1. SYNOPSIS

Title:	Phase II study of pembrolizumab plus ramucirumab in metastatic gastric or GEJ adenocarcinoma as salvage treatment
Design:	A single-arm, open-label, single-center Phase II study
Sponsor:	Samsung Medical Center Principal Investigator :Professor Jeeyun Lee M.D, Ph.D.
Objective	**1) Primary Objective:** To estimate preliminary overall response rate (ORR) of combination therapy of Ramucirumab and Pembrolizumab in patients with metastatic gastric or GEJ adenocarcinoma . **2)Secondary Objectives:** To assess secondary measures of clinical efficacy - Best Overall Response Rate: BORR - Disease Control Rate: DCR - Progression–Free Survival:PFS - Overall Survival: OS - Duration of Overall Response: DOR & maximal tumor shrinkage **3) Biomarker Objectives:** Integrative immune-genomic analysis to identify association of response with prevalent markers (e.g. PD-L1 expression, EMT signature, T-cell and cytolytic immune signatures, RNA-seq, hypermutation, pre and post cfDNA cancer panel genomics (Changes of TMB and landscape of genome), PFS/OS/safety ✓ Fresh tissues at baseline if clinically feasible/ in advanced to 3 cycles(if clinically feasible) ✓ (archival tissue only is not acceptable for study entry due to limited analysis on archival tissues) ✓ RNA sequencing to understand the mechanism of action of pembrolizumab and ramucirumab in responders and non-responders. ✓ Evaluating changes of component of Immune cells and cytokines in blood. ✓ Describe the association between EBV gastric cancer /or high PDL1 MSS and clinical activity in subjects who metastatic gastric or GEJ adenocarcinoma.
Subjects:	Patients with metastatic gastric or GEJ adenocarcinoma; EBV positive or PDL1 CPS≥5 .
Inclusion & Exclusion Crieteria	**Inclusion Criteria** Each patient must meet the following criteria to be enrolled in this study: 1. The patient is ≥18 years of age.

2. The patient who has received an adequate information and provided informed consent for all the study-specific procedures in advance
3. The patient has histologically or cytologically confirmed gastric carcinoma, including gastric adenocarcinoma or GEJ adenocarcinoma. (Patients with adenocarcinoma of the distal esophagus are eligible if the primary tumor involves the GEJ.) patient has metastatic disease or locally recurrent, unresectable disease.
4. The patient's tumor tissue must have the pre-defined characteristics as follows; EBV+ or PDL1 CPS≥5
5. The patient has measureable or evaluable disease as determined by standard computed tomography (CT) or magnetic resonance imaging (MRI) imaging. Examples of evaluable, nonmeasurable disease include gastric, peritoneal, or mesenteric thickening in areas of known disease, or peritoneal nodules that are too small to be considered measurable by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1)
6. The patient has experienced disease progression during first-line treatment or second-line therapy for metastatic disease.
   - Acceptable prior chemotherapy regimens for this protocol are combination chemotherapy regimens that include platinum and/or fluoropyrimidine components (acceptable prior platinum agents are cisplatin, carboplatin, or oxaliplatin; acceptable prior fluoropyrimidine agents are 5-FU, capecitabine, or S-1). Regimens including a third agent, such as an anthracycline or a taxane, are acceptable provided a fluoropyrimidine and/or a platinum were used.
   - Recurrence during or within 6 months of completion of adjuvant chemotherapy (capecitabine, 5-FU, or TS-1) will be considered as first-line chemotherapy.
7. No prior exposure to anti-PD1 antibody or ramucirumab
8. The patient has an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1.
9. Patients must have acceptable bone marrow, liver and renal function measured within 28 days prior to administration of study treatment as defined below:
   - ✓ Haemoglobin ≥9.0 g/dL
   - ✓ Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - ✓ Platelet count ≥100 x 10^9/L
   - ✓ Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN
   - ✓ AST (SGOT)/ALT (SGPT) ≤ 3.0 x institutional upper limit of normal unless liver metastases are present in which case it must be ≤ 5x ULN
   - ✓ Serum creatinine ≤1.5 x institutional ULN
   - ✓ Glomerular filtration rate < 45 mL/min in assessed by standard methods in the laboratory
   - ✓ Urinary protein is ≤1+ on dipstick or routine urinalysis
   - ✓ (INR) ≤1.5 and (PTT) ≤5 seconds above the ULN (unless receiving anticoagulation therapy). Patients on anticoagulation therapy with

unresected primary tumors or local tumor recurrence following resection are not eligible

10. Female patients of childbearing potential must have a negative pregnancy test (urine), must not be breastfeeding and using adequate contraceptive measures.

Female patients must use a highly effective contraceptive measure from screening until 4months after the last dose of drug. All methods of contraception (except for total abstinence) should be used in combination with the use of a condom by a male sexual partner for intercourse (see Restrictions below). (or vasectomy)

Female patients must have evidence of non-childbearing potential by fulfilling one of the following criteria at screening:

a. Post-menopausal women defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatment.

b. Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, but not tubal ligation.

11-1. For the duration of the study and for 1 week after the last study drug administration, sexually active male patients must be willing to use barrier contraception i.e. condoms with all sexual partners. Where the sexual partner is a 'women of child-bearing potential' who is not using effective contraception, men must use a condom (with spermicide) during the study and for 6 months after the last dose of a study drug. (or vasectomy)

12. Mandatory biopsy during the screening window prior to dosing and at progression (if clinically feasible)

Exclusion Criteria

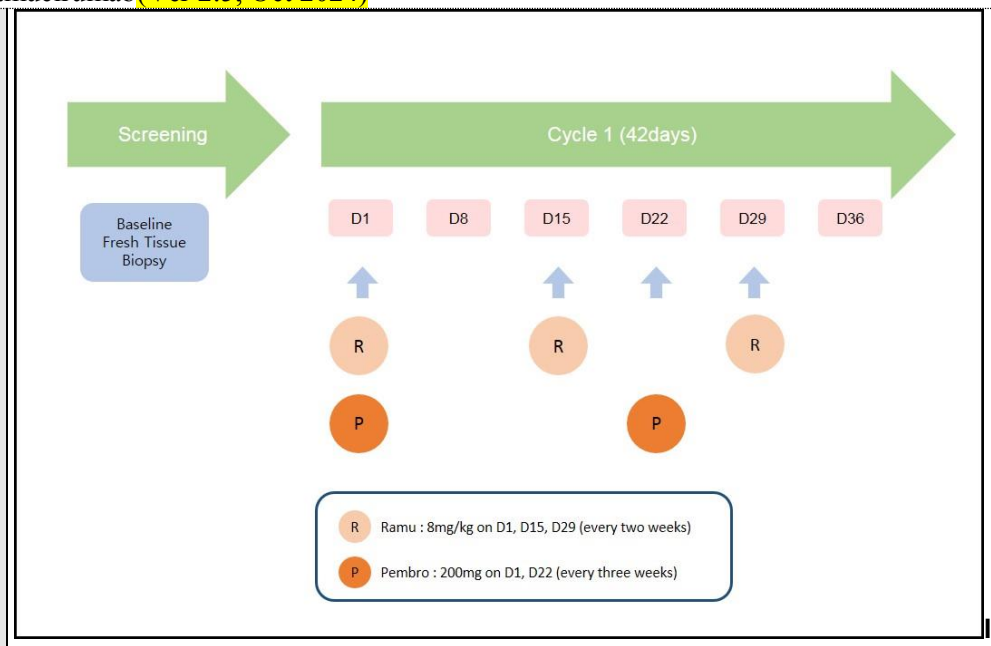
Patients who meet any of the following criteria will be excluded from participation in this study:

1. The patient has documented and/or symptomatic, encephalitis, brain or leptomeningeal metastases.
2. The patient has experienced any Grade 3 to 4 GI bleeding within 3 months prior to enrollment.
3. The patient has experienced myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to enrollment.
4. 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.
5. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin

(BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

6. The patient has an ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, uncontrolled thrombotic or hemorrhagic disorder, or any other serious uncontrolled medical disorders in the opinion of the treating physician.
7. The patient has ongoing or active psychiatric illness or social situation that would limit compliance with treatment.
8. The patient has uncontrolled or poorly controlled hypertension (>160 mmHg systolic or
    i. >100 mmHg diastolic for >4 weeks) despite standard medical management.
9. The patient has a serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to enrollment.
10. The patient has received chemotherapy, radiotherapy, immunotherapy, or targeted therapy for gastric cancer within 2 weeks prior to enrollment.
11. The patient has received any investigational therapy within 30 days prior to enrollment.
12. The patient has undergone major surgery within 28 days prior to enrollment, or subcutaneous venous access device placement within 7 days prior to enrollment.
13. The patient has received prior therapy with an agent that directly inhibits VEGF (including bevacizumab), or VEGF Receptor 2 activity, or any antiangiogenic agent and immunotherapy.
14. The patient is receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti- inflammatory drugs (NSAIDs; including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.
15. The patient has a known allergy to any of the treatment components.
16. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
17. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
18. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
19. Has an active infection requiring systemic therapy.
20. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
21. Has known active Hepatitis B or Hepatitis C (e.g., HCV RNA [qualitative]

	is detected). Chronic HBV infection with anti-viral agent prophylaxis is allowed. 22. Has known liver 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. 23. The patient is pregnant or breastfeeding
Goal:	To estimate efficacy and safety of combination therapy of Ramucirumab and Pembrolizumab in patients with metastatic gastric or GEJ adenocarcinoma
Planned Sample Size:	: A maximum of 26patients(considering 5% drop out rate) will be recruited to this single-arm phase II trial. In this single-arm phase II trial, 25 people were calculated using Simon's two-stage design and a total of 26 patients will be recruited to account for a 5% dropout rate. The sample size is calculated by use of a two-stage minimax Simon's design to control the type I error at 5 % for null hypothesis that, for arm, the true response was 15 % or below and to have 85 % of power if the true response was 40 % or higher. 15 evaluable patients are to be treated in the first stage. If 1 or fewer response are observed in the first stage, the arm will be stopped. If at least 2 responses are observed in the first stage, 10 additional evaluable patients are to be entered onto the second stage. At the final analysis, the null hypothesis will be rejected if at least 7 responses are observed in 25 evaluable patients. RR is reported with its exact 95% CI.
Duration of Study:	Uitll 100% enrollment from approval regulatory authority
Study design(Dosage & Treatment):	Patients will continue to receive study treatment, until they demonstrate objective disease progression (determined by modified RECIST 1.1) or until they meet any other discontinuation criteria. - Ramucirumab 8mg/kg on q2W - Pembrolizumab 200mg on q3W (pembrolizumab first followed by ramucirumab when concurrently administered on the same day)



If ramucirumab had to be stopped due to intolerable toxicity, pembrolizumab will be continued until unacceptable toxicity, disease progression or upto 35 cycles.

Specimen for biomarker and Genetic analysis

1. Tumor Biopsy

Tumor biopsies will be obtained from all subjects in the study. However, tumor biopsy can be exempted in cases considered as not safe or not accessible. It may be performed twice as below if possible.

1) Pre-treatment : Obtained at screening (Day 28) from the primary site.
2) If disease progresses, optional tumor biopsy may be obtained after it is confirmed.

2. Blood Collection

For analysis of biomarker(ct DNA), peripheral blood of 10 ml will be collected from all patients at every cycle D1 and at confirmed disease progression.

Method for Assessment:

1. Efficacy assessment

Objective Response Rate (ORR) : The proportion of the patients who have achieved complete response (CR) or partial response (PR) with confirmation. (Tumor response will be evaluated according to RECIST Ver. 1.1)

CT or MRI scans of the chest, abdomen, and pelvis, the tumor burden assessment method used at baseline, should also be used for each subsequent follow-up assessment.

If a patient discontinues treatment prior to progression (and/or is receiving follow-up cancer treatment), the patients' follow up monitoring should be continued until objective disease progression as defined by RECIST 1.1.

