib Treatment in HER2-Positive Gastric Cancer with 18F-FDG and 89Zr-Trastuzumab PET. J Nucl Med, 2013
27. Bass AJ, Thorsson V, Shmulevich I, et al: Comprehensive molecular characterization of gastric adenocarcinoma. Nature 513:202-209, 2014
28. Cheng DT, Mitchell TN, Zehir A, et al: Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): A Hybridization Capture-Based Next-Generation Sequencing Clinical Assay for Solid Tumor Molecular Oncology. The Journal of Molecular Diagnostics 17:251-264, 2015
29. Gao J, Aksoy BA, Dogrusoz U, et al: Integrative Analysis of Complex Cancer Genomics and Clinical Profiles Using the cBioPortal. Science signaling 6:pl1-pl1, 2013
30. Riches JC, Schultz N, Ku GK, et al: Genomic profiling of esophagogastric (EG) tumors in clinical practice. J Clin Oncol 33, 2015 (suppl 3; abstr 57), 2015

31. Leto SM, Sassi F, Catalano I, et al: Sustained inhibition of HER3 and EGFR is necessary to induce regression of HER2-amplified gastrointestinal carcinomas. Clinical Cancer Research, 2015