Categorization of objective tumor response assessments will be based on the modified RECIST 1.1 response criteria: CR (complete response), PR (partial response), SD (stable lesion), and PD (disease progression).

The progression of the target lesion (TL) is calculated compared to when the tumor burden was at a minimal level (ie, the minimum sum of diameters previously recorded during the trial). If not advanced, tumor response (CR, PR, SD) is calculated compared to baseline tumor measurements obtained prior to initiation of treatment.

For patients with only non-measurable disease from at baseline, categorization of objective tumor response assessment will be based on the modified RECIST 1.1 response criteria: CR, PD, non-CR/non-PD.

If the investigator is not sure whether progression has occurred, especially if there is a reaction to a non-target lesion (NTL) or a new lesion develops, if clinically necessary, dosing can be continued before next scheduled visit and be advisable to re-evaluate the patient's condition.

If progress is confirmed in the repeat scan, the progress date should be declared as the first scan date.

Secondary efficacy assessment will be conducted as follows:

A. Best Overall Response Rate (BORR) is defined as the proportion of the patients who have achieved CR or PR at least once.
B. Disease Control Rate (DCR) is defined as the proportion of the patients with a documented CR, PR, and SD (results will be provided by confirmed and unconfirmed).
C. Progression-Free Survival (PFS) is defined as the time from first administration of investigational drug to the earlier date of PD or death due to any cause.
D. Overall Survival (OS) is defined as the time from first administration of investigational drug to death due to any cause.
E. Duration of Overall Response (DOR) is defined as the time from the first date of assessment as CR or PR to the earlier date of PD or death due to any cause.
F. Maximal Tumor Shrinkage(MTS) is defined as rate of change in tumor size relative to the baseline at the time of best improvement.

2. Safety assessment

The severity of all AEs will be graded for laboratory toxicity and symptoms according to NCI-CTCAE Ver. 5.0. For the events that are not pre-defined in terms under NCI-CTCAE, Investigator should assign a numeric grade of "1" to "5" using the definitions as Mild, Moderate, Severe, Life-threatening, Death, respectively based on maximal intensity.

3. Biomarker assessment

To collect and store diagnostic and/or archival tumour samples and any fresh tumour biopsies (pre-treatment if clinically feasible and before 3 cycles if clinically feasible) for potential future exploratory research into factors that may influence development and/or response to ramucirumab in combination with pembrolizumab. Next generation sequencing from these samples and/or other protein based exploratory analysis will be carried out. Fresh tissues at baseline is required if clinically feasible

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

5-FU	5-fluorouracil
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
ATE	arterial thrombotic events
β-HCG	serum beta-human chorionic gonadotrophin (pregnancy test)
BP	blood pressure
BSC	best supportive care
CF	cisplatin + 5-fluorouracil
CFR	Code of Federal Regulations
CHF	congestive heart failure
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
CR	complete response
CRF	case report form
CRP	clinical research physician
CT	computed tomography
CTD	Clinical Trial Directive
DCSI	Development Core Safety Information
DVT	deep vein thrombosis
ECF	epirubicin + cisplatin + 5-fluorouracil
ECOG PS	Eastern Cooperative Oncology Group performance status
ECX	epirubicin + cisplatin + capecitabine
enroll	The act of assigning a patient to treatment. Patients who are enrolled in the trial are those who have been assigned to treatment.
enter	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the Informed Consent Form directly or through their legally acceptable representatives.
EOF	epirubicin + oxaliplatin + 5-fluorouracil
EOX	epirubicin + oxaliplatin + capecitabine
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GEJ	gastroesophageal junction
GI	gastrointestinal
HCC	hepatocellular cancer

HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IgG_1	immunoglobulin G, subclass 1
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRR	infusion-related reaction
I.V.	intravenous
LV	left ventricular
MAb	monoclonal antibody
MAP	mitogen-activated protein
MRI	magnetic resonance imaging
MUGA	multiple gated acquisition scan
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAID	nonsteroidal anti-inflammatory drug
OS	overall survival
PD	progressive disease
PE	pulmonary embolism
PFS	progression-free survival
PR	partial response
PTT	partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SAER	serious adverse event report
SD	stable disease
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TPO	third party organization
TTP	time-to-progression
UA	urinalysis
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

4. INTRODUCTION

4.1 Gastric Cancer

4.1.2 Background

It is expected that more than 23,000 cases of gastric cancer (gastric adenocarcinoma) will have been diagnosed in the United States (US) in 2012, with approximately 10,500 deaths attributable to this form of malignancy (1). The incidence of this condition among white males living in the US increased more than 3.5-fold in the 20-year period beginning in 1974 (2). Within the European Union, there were an estimated 83,000 new cases of gastric cancer in 2008, and globally, there was an estimated 988,000 cases of gastric cancer diagnosed (3).

Internationally, the disease occurs with higher frequency among males. Gastric cancer incidence worldwide is more than double in men than in women (rate ratio 2.2:1.0). There is an 11-fold variation in male incidence rates between the regions of the world, and an 8-fold variation in female rates. In 2008, the highest incidence rates for both sexes were in Eastern Asia (42 and 18 per 100,000 in males and females, respectively), and the lowest were in Northern and Southern Africa (4 and 2 per 100,000 in males and females, respectively). The countries with the highest incidence rates in 2008 were Republic of Korea for males (62 per 100,000) and Guatemala and Republic of Korea for females (26 and 25 per 100,000, respectively) (4). Overall, gastric cancer is a major cause of cancer-related death worldwide (4), estimated to be responsible for a tenth, or nearly 740,000, of all cancer deaths in 2008. Gastric cancer mortality rates closely follow the trend for incidence rates (the ratio of mortality to incidence was 0.75 in 2008), with a similar variation in rates across the regions of the world (4).

4.1.2 First-Line Therapy

While surgical resection is the preferred approach to treatment, approximately two-thirds of patients present with disease that is advanced or metastatic at diagnosis (6). For such patients, the prognosis is limited; the median survival for patients with untreated metastatic gastric cancer is 3 to 5 months (5,7,8,9). At present, systemic chemotherapy is the mainstay of treatment for advanced and metastatic gastric cancer (2). Combination chemotherapy, particularly containing fluoropyrimidines and platinum-based agents, has been shown to confer survival benefit compared with single-agent chemotherapy and supportive care (2,8). However, there have been relatively few Phase 3 trials in this setting, and the studies that have been performed have been characterized by nonstandardized patient selection, methodology, and data monitoring processes, making it difficult to compare the results from disparate trials. For this reason, there is no single, accepted, first-line regimen for the treatment of advanced/metastatic gastric cancer (5).

In the last several decades, the incidence and prevalence of cancers of the gastroesophageal junction (GEJ), and particularly adenocarcinomas of the GEJ, have markedly increased (10). There

is controversy as to whether such cancers should properly be classified as gastric, esophageal, or as a third independent entity, for the purposes of staging and research (11). In practice, systemic therapy for GEJ cancer has been based on that used for gastric cancer, and several major studies have included both tumor types for the purposes of treatment analysis (2,12,13,14). Results of a large, recently conducted study involving 1002 patients with metastatic gastroesophageal cancers demonstrated that prognosis (in the metastatic setting) did not differ between gastric and GEJ adenocarcinomas (15).

In a 2008 report, Cunningham et al. described the results of a large, multicenter, Phase 3 study evaluating multiple strategies for the treatment of advanced esophagogastric cancer (15). Participants were randomized to 1 of 4 regimens:

- epirubicin + oxaliplatin + 5-fluorouracil (5-FU) (EOF);
- epirubicin + cisplatin + capecitabine (ECX);
- epirubicin + cisplatin + 5-FU (ECF);
- epirubicin + oxaliplatin + capecitabine (EOX).

No significant differences were observed in terms of response rate or progression-free survival (PFS). Overall survival (9.9 months, 9.3 months, 9.9 months, and 11.2 months for ECF, EOF, ECX, and EOX, respectively) was longer in patients receiving EOX versus ECF. These results demonstrate an efficacy of capecitabine equivalent to that of 5-FU and an efficacy of oxaliplatin equivalent to that of cisplatin.

A study published in 2006 by Van Cutsem et al. demonstrated that adding docetaxel to a regimen of cisplatin + 5-FU (CF) increased overall survival (OS), with the 2-year survival rate increasing to 18% from 9% compared with CF alone. However, the addition of docetaxel was associated with an increase in toxicity (5). Specifically, the addition of docetaxel was associated with increased Grade 3 and 4 neutropenia (82% versus 57% with CF alone), complicated neutropenia (29% versus 12%), Grade 3 and 4 diarrhea (19% versus 8%), and Grade 3 and 4 lethargy (19% versus 14%). Due in part to this increased toxicity, incorporation of docetaxel into first-line gastric cancer regimens has been limited.

Overall, none of the available first-line therapeutic regimens has been clearly established as a preferred option, and median survival associated with any of the available regimens remains limited. Almost all patients develop refractory disease; however, second-line treatment options are limited.

4.2 Vascular Endothelial Growth Factor and Angiogenesis

Angiogenesis, the formation of new capillaries and blood vessels, is a tightly controlled, multistep

process that is a component of normal physiology (including development of the embryonic vasculature, wound healing, ovulation, and menstruation). Pathologic angiogenesis contributes to tumor growth and metastasis, as well as other human diseases, such as diabetic retinopathy, rheumatoid arthritis, and psoriasis (28,29,30). A number of growth factors have been identified as positive regulators of angiogenesis, including members of the vascular endothelial growth factor (VEGF) family, basic fibroblast growth factor, transforming growth factor alpha, transforming growth factor beta, tumor necrosis factor, platelet-derived endothelial growth factor, hepatocyte growth factor, angiogenin, interleukin-8, and placental growth factor (31,32).

4.3 The Role of VEGF and VEGF Receptor 2 in Angiogenesis and Tumor Growth

The importance of VEGF and VEGF Receptor 2 in angiogenesis and tumor growth has been demonstrated in several animal models. Vascular endothelial growth factor-2 expression is associated with activated endothelium and is strongly upregulated in tumor endothelium (33,34).

Inhibiting the function of the VEGF/VEGF Receptor 2 pathway via a number of approaches, including anti-VEGF antibodies, anti-VEGF Receptor 2 antibodies, anti-VEGF antisense ribonucleic acid expression, VEGF-based immunotoxins, soluble VEGF receptors, ribozymes to VEGF receptors, and small molecule VEGF Receptor 2 tyrosine kinase inhibitors, has been shown to prevent new blood vessel formation and tumor growth in a variety of animal models (35,36,37,38).

Vascular endothelial growth factor and VEGF Receptor 2 are overexpressed in the great majority of human cancers, including carcinomas of the gastrointestinal (GI) tract, pancreas, breast, cervix, bladder, ovary, uterus, endometrium, and kidney; Kaposi's sarcoma, glioblastoma multiforme, and hemangioblastomas. In addition, messenger ribonucleic acid for both VEGF Receptor 1 and VEGF Receptor 2 is greatly upregulated in tumor-associated endothelial cells, but not in the vasculature of the surrounding normal tissue. A correlation between VEGF Receptor 2 expression and tumor microvessel density has been associated with poor prognosis, advanced disease, increased risk of metastasis and recurrence, and lower relapse-free survival in patients with a variety of cancers (30,38).

4.4 Ramucirumab

Ramucirumab is a recombinant human MAb of the immunoglobulin G, subclass 1 (IgG_1) that specifically binds to the extracellular domain of VEGF Receptor 2 with high affinity. This antibody blocks the binding of the VEGF ligand to VEGF Receptor 2, inhibits VEGF-stimulated activation of both VEGF Receptor 2 and p44/p42 mitogen-activated protein (MAP) kinases, and neutralizes VEGF-induced mitogenesis of human endothelial cells.

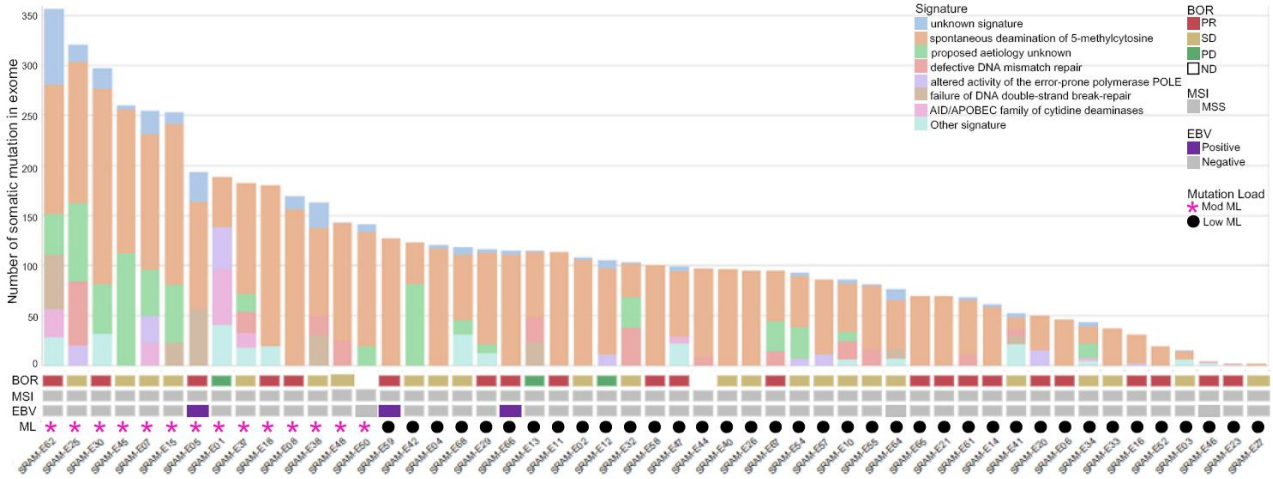
Ramucirumab has been shown to block the interaction of VEGF and VEGF Receptor 2 (with a

concentration that inhibits binding by 50% of approximately 1 nM), and to inhibit VEGF-stimulated proliferation of endothelial cells and VEGF-induced migration of human leukemia cells (39,40).

Preclinical pharmacodynamic data demonstrate that ramucirumab binds specifically and with high affinity to the VEGF Receptor 2 and is capable of inhibiting certain in vitro biological processes. These include VEGF/VEGF Receptor 2 interaction, VEGF-stimulated VEGF Receptor 2 activation, proliferation of human endothelial cells, VEGF-induced migration of human leukemia cells, and VEGF-induced phosphorylation of VEGF Receptor 2 in both human umbilical vein endothelial cells and porcine aortic endothelial cells engineered to overexpress VEGF Receptor 2 (40). These processes are likely involved in tumor angiogenesis. Potent angiogenic and antitumor effects are observed when DC101, a rat antibody to murine VEGF Receptor 2, is administered to mice bearing syngeneic tumors or human tumor xenografts. The results of these preclinical pharmacodynamic studies support the investigation of ramucirumab in the treatment of solid tumors.

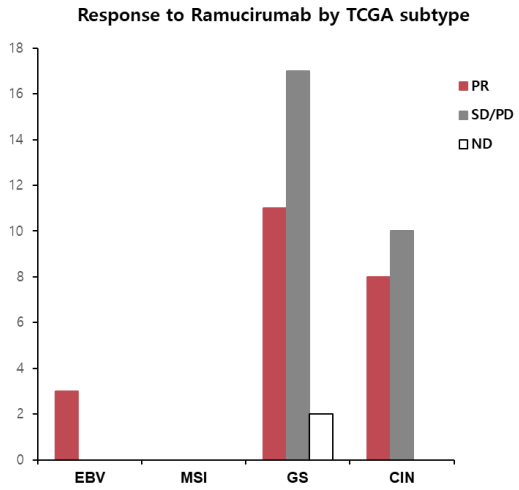
Currently, we are analyzing ramucirumab/taxol (66 patients) as an investigator sponsored trial: baseline biopsy using WES/RNA sequencing and serial ctDNA sequencing. We will use the genomic profiling on this trial to optimize understanding of responders to ramucirumab/pembrolizumab in GC. Some of the initial analysis from this phase II study are summarized below:

1) The somatic mutation landscape for 51 GC patients (WES) (unpublished)

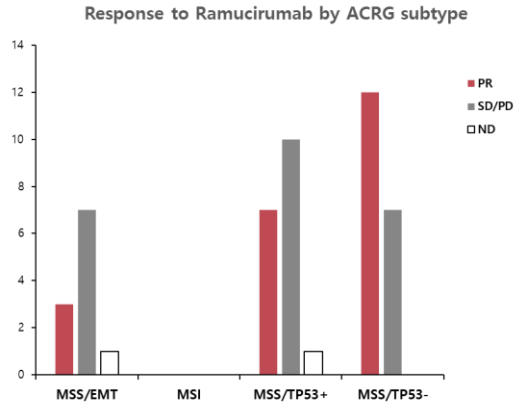


2) Response to ramucirumab according to TCGA subtypes:

Pembrolizumab + Ramucirumab(Ver 2.5, Oct 2024)

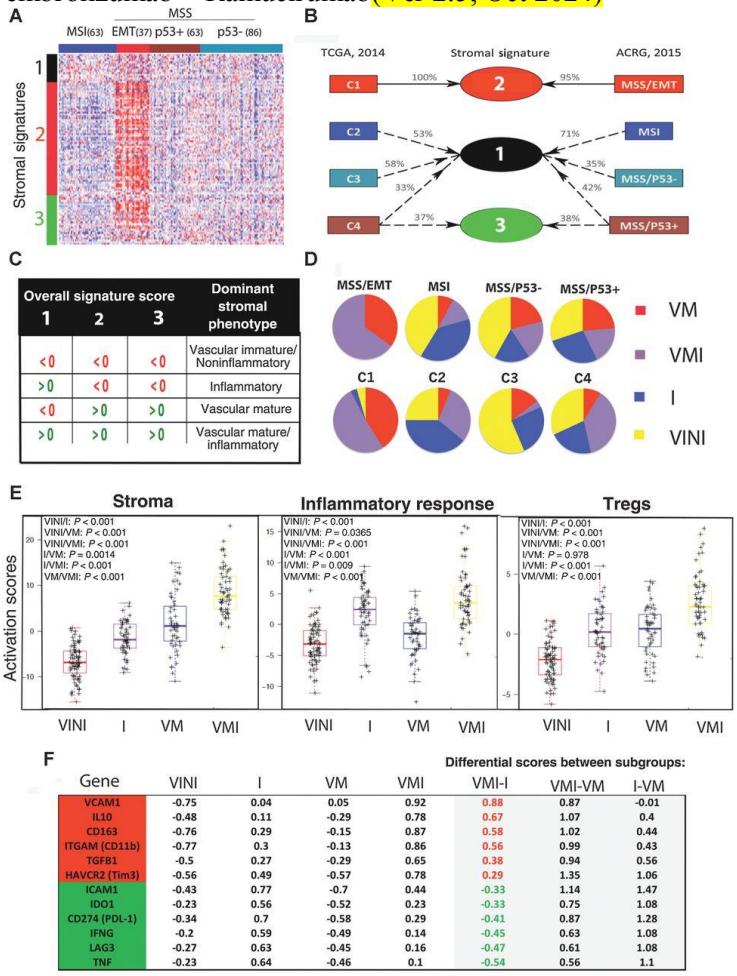


3) Response to ramucirumab according to ACRG subtypes



Therefore, our data suggest that ramucirumab responders are distributed throughout subtypes and interestingly, the response rate in GS subtype (or EMT subtype) was higher than expected.

In addition, Lilly researchers have demonstrated that the ACRG subtypes and angiogenesis signatures are important in identifying responders to ramucirumab (Uhlik MT et al Cancer Research 2016).



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Differential scores between subgroups:

Gene	VINI	I	VM	VMI	VMI-I	VMI-VM	I-VM
VCAM1	-0.75	0.04	0.05	0.92	0.88	0.87	-0.01
IL10	-0.48	0.11	-0.29	0.78	0.67	1.07	0.4
CD163	-0.76	0.29	-0.15	0.87	0.58	1.02	0.44
ITGAM (CD11b)	-0.77	0.3	-0.13	0.86	0.56	0.99	0.43
TGFB1	-0.5	0.27	-0.29	0.65	0.38	0.94	0.56
HAVCR2 (Tim3)	-0.56	0.49	-0.57	0.78	0.29	1.35	1.06
ICAM1	-0.43	0.77	-0.7	0.44	-0.33	1.14	1.47
IDO1	-0.23	0.56	-0.52	0.23	-0.33	0.75	1.08
CD274 (PDL-1)	-0.34	0.7	-0.58	0.29	-0.41	0.87	1.28
IFNG	-0.2	0.59	-0.49	0.14	-0.45	0.63	1.08
LAG3	-0.27	0.63	-0.45	0.16	-0.47	0.61	1.08
TNF	-0.23	0.64	-0.46	0.1	-0.54	0.56	1.1

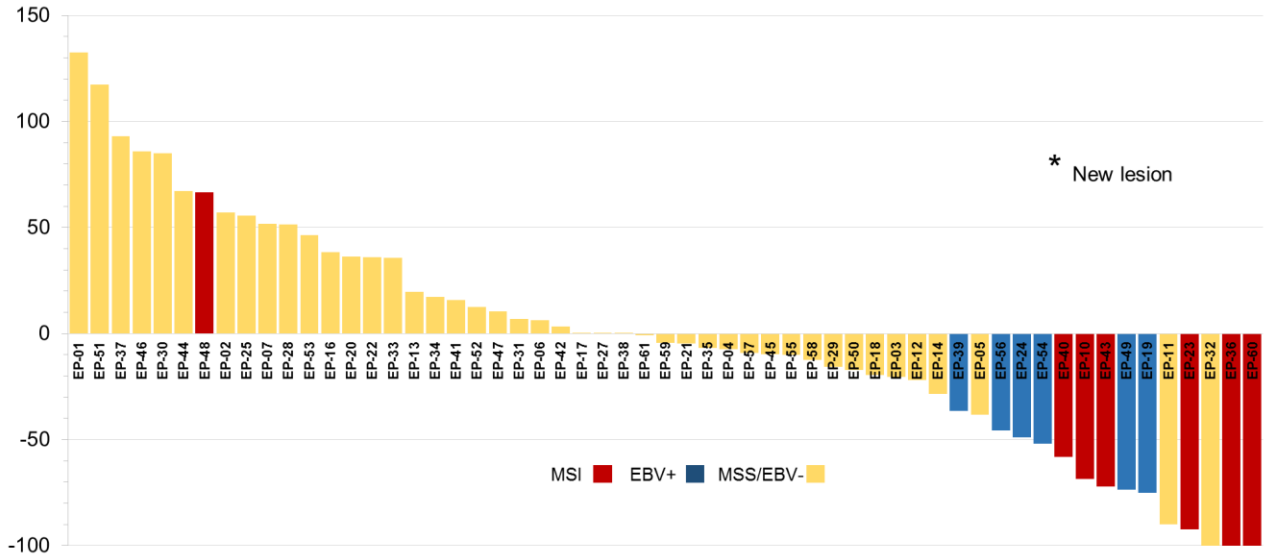
4.4.1 Immunotherapy in GC

Pembrolizumab is a selective, humanised, high-affinity IgG4-κ monoclonal antibody designed to bind to PD-1 and thus block the interaction between PD-1 and its ligands.4 Pembrolizumab has a manageable safety profile and has shown promising anti-tumour activity in several types of advanced solid tumours and hematological malignancies, raising hopes that this therapy may have efficacy in gastric cancer.5 Indeed, genomic sequencing analysis across multiple tumors demonstrated that gastric adenocarcinoma commonly possess relatively high mutational load, suggesting the presence of novel tumor antigens which could mark patients who may respond to pembrolizumab or other immune checkpoint inhibitors6.

Pembrolizumab (Keytruda®, Merck) is currently approved in the US for the treatment of GC and nivolumab (Opdivo®) has been approved in Japan and Korea for salvage treatment in GC. Early trials demonstrating the potential for PD-1 therapy in GC were performed in patients with positive immunohistochemcial expression of PD-L1, a ligand for PD-1 7,8. In KEYNOTE-012 trial, 39 PDL-1-positive GC patients with chemotherapy-refractory metastatic disease were treated with pembrolizumab and 8 patients had a response (22%, 95% CI 10 – 39), including 8 partial responses and 0 complete response9. A subsequent study, the KEYNOTE-059 (NCT#02335411) phase II trial of pembrolizumab in an unselected population of metastatic GC patients who specifically

received 2 prior lines of therapy (n=133) demonstrated an overall response rate (ORR) of 16.4%10.

In a recent collaborative project with Merck on phase II pembrolizumab trial in metastatic GC, we have found that dramatic responders are EBV+, high mutational load, or MSI-high patients (Nature Medicine 2018 published July 16 2018, Waterfall chart).



In recent our study, CR was achieved in 3 patients (4.9%, 95% CI: 1.3–13.7), 12 patients achieved confirmed PRs (PR; 19.7%, 95% CI: 10.6 – 31.8), and 20 patients (32.8%, 95% CI: 21.3–46.0) had stable disease, resulting in an ORR of 24.6% (95% CI: 14.7 – 37.3) and a disease control rate (DCR) of 57.4% (95% CI 44.1-70.0). This response rate of 24.6% was consistent to previous other immunotherapy-trials in GC. (Kim ST/Lee J et al Nature Medicine 2018 July 16 published)

4.4.2 Rationale for the Use of Ramucirumab and Pembrolizumab in the Treatment of Metastatic Gastric Carcinoma

Immunotherapeutic strategies are most effective against tumors with an inflammatory microenvironment. Three main inflammatory states in tumors have been described on the basis of having either high levels of active tumor infiltrating lymphocyte (TIL), a rim of excluded lymphocytes around the tumor or lack of TIL or excluded lymphocytes11. The limited presence of lack of immune cell infiltration in tumors is an important aspect that compromises the efficacy of many types of immunotherapy. Various strategies are being pursued with the aim of promoting immune cell infiltration into tumors and reverting the effect of an immunosuppressive tumor microenvironment12. One such strategy is the use of drugs originally designed to inhibit angiogenesis. Angiogenesis and immunosuppression are closely related process. Various

angiogenic factors can also immunosuppressive functions. Several pre-and angiogenic molecules have been shown to be associated with a range of immunosuppressive effects at successive steps in cancer immunity cycle, such as antigen presentation, T cell priming, T cell trafficking and T cell tumor infiltration13. Furthermore, anti-angiogenetic agents increased PD-L1 expression of tumors. Therefore, anti-angiogenic agents can stimulate an immune response which can then be exploited to boost anti-tumor immune response.

4.4.3 Molecular classifications in GC

The molecular classification of GC and the relevance of pre-clinical models are not well established, creating challenges in discovering novel molecularly targeted therapies. In order to address these issues, we conducted an integrated molecular data analysis of three hundred Asian Gastric tumors through the Asian Cancer Research Group (ACRG). We performed an integrated genomic analyses based on target sequencing, gene expression profiling, copy number variations, Lauren's histological classification, Epstein Barr Virus (EBV) status, TP53 status in three hundred GC specimens. We first divided GC into four subgroups based on gene expression profiling and TP53 status: 1) epithelial MSS-TP53 inactive; 2) epithelial MSS-TP53 active; 3) MSI; and 4) mesenchymal. With an integrative analysis with target sequencing and copy number variations, epithelial MSS-TP53 inactive GCs are characterized by predominantly hypermutated intestinal tumors (including majority of mutations in KRAS) with MLH1 loss through promoter methylation and MSS-TP53 active GCs are characterized by intact TP53 pathway with high frequency of EBV infection or frequently mutated oncogenes (e.g. PIK3CA). MSI subtype with TP53 pathway inactive characterized by TP53 loss through deleterious mutations in TP53 or MDM2 amplification and further characterized by both focal amplifications in oncogenes such as HER2, EGFR, cMET, CCNE1 as well as large scale chromosomal gains and losses. The above subtypes exhibited differential prognosis with the mesenchymal subtype displaying the worst survival (2.2 years) and the MSI subtype the most favorable survival (5.6 years). The GC subtypes and their association with prognosis were independently validated in three GC cohorts. In this study, we plan to analyze responders vs non-responders according molecular subtypes for combination therapy with ramucirumab and pembrolizumab. In addition, we aim to investigate whether the addition of ramucirumab will prolong response to pembrolizumab in EBV(+) GC tumors.

5.0 Objective

5.1 Primary Objective:

To estimate preliminary overall response rate (ORR) of combination therapy of Ramucirumab and Pembrolizumab in patients with metastatic gastric or GEJ adenocarcinoma

5.2 Secondary Objectives:

To assess secondary measures of clinical efficacy

- Best Overall Response Rate:BORR

- Disease Control Rate: DCR
- Progression–FreeSurvival:PFS
- OverallSurvival: OS
- Duration of Overall Response: DOR & maximal tumor shrinkage

5.3 Biomarker Objectives:

Integrative immune-genomic analysis to identify association of response with prevalent markers (e.g. PD-L1 expression, EMT signature, T-cell and cytolytic immune signatures, RNA-seq, hypermutation, pre and post cfDNA cancer panel genomics (Changes of TMB and landscape of genome), PFS/OS/safety

- ✓ Fresh tissues at baseline pre-treatment if clinically feasible and before 3 cycles if clinically feasible)
- ✓ (archival tissue only is not acceptable for study entry due to limited analysis on archival tissues)
- ✓ RNA sequencing to understand the mechanism of action of pembrolizumab and ramucirumab in responders and non-responders.
- ✓ Evaluating changes of component of Immune cells and cytokines in blood
- ✓ Describe the association between EBV gastric cancer /or MSI and clinical activity in subjects who metastatic gastric or GEJ adenocarcinoma.

6. POPULATION SELECTION

Male and female patients with histologically or cytologically confirmed metastatic or locally recurrent unresectable gastric or GEJ adenocarcinoma and disease progression on prior fluoropyrimidine and/or platinum combination chemotherapy will be enrolled. In addition, patients who received taxane, irinotecan and other regimens except anti-angiogenetic agent and immunotherapy as 2nd or 3rd line therapy will be enrolled in this study. A record of the most recent pretreatment evaluations will be reviewed to determine the eligibility of a patient for this study.

6.1 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study:

1. The patient is ≥18 years of age.
2. The patient who has received an adequate information and provided informed consent for all the study-specific procedures in advance
3. The patient has histologically or cytologically confirmed gastric carcinoma, including gastric adenocarcinoma or GEJ adenocarcinoma. (Patients with adenocarcinoma of the distal esophagus are eligible if the primary tumor involves the GEJ.) patient has metastatic disease or locally recurrent,

unresectable disease.

4. The patient's tumor tissue must have the pre-defined characteristics as follows ; EBV+ or PDL1 CPS≥5
5. The patient has measureable or evaluable disease as determined by standard computed tomography (CT) or magnetic resonance imaging (MRI) imaging. Examples of evaluable, nonmeasurable disease include gastric, peritoneal, or mesenteric thickening in areas of known disease, or peritoneal nodules that are too small to be considered measurable by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1)
6. The patient has experienced disease progression during first-line treatment or second-line therapy for metastatic disease.
   - Acceptable prior chemotherapy regimens for this protocol are combination chemotherapy regimens that include platinum and/or fluoropyrimidine components (acceptable prior platinum agents are cisplatin, carboplatin, or oxaliplatin; acceptable prior fluoropyrimidine agents are 5-FU, capecitabine, or S-1). Regimens including a third agent, such as an anthracycline or a taxane, are acceptable provided a fluoropyrimidine and/or a platinum were used.
   - Recurrence during or within 6 months of completion of adjuvant chemotherapy (capecitabine, 5-FU, or TS-1) will be considered as first-line chemotherapy.
7. No prior exposure to anti-PD1 antibody or ramucirumab. Or ramucirumab can participate if the investigator determines that there is a clinical benefit.
8. The patient has an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1.
9. Patients must have acceptable bone marrow, liver and renal function measured within 28 days prior to administration of study treatment as defined below:
   - ✓ Haemoglobin ≥9.0 g/dL
   - ✓ Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - ✓ Platelet count ≥100 x 10^9/L
   - ✓ Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
   - ✓ AST (SGOT)/ALT (SGPT) ≤ 3.0 x institutional upper limit of normal unless liver metastases are present in which case it must be ≤ 5x ULN
   - ✓ Serum creatinine ≤1.5 x institutional ULN
   - ✓ Glomerular filtration rate < 45 mL/min in assessed by standard methods in the laboratory
   - ✓ urinary protein is ≤1+ on dipstick or routine urinalysis
   - ✓ (INR) ≤1.5 and (PTT) ≤ x5 seconds above the ULN (unless receiving anticoagulation therapy). Patients on anticoagulation therapy with unresected primary tumors or local tumor recurrence following resection are not eligible.

11. Female patients of childbearing potential must have a negative pregnancy test (urine or serum), must not be breastfeeding and using adequate contraceptive measures.

Female patients must use a highly effective contraceptive measure from screening until 4months after the last dose of drug. All methods of contraception (except for total abstinence) should be used in combination with the use of a condom by a male sexual partner for intercourse (see Restrictions below). (or vasectomy)

Female patients must have evidence of non-childbearing potential by fulfilling one of the following criteria at screening:

a. Post-menopausal women defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatment.

b. Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, but not tubal ligation.

11-1. For the duration of the study and for 1 week after the last study drug administration, sexually active male patients must be willing to use barrier contraception i.e. condoms with all sexual partners. Where the sexual partner is a 'women of child-bearing potential' who is not using effective contraception, men must use a condom (with spermicide) during the study and for 6 months after the last dose of a study drug. (or vasectomy)

12. Biopsy during the screening window prior to dosing and at before cycle 3 (if clinically feasible)

6.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in this study:

1. The patient has documented and/or symptomatic encephalitis, brain or leptomeningeal metastases.
2. The patient has experienced any Grade 3 to 4 GI bleeding within 3 months prior to enrollment.
3. The patient has experienced myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to enrollment.
4. 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.
5. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal

influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed

6. The patient has an ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, uncontrolled thrombotic or hemorrhagic disorder, or any other serious uncontrolled medical disorders in the opinion of the treating physician.
7. The patient has ongoing or active psychiatric illness or social situation that would limit compliance with treatment.
8. The patient has uncontrolled or poorly controlled hypertension (>160 mmHg systolic or >100 mmHg diastolic for >4 weeks) despite standard medical management.
9. The patient has a serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to enrollment.
10. The patient has received chemotherapy, radiotherapy, immunotherapy, or targeted therapy for gastric cancer within 2 weeks prior to enrollment.
11. The patient has received any investigational therapy within 30 days prior to enrollment.
12. The patient has undergone major surgery within 28 days prior to enrollment, or subcutaneous venous access device placement within 7 days prior to enrollment.
13. The patient has received prior therapy with an agent that directly inhibits VEGF (including bevacizumab), or VEGF Receptor 2 activity, or any antiangiogenic agent and immunotherapy.
14. The patient is receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs; including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.
15. The patient has a known allergy to any of the treatment components.
16. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
17. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
18. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
19. Has an active infection requiring systemic therapy.
20. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
21. Has known active Hepatitis B or Hepatitis C (e.g., HCV RNA [qualitative] is detected) and liver cirrhosis. Chronic HBV infection with anti-viral agent prophylaxis is allowed.
22. Has known liver 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.
23. The patient is pregnant or breastfeeding.

6.3 DISCONTINUATIONS

The criteria for enrollment must be followed explicitly.
patients will be discontinued from the study in the following circumstances:

- enrollment in any clinical trial involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- treating physician decision
  - ✓ Unacceptable toxicity as determined by the participant or site Investigator
  - ✓ The Investigator determines that continuation of treatment is not in the participant's best interests.
  - ✓ Delay of day 1 treatment for >28 days due to treatment-related adverse events. For delays >28 days due to due to reasons other than treatment-related adverse events, patints may stay on drug if receiving clinical benefit.
  - ✓ if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the patient's gastric or GEJ cancer, discontinuation from the ramucirumab and/or pembrolizumab occurs prior to introduction of the new agent
- patient decision
  - o the patient (or the patient's legally acceptable representative) requests to be withdrawn from the study

The reasons for discontinuing treatment will be documented in the participant's medical record.

7. CARE PLAN

7.1 Study Design and Plan

This study is a single arm, open label, single center phase II study of ramucirumab in combination with pembrolizumab in EBV+ or CPS≥5 patients with advanced gastric adenocarcinoma including gastric adenocarcinoma or GEJ adenocarcinoma as a second or third line chemotherapy

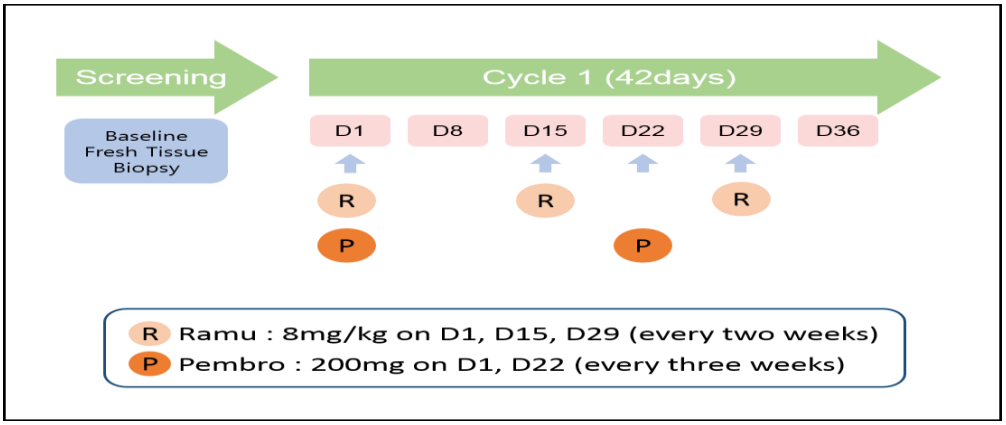
Patients will receive ramucirumab plus pembrolizumab combination regimen. This study recruits a maximum of 35 patients.

Lilly will only supply ramucirumab and Merck will supply pembrolizumab. Lilly and Merck will not supply other medications used in the care of patients while on this study.

Patients will receive ramucirumab, administered via intravenous (I.V.) infusion over approximately 1 hour, every 2 weeks , at a dose of 8 mg/kg, and pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. (pembrolizumab first followed by

ramucirumab when concurrently administered on the same day)

- Ramucirumab 8mg/kg on q2W
- Pembrolizumab 200mg on q3W



Assessment of disease control is recommended every 6 weeks (every cycle).

It is recognized that in the course of clinical cancer care, it is not always possible to schedule therapeutic infusions precisely 2 weeks-ramucirumab/3 weeks-pembrolizumab following a prior infusion (because of holidays, travel difficulties, or other circumstances). Accordingly, infusions administered within 3 days before or after the planned time point are acceptable. Administration beyond this window is strongly discouraged.

All patients may continue to receive treatment with the IP, ramucirumab, until there is evidence of progressive disease (PD), unacceptable toxicity, the patient is withdrawn from the study for any other reason, or ramucirumab becomes commercially available and accessible to patients after local marketing authorization. Also, if ramucirumab stops then pembrolizumab be discontinued as well.

Treatment may be discontinued as outlined in Section 6.3

7.2 Enrollment/screening Period

The following assessments and procedures should be performed within 28 days prior to first dose of study treatment. For details of the schedule and nature of the assessments, see below.

- Signed informed consent for the study; include main inform consent
- Results of EBV IHC or PDL1 (EBV positive or PDL1 CPS≥5)

EBV test: (all centralized at CAP-certified pathology lab/SMC): he entire procedure was performed on a fully automatic system (BOND-MAX) for in situ hybridization with an EBV-encoded RNA probe from Leica (Newcastle, UK) following manufacturer's instructions (ref: Gastroenterology

2010 vol 139, pages 84-92).

PDL1 test: IHC staining will be carried out on Dako Autostainer Link 48 system (Agilent Technologies, Santa Clara, CA) using Dako PD-L1 IHC 22C3 pharmDx kit (Agilent Technologies) with EnVision FLEX visualization system and counterstained with hematoxylin according to the manufacturer's instructions. PD-L1 protein expression will be determined by using Combined Positive Score (CPS), which was the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. (ref: https://www.agilent.com/cs/library/usermanuals/public/29158_pd-l1-ihc-22C3-pharmdx-nsclc-interpretation-manual.pdf)

- Date of birth, race and ethnicity
- Medical and surgical history
- Current and concomitant medications including previous cancer therapies (if applicable)
- Physical examination
- ECOG performance status
- Vital signs (blood pressure, pulse and body temperature), body weight and height.
- Hamatology, clinical chemistry and urinalysis,TFT
- Menopausal status; serum or urine pregnancy test for women of childbearing potential (within 7 days prior to study treatment start
- ECG
- Echocardiogram/MUGA Should be completed if patients had received prior anthracycline therapy
- Tumor assessment (scans of the abdomen/pelvis/other sites as clinically indicated for assessment of disease [CT/MRI]), performed within 14 days prior to enrollment, idealy should be performed as close as possible to the start of the treatment. Scans that were performed as part of standard of care prior to signature of the informed consent form can be analysed for the purposes of the study if they were performed within the correct time frame and consistent with modified RECIST guidelines for CT or MRI
- CEA, CA19-9
- Concomitant medications
- Adverse events must be captured from time of consent
- Mandatory baseline fresh biopsy
- cfDNA sample (mandatory) & cytokines

.

Screening numbers and Enrollement numbers will be assigned as follows.

-Screening number: S001,S002,S003…
-Enrollment number: E001, E002, E003….

7.3 Treatment Period

The visit schedule is based on day periods. Patients will attend the clinic on every administration during the 1 cycle, and from the 2cycle attend the clinic every 3 weeks. The following assessments will be performed at time points specified in the study schedule (appendix 1)

- Vital sign measurements, including temperature, pulse rate, respiration rate, and BP, should be obtained before, during, and at the completion of each infusion of ramucirumab and pembrolizumab.
- Physical examination including ECOG performance status
- Hamatology and clinical chemistry
- coagulation profiles;
- Urinalysis (every cycle)
- TFT(every cycle)
- AE (every visit)
- Concomitant medications (every visit)
- Tumor assessments via CT or MRI (every 6 weeks until objective disease progression)
- CEA,CA19-9 ,every tumor assessment
- cfDNA(mandatory), every tumor assessment

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of the scheduled visit ± 1 week window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Patients will be evaluated until objective disease progression by modified RECIST1.1, as per the study schedule (see Appendix 1), and then followed for survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

7.4 End of Therapy

Patients should be discontinued from study treatment if any discontinuation criteria are fulfilled. The assessments to be carried out at the visit are detailed in the study schedule

- Physical examination including ECOG performance status
- Vital Sign
- hematology, chemistry, and coagulation profiles;
- Urinalysis
- Imaging studies with tumor measurements/disease response assessments if the patient was discontinued for reasons other than PD;
- ~~Fresh Biopsy sample prior to dosing and at documented disease progression (if feasible)~~
- CEA,CA19-9
- cfDNA

- Concomitant medications & AE

7.5 Post-Treatment Follow-Up Evaluations

Follow-up safety evaluations will occur 30 days (± 7 days) after last dose of study drug or until resolution of any drug-related toxicity (telephone contact is acceptable). All patients will be followed for a minimum 30 days after discontinuation of the study drug. All AEs or SAEs occurring during the 30-day post treatment safety follow-up period will be captured. Unresolved study drug related AEs and SAEs at the time of treatment discontinuation or new study drug related AEs and SAEs that occur during the 30-day safety follow-up period will be followed until they have, in opinion of the Investigator, resolved to baseline, have stabilized, or are deemed to be irreversible.

7.6 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.7 Follow-Up

Follow-up and treatment of patients post discontinuation ramucirumab/pembrolizumab is at the discretion of the treating physician. The attending physician will be asked to complete the final case report form (CRF) indicating whether he/she believed the patient derived benefit from ramucirumab/pembrolizumab and whether there are plans to commence another form of systemic therapy.

8. TREATMENT

8.1 Treatments Administered

8.1.1 Ramucirumab

Different drug product lots must not be mixed in a single infusion.

Patients will receive 8 mg/kg of ramucirumab every2 weeks, administered as an I.V. infusion over approximately 1 hour (maximum infusion rate 25 mg/min). The dose of ramucirumab will be dependent upon the patient's baseline body weight in kilograms. This dose will be recalculated if there is a ≥10% change in body weight from baseline. Refer to the IB for more details.

8.1.2 Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites

should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

8.2 Materials and Supplies

For instructions on reconstitution and administration of ramucirumab, refer to the IB (Safe Handling and Administration). Calculate the dose and volume of ramucirumab needed to prepare the infusion solution. Vials contain either 100 mg or 500 mg as a 10 mg/mL solution of ramucirumab. Only use sterile sodium chloride (0.9%) solution for injection as a diluent.

Administer via an infusion pump. A separate infusion line must be used for the infusion and the line must be flushed with sterile sodium chloride (0.9%) solution for injection at the end of the infusion.

As infusion-related reactions (IRRs) may occur during or after the administration of ramucirumab, premedication is recommended with a histamine H1 antagonist (such as, diphenhydramine hydrochloride or equivalent) intravenously prior to administration of ramucirumab.

If a patient experiences a Grade 1 or 2 IRR, premedication must be given for all subsequent infusions. If a patient has a second Grade 1 or 2 IRR, administer dexamethasone (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine hydrochloride (or equivalent)

Vials should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light. DO NOT FREEZE OR SHAKE the vial.

The chemical and physical stability for the ramucirumab infusion solution was demonstrated for up to 24 hours at 2°C to 8°C (36°F to 46°F) or for 4 hours at room temperature (below 25°C (77°F)). DO NOT FREEZE OR SHAKE the ramucirumab infusion solution.

8.3 METHOD OF ASSIGNMENT TO TREATMENT

This is a single-arm study and all patients enrolled will receive ramucirumab/pembrolizumab.

8.4 Special Treatment Considerations

8.4.1 Dose Adjustments and Delays

Ramucirumab

Dose modifications are permitted for ramucirumab in the setting of non-life-threatening, reversible Grade 3 and 4 AEs (that is, fatigue, anorexia, or fever) that resolve to Grade ≤1 within 1 treatment cycle (approximately 2 weeks). In this setting, ramucirumab may be readministered. If a second

instance of such an event occurs, ramucirumab should be subsequently readministered at a dose of 6 mg/kg every other week. A second dose reduction to 5 mg/kg every other week is permitted for this level of event (Grade 3 and 4). If a Grade 4 AE occurs and is deemed at least possibly related to ramucirumab, then ramucirumab should be discontinued except in specific case of Grade 4 fever or Grade 4 laboratory abnormalities. If Grade 4 fever or laboratory abnormalities resolve to Grade ≤1 or pretreatment baseline within one treatment cycle (approximately 2 weeks), treatment with ramucirumab may be continued at the discretion of the treating physician. Criteria for dose reduction in the setting of hypertension or proteinuria and other AESIs are detailed in Section 11

Patients who enter the study with symptoms or laboratory values equivalent to NCI-CTCAE Version 4.03 Grade 1 to 2 AEs should not have dose reductions related to the persistence or mild worsening of those symptoms or laboratory values; dose reductions may be warranted if worsening of symptoms or laboratory values is clinically significant in the opinion of the patient's physician. Asymptomatic Grade 3 to 4 laboratory abnormalities should not result in dose interruptions, modifications, or discontinuation of protocol therapy unless determined to be clinically significant by the patient's physician (or unless otherwise specified in this protocol).

The treatment schedule remains static regardless of interruptions in ramucirumab administration. Dose delays are only permitted within 3 days after the date of a regularly scheduled treatment. If a patient is unable to receive treatment on or within 3 days before or after the date of his/her regularly scheduled dose for any reason (including AEs), the next dose of ramucirumab should be administered at the first regularly scheduled treatment time point following the resolution of the event causing the delay. (Treatment in this situation [missed dose/cycle] is considered to occur at the subsequently numbered cycle.) Make-up doses occurring between regularly scheduled, every-treatment time points are not recommended.

The patient's physician may discontinue ramucirumab for lack of disease control or toxicity. Patients who experience an AE requiring dose reduction after 2 prior dose reductions should discontinue ramucirumab therapy. In addition, the patient's physician may withdraw a patient from ramucirumab for disease progression, toxicity, or if the treating physician team determines it is in the patient's best interests for any reason. Patients whose performance status worsens by ≥2 units should be discontinued from study therapy.

After termination of ramucirumab therapy, the patient will be treated as clinically indicated by the treating physician.

Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or

several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table below. Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record.

8.4.2 Hematologic Toxicity

Reduced leukocyte or platelet counts are not anticipated ramucirumab-related AEs. ~~However, on the planned day of treatment, ramucirumab should only be administered if:~~

- ~~ANC is ≥1000/µL; and~~
- ~~platelet count is ≥75,000/µL.~~

9. CONCOMITANT THERAPY

9.1 Ramucirumab

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be offered to all patients on this study. This may include but is not limited to antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Medical teams are advised to prescribe these agents according to American Society of Clinical Oncology (ASCO) or local guidelines.

The use of other chemotherapy, experimental medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, surgery for cancer, or experimental medications is indicative that the patient's disease or clinical condition is worsening and should be discontinued from this study. Combining any other form of anticancer therapy with ramucirumab is strongly discouraged as there is no information supporting that this can be done safely in this clinical situation.

Ramucirumab has not been studied in conjunction with radiation. Therefore, it is recommended that sites contact the lead Lilly CRP or designate prior to administering palliative radiation. If palliative radiation is being administered to new symptomatic areas, this may represent progression of disease in which case the patient should discontinue ramucirumab therapy. Patients should not receive chronic antiplatelet therapy, including NSAIDs (including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents.

Aspirin is permitted at doses ≤325 mg once daily. Ongoing aspirin therapy at doses exceeding 325 mg/day is not permitted.

Anticoagulation therapy is permitted as follows:

At entry into the protocol, patients on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin. If on warfarin, the patient

must have an INR ≤3 and no active bleeding or pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices).

Patients who develop venous thromboembolism during protocol therapy may continue study therapy but must receive low molecular weight heparin, not oral anticoagulation.

The effects of ramucirumab on wound healing are not known. Bevacizumab (an antibody to VEGF-A ligand) is associated with a higher incidence of serious wound-healing complications.

In one study, 6 of 39 patients (15%) requiring surgery during or following bevacizumab experienced complications related to wound healing or bleeding; in a second study, complications were experienced by 1 of 25 patients (4%) requiring surgery (50). Hence, it is recommended that major surgery either be performed more than 28 days prior to enrollment or be postponed until at least 28 days after last dose of ramucirumab, when possible, and that subcutaneous venous access devices be placed at least 7 days prior to enrollment if their use is likely to be warranted. If major surgery is required during study therapy, the surgeon should be informed that the patient is receiving an agent that may be associated with a higher incidence of wound-healing complications. If subcutaneous venous access device placement is required during the course of protocol therapy, it is recommended that a 7-day treatment-free period occur both prior to and following placement.

Although emesis is not an expected adverse drug reaction to ramucirumab, the use of antiemetic agents is permitted at the discretion of the treating physician.

The use of analgesic agents is permitted at the discretion of the treating physician. Opiate and nonopiate analgesic agents are permitted (including acetaminophen); however, the use of NSAIDs and/or aspirin is prohibited as detailed above.

The use of appetite stimulants is permitted at the discretion of the treating physician.

Although neutropenia is not an expected adverse drug reaction of ramucirumab, the use of granulocyte colony stimulating factors (G-CSF) is permitted in accordance with ASCO or local guidelines.

The use of erythroid-stimulating factors (for example, erythropoietin) is permitted in accordance with ASCO or local guidelines.

The use of benzodiazepines, antidepressants, laxatives, and other agents that may be helpful in controlling disease-related symptoms are also permitted and encouraged, except as prohibited as outlined above.

9.2 Pembrolizumab

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Merk.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

10. EFFICACY AND SAFETY EVALUATION

10.1 EFFICACY

This study will assess the efficacy of ramucirumab when given in combination with pembrolizumab in patients with metastatic gastric or GEJ adenocarcinoma.

10.1.1 Tumor Evaluation

Modified RECIST 1.1 criteria will be used to assess patient response to treatment by determining PFS and ORR. The modified RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease).

The methods of assessment of tumour burden used at baseline, CT or MRI scans of chest, abdomen and pelvis must be used at each subsequent follow-up assessment.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments every 6 weeks relative to date of first dose until objective disease progression as defined by modified RECIST 1.1. See Study Schedule (Table 1) for further details.

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression as defined by modified RECIST 1.1.
Categorisation of objective tumour response assessment will be based on the modified RECIST 1.1 criteria of response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.
For patients with non-measurable disease only at baseline, categorisation of objective tumor response assessment will be based on the modified RECIST 1.1 criteria of response: CR, PD and Non CR/Non PD.
If the investigator is in doubt as to whether progression has occurred, particularly with response to NTL (non-target lesion) or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

Following progression, patients should continue to be followed up for survival weeks as outlined in the Study Schedule (see Appendix 1).
It is important to follow the assessment schedule as closely as possible.

10.2 Safety assessments

10.2.1 SAFETY EVALUATIONS

Treating physicians are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly & Merck its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The treating physician is responsible for the appropriate medical care of patients while on this study.

The treating physician remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to care received while on this study, or that caused the patient to discontinue from the study. The patient should be followed until the event is resolved or explained. The frequency of follow-up evaluation is left to the discretion of the patient's physician.

10.2.2 Adverse Events

Lack of drug effect is not an AE in this study.
Cases of pregnancy that occur during maternal or paternal exposures to ramucirumab/pembrolizumab should be reported. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

Site personnel will record in the patient's medical record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment.

After the ICF is signed, site personnel will record the occurrence and nature of any AEs targeted for collection in this study. Information on the AEs collected during the patient's time on the Study will be reported to Lilly & Merck or its designee at the time the patient discontinues ramucirumab and pembrolizumab. Adverse events must also be documented at the time of discontinuation and for 30 days after last dose of protocol therapy.

The treating physician will decide whether he or she interprets the recorded AEs as related to disease, study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug or procedure, the following terminologies are defined:

- **Probably related**: A direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly related**: A cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Does not know**: The treating physician cannot determine.
- **Not related**: Without question, the AE is definitely not associated with the study treatment.

The treating physician should classify all "probably related," "possibly related," or "does not know" AEs and SAEs as related to study drug/study procedure.

Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits.

The NCI-CTCAE (v5.0) will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the NCI-CTCAE (v5.0) criteria, the treating physician will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event.

Apart from SAEs and AESIs, only those AEs Grade 3 or worse will be reported at the time the patient discontinues ramucirumab/pembrolizumab therapy.

10.2.3 Serious Adverse Events

A serious adverse event is any AE from this study that results in one of the following outcomes:

- death
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- initial or prolonged inpatient hospitalization
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse event collection begins after the patient has signed informed consent and has received ramucirumab. If a patient experiences an SAE after signing informed consent, but prior to receiving ramucirumab, the event will not be reported as an SAE unless the investigator feels the event may have been caused by a protocol required procedure. Serious adverse events must also be documented at the time of discontinuation and for 30 days after last dose of protocol therapy. Serious adverse events that occur more than 30 days after last dose of protocol therapy must be reported if deemed related to protocol procedures or study drug by the patient's physician.

Study personnel must report SAE to IRB according to the institutional regulation. Lily adheres to procedures for SUSAR records and expedited reporting consistent with worldwide regulations and relevant detailed guidelines. SAE reporting to Merck Global Safety (to: Worldwide Product Safety, FAX :+1-800-547-5552) should be reported within 2 business days but no longer than 3 calendar days of learning of event.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has

worsened after commencing ramucirumab & pembrolizumab therapy.

Planned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

Death due to disease progression should not be reported as an SAE unless the treating physician also deems there to be a contribution possibly related to the study drug.

If a treating physician becomes aware of an SAE occurring after the patient's participation in the study has ended, and the treating physician believes that the SAE is related to ramucirumab and pembrolizumab, the treating physician should report the SAE to the Lilly and Merck, and the SAE will be entered in the pharmacovigilance system.

All SAEs identified while a patient is on this study will be reported to Lilly and Merck as noted above.

10.2.4 Suspected Unexpected Serious Adverse Events

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Development Core Safety Information (DCSI) in the IB and that the treating physician identifies as related to the IP or study procedure. United States 21 Code of Federal Regulations (CFR) 312.32 and European Union Clinical Trial Directive (CTD) 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

10.2.5 Adverse Events of Special Interest (AESIs)

Adverse events of special interest, which may or may not be associated with ramucirumab therapy, include infusion-related reactions, hypertension, arterial or venous thrombotic events, bleeding (hemorrhagic) events, proteinuria, gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome (RPLS), congestive heart failure (CHF), impaired wound healing, and liver failure and other significant liver injury. The worst grade of each of these events, if they occurred, will be reported on the designated CRF at the time the patient discontinues ramucirumab therapy.

10.2.6 Infusion-related Reactions

Infusion-related reactions are defined according to the NCI-CTCAE Version 4.03 definition of

allergic reaction/hypersensitivity, as follows:

- Grade 1: Mild, transient reaction; infusion interruption not indicated; intervention not indicated
- Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDS, narcotics, I.V. fluids); prophylactic medications indicated for ≤24 hours
- Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
- Grade 4: Life-threatening consequences; urgent intervention indicated

Consistent with usual medical practice, selected parenteral medications may be utilized for Grade 2 allergic/hypersensitivity reaction as detailed below.

The following are suggested treatment guidelines for all infusion-related reactions:
Grade 1 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 discretion of the patient's physician.

Grade 2

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

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

Grade 3

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), dexamethasone 8-10 mg I.V. (or equivalent), bronchodilators for bronchospasm, and other medications/treatment as medically indicated.
- Patients who have a Grade 3 infusion reaction must not receive further treatment with ramucirumab.

Grade 4

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), dexamethasone 8-10 mg I.V. (or equivalent), and other medications/treatment as medically indicated.
- Give epinephrine or bronchodilators as indicated.
- Hospital admission for observation may be indicated.
- Patients who have a Grade 4 infusion reaction must not receive further treatment with ramucirumab and will be cared for at the discretion of the treating physician.

The specific infusion related reaction to pembrolizumab will be managed as follows;

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

10.3 Biomarker Evaluation

We will conduct Biomarker Research on specimens collected during this clinical trial. This research may include genetic analyses(DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Genomic analysis: Whole Exome Sequencing at baseline if it is feasible, RNA-seq pre and post (Whole Exome Sequencing/RNA sequencing will be performed at SMC using vendor (Macrogen INC., Korea) and analyzed together with the BI team at SMC with Merck MSD or Lilly.

The objective of collecting specimens for Biomarker Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. Integrative genomic analysis (i.e. gene signature, etc.) measured may be a predictive biomarker for patients who receive pembrolizumab treatment.

Integrative immune-genomic analysis to identify association of response with prevalent markers (e.g. PD-L1 expression, EMT signature, T-cell and cytolytic immune signatures, RNA-seq, hypermutation, cfDNA cancer panel genomics).

Pre and post (on-drug biopsy at 6 weeks): RNA sequencing and cfDNA cancer panel genomics to understand the mechanism of action of pembrolizumab/ramucirumab in responders and non-responders.

Pre and post (at baseline, at 3-week and at 6-week post-treatment) to evaluating immune-priming effect of chemotherapy alone and pembrolizumab:

i) The assessment of plasma or cell free tumor DNA (ctDNA) variant allele frequency (VAF) and tumor mutation burden (TMB) at baseline, at 3-week and at 6-week post-treatment;

ii) The assessment of integrated molecular profiling (including T cells-

CD3+,CD8+,CD45RO+, Tregs-FOXP3+ and macrophages-CD163+, MHC-1, and PDL1 expression) will be assessed using single cell sequencing (blood and tissue) via 10X genomics.

As an exploratory analysis, we will isolate T cells using FACS sorting and sequence these cells. In addition, in order to identify the relationship between neoantigen drivers like infection and response to pembrolizumab, we will prospectively collect serum antigens from blood at baseline. FACS (Cytek) 20-panel antibody will be used.

11. Adverse Events and Dose Modification

11.1 Ramucirumab

11.1.1 Hypertension

If a patient develops hypertension while on protocol therapy, he or she should be treated with antihypertensive medications according to standard medical practice.

Grade <3

- For controlled hypertension (<160/100 mm Hg), ramucirumab therapy should continue without interruption.
- For asymptomatic hypertension, continue ramucirumab with initiation of antihypertensive therapy.
- If the hypertension is associated with symptoms, hold ramucirumab until symptoms resolve and initiate antihypertensive therapy.

If ramucirumab is held for hypertension (ie, symptomatic hypertension, markedly elevated BP unresponsive to antihypertensive therapy), the dose of ramucirumab should be reduced to 6 mg/kg every other week upon re-treatment. A second dose reduction to 5 mg/kg every other week should be undertaken if an additional (third) postponement of therapy is required.

Grade 3 (systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg; medical intervention indicated: more than 1 drug or more intensive therapy than previously used indicated)

- For Grade 3 hypertension not associated with symptoms, continue ramucirumab with more intensive antihypertensive therapy. If systolic BP remains >160 mm Hg or diastolic BP >100 mm Hg more than 2 weeks after initiation of additional antihypertensive therapy (as noted above), study ramucirumab will be held while continuing appropriate antihypertensive therapy.

- If hypertension is associated with symptoms, hold ramucirumab until symptoms resolve and initiate antihypertensive therapy.

If ramucirumab is held more than once for hypertension (ie, symptomatic hypertension, markedly elevated BP unresponsive to antihypertensive therapy), the dose of ramucirumab should be reduced to 6 mg/kg every other week upon re-treatment. A second dose reduction to 5 mg/kg every other week should be undertaken if an additional (third) postponement of therapy is required.

Grade 4 or refractory

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

11.1.2 Thrombotic Events

Physicians should perform all testing required to fully characterize arterial or venous thrombotic/vascular events. In the REGARD study, venous thrombotic events (VTEs) were more frequent on the placebo arm than on ramucirumab (all grade 7.0% versus 3.8%; and Grade 3 or greater 4.3% and 1.3%, respectively). Arterial thrombotic events (ATEs) occurred in patients treated with ramucirumab (1.7% all grade; 1.3% Grade 3 or greater) and in no patients treated with placebo. In RAINBOW, the overall incidence of all grade and Grade ≥3 VTEs and arterial thromboembolic events were low and similar in both treatment arms (ramucirumab plus paclitaxel vs. placebo plus paclitaxel: all grade VTEs [4.0% vs. 5.5%] and Grade 3 or greater VTEs [2.4% vs. 3.3%]; all grade ATEs [1.8% vs. 1.5%] and Grade 3 or greater ATEs [0.9% vs. 0.9%]).

Because therapy with antiangiogenic agents has been shown to be feasible in the setting of anticoagulation in patients with upper GI malignancies (12), patients who develop Grade 3 and 4 venous thrombotic events (deep vein thrombosis [DVT] or pulmonary embolism [PE]) may continue ramucirumab therapy if the event is not considered to be life-threatening in the opinion of the patient's physician, the patient is asymptomatic, and/or the event can be adequately treated with low molecular weight heparin-based therapy.

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

Grade 3 and 4 arterial thromboembolic events, or any PE/DVT occurring or worsening during anticoagulant therapy, require permanent discontinuation of ramucirumab therapy. Any venous

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

11.1.3 Bleeding (Hemorrhagic) Events

Serious hemorrhagic AEs have been reported from clinical studies investigating ramucirumab. Hemorrhagic complications are associated with some malignancies (ie, 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 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, although ongoing surveillance and identification (and exclusion) of patients with high bleeding risk remain essential.

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

11.1.4 Proteinuria

If, while on therapy, a patient has proteinuria ≥2+ per a dipstick or routine UA, a 24-hour urine collection should be conducted. If the protein level is 2g to 3g/24 hours, protocol therapy will be temporarily discontinued for up to 2 weeks and a 24-hour urine collection will be repeated. Ramucirumab will resume at a reduced dose level (6 mg/kg every other week) once the protein level returns to <2 g/24 hours. A second dose reduction (to 5 mg/kg every other week) is permitted if the protein level >2 g/24 hours recurs. 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 <2 g/24 hours within 2 weeks.

11.1.5 Gastrointestinal Perforation

Patients with unresected (or recurrent) primary tumors, mesenteric or peritoneal disease who participate in this clinical trial may be at increased risk for gastrointestinal perforation and/or fistula due to the nature of their metastatic gastric cancer. All cases of perforation and fistula should be reported via the SAE mechanism.

Ramucirumab should be permanently discontinued in the event of a gastrointestinal perforation.

11.1.6 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 (51). 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 (50,52,53). Magnetic resonance imaging represents the most reliable method for the diagnosis (52). Clinical symptoms and MRI abnormalities usually recover within days to weeks with proper management, although permanent neurologic dysfunction has been reported (50,51,52,54).

Reversible posterior leukoencephalopathy syndrome has been associated with multiple clinical conditions including hypertensive encephalopathy, eclampsia, and renal failure with hypertension as well as the use of both immunosuppressive and cytotoxic drugs (51,55). Reversible posterior leukoencephalopathy syndrome has been associated with the use of the anti- VEGF agent bevacizumab, as described in the prescribing information for this agent (54,56).

While the precise pathogenesis of RPLS has not been established, the pathophysiology may involve impaired cerebrovascular autoregulation leading to blood-brain barrier disruption and vasogenic edema (57). Although the pathogenesis of RPLS appears to be multifactorial, drug-induced endothelial damage and acute hypertension are frequently proposed causes of cerebrovascular dysfunction in RPLS (54).

Reversible posterior leukoencephalopathy syndrome should be identified and treated promptly in order to minimize potential for permanent neurological damage. Treatment encompasses careful control of BP, withdrawal of potentially causative medication, and administration of anticonvulsant agents to those experiencing seizures (56).

One SAE of RPLS has been reported in the double-blind, randomized, placebo-controlled Phase 3 colorectal cancer study CP12-0920 (I4T-MC-JVBB). The event was determined to be related to administration of all study drugs, including blinded investigational drug product. (The treatment assignment for this patient remains blinded.) Because hypertension is an identified risk for ramucirumab, physicians should control BP in accordance with established guidelines.

In addition, physicians should consider a diagnosis of RPLS in the setting of seizures, headache, nausea, delirium, visual changes, and/or other unexplained neurological symptoms, especially in combination with hypertension and MRI findings of hyperintensity on T2-weighted and fluid-attenuated inversion recovery images.

No cases of RPLS have been specifically associated with ramucirumab therapy to this time. If the diagnosis of RPLS is confirmed, ramucirumab must be permanently discontinued. All cases of RPLS must be reported via the SAE mechanism.

11.1.7 Congestive Heart Failure (CHF)

An increased risk of CHF has been associated with some antiangiogenic therapeutic agents, particularly in patients with metastatic breast cancer previously/concomitantly treated with anthracyclines or with other risk factors for CHF, including prior radiotherapy to the left chest wall. Findings have ranged from asymptomatic declines in left ventricular (LV) ejection fraction to symptomatic CHF requiring treatment or hospitalization. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as preexisting 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.

11.1.8 Impaired Wound Healing

Impaired wound healing has 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 randomization. Patients with postoperative and other nonhealing wound complications are excluded, as are patients for whom major surgical procedures are planned.

11.1.9 Liver Failure

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.

11.2 Pembrolizumab

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

12. SAMPLE SIZE

Sample Size Calculation

A maximum of 26 patients will be recruited to this single-arm phase II trial. The primary endpoint of this trial is overall response (OR=PR+CR).

In this single-arm phase II trial, 25 people were calculated using Simon's two-stage design and a total of 26 patients will be recruited to account for a 5% dropout rate.
The sample size is calculated by use of a two-stage minimax Simon's design to control the type I error at 5 % for null hypothesis that, for arm, the true response was 15 % or below and to have 85 % of power if the true response was 40 % or higher. 15 evaluable patients are to be treated in the first stage. If 1 or fewer response are observed in the first stage, the arm will be stopped. If at least 2 responses are observed in the first stage, 10 additional evaluable patients are to be entered onto the second stage. At the final analysis, the null hypothesis will be rejected if at least 7 responses are observed in 25 evaluable patients. RR is reported with its exact 95% CI.

13. STATISTICAL ANALYSIS PLAN

13.1 Efficacy

13.1.1 ORR

The intention to treat (ITT) population included all patients who received at least one dose of any study treatment. ORR was calculated with two-sided 95% confidence intervals for the overall population. ORR was defined as (CR + PR)/(number of ITT population).

13.1.2 Biomarker

To explore and identify biomarkers (inform the scientific understanding of diseases and/or their therapeutic treatment), the contingency tables will be presented by response for each of tumor histology, molecular signatures, immune pathways and etc..

13.2 Safety

Safety will be assessed by clinical review of all relevant parameters including, adverse events (AEs), laboratory tests, vital signs, etc.
No statistical hypothesis tests will be performed on safety variables. These will be summarized by descriptive statistics or categorical tables.

14.Clinical Tests

14.1 Laboratory Parameters

All laboratory tests will be performed at local labs and should be done to ensure patients meet all eligibility criteria and criteria to continue on the protocol:

Hematology Profile – Includes a complete blood count with differential and platelet count.

Coagulation Profile – Includes INR, prothrombin time, and PTT.

Chemistry Profile – Includes creatinine, AST, ALT, alkaline phosphatase, total protein, and bilirubin.

NOTE: If pretreatment serum creatinine is >1.5 times the ULN, calculate creatinine clearance

Urinalysis – Includes routine UA or dipstick measurements and, if clinically indicated, microscopic analysis

Serum -HCG Pregnancy Test – Minimum sensitivity 25 IU/L or equivalent units of β-HCG, to be performed within 28 days prior to enrollment for WOCBP.

TFT Test - T3, FT4 and TSH

14.2 Other Tests and Evaluations

Echocardiogram– Pretreatment only, to be obtained within 28 days prior to enrollment **only** for patients who have received prior anthracycline therapy. Subsequent evaluations are not required, but may be done at the discretion of the patient's physician if warranted by dyspnea or other relevant symptoms.

14.3 Symptomatic Deterioration (Clinical Progression)

deterioration in ECOG PS of ≥2 units compared to baseline is criteria for removal from ramucirumab and pembrolizumab therapy. Patients may also be removed from therapy if the attending physician determines any clinical deterioration is such that it is not in the patient's best interest to continue on therapy

14.4 Determination of Overall Response

No other evaluation of disease control will be requested. At discontinuation, information about planned subsequent therapy will be collected.

15. LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

15.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.
Clinical Supplies will be provided by Lilly and Merck as summarized in Table.

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection
Ramucirumab 100mg	1vial(10mL), Solution for Injection
Ramucirumab 100mg	1vial(50mL) Solution for Injection

15.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

15.3 Clinical Supplies Disclosure

15.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

15.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

16. INFORMED CONSENT, ETHICAL REVIEW AND REGULATORY CONSIDERATIONS

16.1 Informed Consent

The patient's physician is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of ramucirumab. Each patient or the patient's legally acceptable representative will be required to read, agree to, and sign a current Institutional Review Board (IRB) approved informed consent form (ICF) prior to being enrolled and/or before any Study -related procedure is performed.

16.2 Ethical Review

Documentation of IRB approval of the protocol and the ICF must be provided to Lilly or its

designee before the study may begin at that site. .

16.3 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that IRB, or regulatory authority representatives may consult trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

16.4 Confidentiality of Data

By signing this protocol, the investigator affirms to the investigator that information furnished will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

16.5 Data Handling

To enable evaluations and/or audits from regulatory authorities, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

17. MONITORING

A clinical monitoring will make regularly scheduled trips to the investigational site to review the progress of the trial. The actual frequency of monitoring trips will depend on the enrollment rate and performance at each site. The investigator will allow monitor, and/or its representatives of designees, access to all pertinent medical records in order to allow for the verification of data gathered in the CRFs and for the review of the data collection process. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

18. Sample Identification

The residual (excess) samples (DNA, RNA) will be stored at the site according to the regulations, up to the retention period specified by the subject in the consent form. Residual samples can be analyzed for research purposes using the next generation gene analysis technique.
However, privacy and De - identification will be thorough.The collected samples are recognized by coded numbers and the participation of this clinical study only collects personal information, such as the subject's name, but that information is not directly used or required by the study. Therefore, the collected information is properly managed under the Privacy Act.

Upon expiration of the retention period determined by subject, the human-derived material shall be destroyed in accordANCe with the standards and methods per the [Wastes Control Act] Article 13.

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APPENDIX 1

Procedure	Screening[a]	Treatment Cycles (1cycle = 42days)						EOT	Follow-Up	
		Cycle 1				Cycle 2~			Post-Treatment Follow-Up	Survival Follow-up
		D1	D15	D22	D29	D1	D22			
	-28 to -1	±3				±3		±3	±3	±7
Informed Consent	X									
Eligibility	X									
Medical/Oncologic History(including record of preexisting toxicity, if any	X									
Pregnancy Test	X[d]									
ECG	X[e]					X[i]				
ECOG PS	X	X	X	X	X	X	X			
Echocardiogram/MUGA	X[m]									
Physical Exam, Height, Weight	X	X	X	X	X	X	X			
Vital Signs (blood pressure, pulse rate, respiration rate, temperature) g	X	X	X	X	X	X	X	X		
Toxicity Assessments/Adverse Events	X	X	X	X	X	X	X	X[j]	X[j]	
Hematology Profile	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X		
Coagulation Profile	X	X	X	X	X	X	X	X		
Chemistry Profile	X	X	X	X	X	X	X	X		
Urinalysis	X					X		X		
T3, FT4 and TSH	X					X				
Imaging (CT/MRI)	X[f]					X[f]		X		
Tumor Assessments(CEA,CA19-9)	X[f]					X[f]		X[j]		
Administer Ramucirumab		X[k]	X[k]		X[k]	X[k]				
Administer Pembrolizumab		X[k]		X[k]		X[k]	X[k]			
Fresh biopsy specimens[n]	X							X		
Blood for genomics (10 ml ACD)[O]	X					X		X		
Survival follow up										X

Post-Enrollment Evaluations

Frequency of Post-Enrollment Evaluations

a. Screening will be performed within 28 days prior to enrollment, unless otherwise specified.

b. Treatment cycle defined herein as 6 weeks; however, there will be no treatment interruption or break between cycles. Patients will continue to undergo treatment according to program protocol until there is evidence of disease progression, toxicity requiring cessation, withdrawal of consent, or until other withdrawal criteria are met.

c. End of therapy evaluations will be performed at the discontinuation of therapy; patients should be followed for at least 30 days after last dose of protocol therapy to ensure sufficient safety monitoring and any AEs reported unless another therapy has been commenced **and** the AE is thought related to post-program therapy. Written informed consent must be obtained prior to any program-specific pretreatment evaluations and before patient enrollment.

d. WOCBP must have a negative serum pregnancy test within 7 days prior to enrollment.

e. To be obtained within 28 days prior to enrollment only for patients with prior anthracycline therapy. Subsequent evaluations are not required, but may be done at the discretion of the patient's physician if warranted by dyspnea or other relevant symptoms.

f. Baseline imaging to determine the extent of disease and identify metastases, and tumor assessments should be performed within 14 days prior to enrollment, and every 6 weeks (±3 days) until documented progression for patients with disease status of complete response (CR), partial response (PR), or stable disease (SD), and/or for patients who have discontinued program therapy due to toxicity or reasons other than progressive disease.

g. Including temperature, pulse rate, respiration rate, and blood pressure; to be obtained before, during, and at the completion of each infusion.

h. In situations where hemoglobin is less than 9 g/dL (5.58 mmol/L) and there are signs or symptoms of bleeding, a hematology profile should be performed weekly until hemoglobin is ≥9 g/dL (5.58 mmol/L) and any bleeding-related signs or symptoms have resolved or been adequately investigated.

i. Every 6 weeks or in accordance with local regulations, whichever is of shorter duration.

j. All SAEs considered at least possibly related to ramucirumab and pembrolizumab will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.

k It is recognized that in the course of clinical cancer care, it is not always possible to schedule therapeutic infusions precisely 2 weeks-ramucirumab/3 weeks-pembrolizumab following a prior infusion (because of holidays, travel difficulties, or other circumstances). Accordingly, infusions administered within 3 days before or after the planned time point are acceptable. Administration beyond this window is strongly discouraged.

m. Should be completed if patients had received prior anthracycline therapy.

n. Fresh tissues will be obtained: preferably from endoscopy. tissue will be collected for DNA/RNA sequencing at baseline and at progression(if Feasible). For ascites, 1 liter of ascites will be collected at baseline and progression and malignant cells will be isolated. For pleural effusion 500 cc to 1 liter will be collected. Any combination of endoscopic biopsy and ascites/pleural/CSF etc will be allowed in the protocol.

o. Blood sample for genomics should be collected at baseline and every cycle(q6weeks) treatment discontinuation.

Appendix 2 (Cyramza Safety Language)

The following items MUST be included in the appropriate Inclusion/Exclusion Criteria/Discontinuation sections as well as in the text of the appropriate or corresponding section of the protocol:

Hematologic Function

To be included in a ramucirumab clinical trial:

The patient has adequate hematologic function, as evidenced by an absolute neutrophil count (ANC) ≥1500/μL, hemoglobin ≥9 g/dL (5.58 mmol/L), and platelets ≥100,000/μL.

Coagulation:

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

For Ramucirumab combined with Chemotherapy studies:

Coagulation: 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.

To be excluded from a ramucirumab clinical trial:

The patient has experienced any Grade 3-4 GI bleeding within 3 months prior to first dose of protocol therapy.

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.

Discontinuation of patient from a ramucirumab clinical trial:

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

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

Hepatic Function

To be included in a ramucirumab clinical trial:

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

To be excluded from a ramucirumab clinical trial:

The patient has:

- 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.

Discontinuation of a patient from a ramucirumab clinical trial:

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.

Renal Function

To be included in a ramucirumab clinical trial:

The patient has adequate renal function as defined by a serum creatinine ≤1.5 times the ULN, or creatinine clearance (measured via 24-hour urine collection) ≥40 mL/minute (that is, if serum creatinine is >1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed). (unless IIT designed to study ramucirumab administration in patients with renal impairment).
The patient's urinary protein is ≤1+ on dipstick or routine urinalysis (UA; if urine dipstick or routine analysis is ≥2+, a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours to allow participation in this protocol).

Discontinuation of a patient from a ramucirumab clinical trial:

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 <2 g/24 hours within 2 weeks.

Cardiac Function

To be excluded in a ramucirumab clinical trial:

The patient has experienced any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to first dose of protocol therapy.
The patient has uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management.

Discontinuation of a patient from a ramucirumab clinical trial:

Patients with grade 4 hypertension must not receive further treatment with Ramucirumab.

Reproductive Precautions

To be included in a ramucirumab clinical trial:

Because the teratogenicity of ramucirumab is not known, the patient, if sexually active, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods). Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to first dose of protocol therapy.

To be excluded from a ramucirumab clinical trial:

The patient is pregnant or breast-feeding.

The patients with lung cancer (NSCLC and SCLC) regardless of tumor histology should be excluded from a ramucirumab clinical trial:

If they experience hemoptysis (defined as bright red blood or ≥ 1/2 teaspoon) within 2 months prior to first dose of protocol therapy or with radiographic evidence of intratumor cavitation or has radiologically documented evidence of major blood vessel invasion or encasement by cancer.

General Medical Disorders

Discontinuation of a patient from a ramucirumab clinical trial:

Patients with grade 3 or 4 infusion-related reactions must not receive further treatment with ramucirumab.

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

If Reversible Posterior Leukoencephalopathy (RPLS) is diagnosed, ramucirumab must be permanently discontinued. All cases of RPLS must be reported via the SAE mechanism.

Prior Medical History Precautions

To be excluded from a ramucirumab clinical trial:

The patient has a prior history of GI perforation/fistula (within 6 months of first dose of protocol therapy) or risk factors for perforation.

The patient has a serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy.

The patient has undergone major surgery within 28 days prior to first dose of protocol therapy, or minor surgery/subcutaneous venous access device placement within 7 days prior to the first dose of protocol therapy. The patient has elective or planned major surgery to be performed during the course of the clinical trial.

Concomitant Medication Precautions

To be excluded from a ramucirumab clinical trial:

The patient is receiving chronic antiplatelet therapy, including dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.

Serious Adverse Event Reporting

The following needs to be included in your protocol regarding reporting of serious adverse events to Lilly:

- to comply with applicable laws, regulations and standards regarding Investigator's and Institution's obligations, as the sponsor of the Study, to collect and report adverse events to regulatory authorities, IRBs, Ethics Committees or other third parties. In addition to the obligations set forth below, Investigator and Institution agree to provide Lilly with a copy of all information Investigator and/or Institution submit to regulators related to any adverse events for the Study Drug that occur during the Study that Investigator and/or Institution have not otherwise provided Lilly;

- to notify Lilly, sub-investigators, and the IRB of any problems involving risk to Study patients and report new safety information to IRBs in accordance with applicable requirements;

- to notify Lilly within fifteen (15) business days of Investigator and/or Institution receiving notification of any "serious" and/or "unexpected" adverse event experienced by a patient participating in the Study and receiving Study Drug that is possibly related, based on Investigator's assessment, to the Study Drug. For purposes of this requirement, "serious" means: (1) death; (2) in-patient hospitalization or prolonged hospitalization; (3) life-threatening; (4) persistent or significant disability or incapacity; (5) congenital anomaly or birth defect; or (6) other serious events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other five listed outcomes. Serious adverse events should be reported to Lilly using a CIOMS Form or other form acceptable to Lilly. Investigator and Institution further agree to make available promptly to Lilly such records as may be necessary and pertinent for Lilly to further investigate an adverse event in the Study that is possibly associated with the Study Drug;