Title: A Phase 1b/2 Study of Ramucirumab in Combination with LY2875358 in Patients with Advanced Cancer.

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1. Protocol I4C-MC-JTBF(b)

A Phase 1b/2 Study of Ramucirumab in Combination with LY2875358 in Patients with Advanced Cancer

Confidential Information

Generic Names: Ramucirumab (IMC-1121B; LY3009806) and LY2875358

This Phase 1b/2 study is a multicenter, non-randomized, open-label, dose escalation study to determine a recommended schedule and dose range for LY2875358 that may be safely administered in combination with a fixed regimen of ramucirumab to patients with advanced and/or metastatic cancer (Part A), followed by tumor-specific expansion cohorts for gastric or gastroesophageal junction adenocarcinoma, hepatocellular carcinoma, or renal cell cancer for dose confirmation and exploration of clinical activity (Part B).

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Protocol Approved by Lilly: 28 October 2013
Amendment (a) Approved by Lilly: 15 September 2014
Amendment (b) Electronically Signed and Approved by Lilly on approval date provided below.

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2. Synopsis

This Phase 1b/2 study is a multicenter, nonrandomized, open-label, dose-escalation study to determine a recommended schedule and dose range for LY2875358 that may be safely administered in combination with a fixed regimen of ramucirumab to patients with advanced and/or metastatic cancer (Part A), followed by tumor-specific expansion cohorts for gastric or gastroesophageal junction adenocarcinoma, hepatocellular carcinoma, renal cell cancer patients, or non-small cell lung cancer for dose confirmation and exploration of clinical activity (Part B). During the first cycle (28 days), the dose-limiting toxicities will be assessed and potential chronic toxicity will be evaluated for the entire treatment period.

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4. Abbreviations and Definitions

Term	Definition
AE	Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
$AUC_{T,ss}$	area under the concentration-time curve during the dosing interval at steady state
audit	A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BP	blood pressure
BSC	best supportive care
CHF	congestive heart failure
CI	confidence interval
CL	systemic clearance
CNS	central nervous system
collection database	A computer database where clinical trial data are entered and validated.
complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CR	complete response
CRF/eCRF	case report form/electronic case report form: Sometimes referred to as clinical report form, a printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician
CRS	clinical research scientist
Css,max	maximum concentration at steady state
Css,min	minimum concentration at steady state
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DCSI	Development Core Safety Information
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least one dose of study treatment.
enter	Patients who are entered in the trial are those who have signed the informed consent form directly
ERB/IRB	ethical review board/institutional review board: /A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
FDG-PET	2-deoxy-2[F-18]fluoro-D-glucose positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in-situ hybridization

GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factors
GEJ	gastroesophageal junction
GI	gastrointestinal
HGF	hepatocyte growth factor
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
IHC	immunohistochemistry
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form (ICF).
INR	International Normalized Ratio
interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for datalock.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	intravenous(ly)
Lilly Safety System (LSS)	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal epithelial transition factor
MET ECD	extracellular cleaved domain of MET

monitor	A person responsible for ensuring the investigator site complies with the monitoring plan, applicable local SOPs (if any), and global Medical SOPs. Monitors are trained on the investigational product(s), the protocol, informed consent document, any other written information provided to subjects, relevant SOPs, International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP), and all applicable laws (for example, privacy and data protection) and regulations.
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participants are aware of the drug therapy received during the study.
ORR	overall response rate
OS	overall survival
patient	A subject with a defined disease.
PCR	polymerase chain reaction
PD	pharmacodynamic
PFS	progression-free survival
PK	pharmacokinetic(s)
PlGF	placental growth factor
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
QTc	corrected QT
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.

re-screen	To screen a patient who was previously declared a screen failure for the same study
RP2D	recommended Phase 2 dose
RPLS	reversible posterior leukoencephalopathy syndrome
RR	response rate
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, scans, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	A patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SE	standard error
sponsor	The party who takes responsibility for the initiation, management and/or financing of a clinical study.
study completion	This study will be considered complete following the final analysis.
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TMDD	Target-Mediated Drug Disposition
TPO	third-party organization
ULN	upper limit of normal
V	volume of distribution
VEGF	vascular endothelial growth factor
VEGFR-2	vascular endothelial growth factor receptor-2
VTE	venous thromboembolic event

A Phase 1b/2 Study of Ramucirumab in Combination with LY2875358 in Patients with Advanced Cancer

5. Introduction

5.1. MET Activation by Anti-angiogenic Therapy

Most angiogenesis inhibitors used in the treatment of cancer block the actions of vascular endothelial growth factor (VEGF) or its receptor, vascular endothelial growth factor receptor-2 (VEGFR-2), which is overexpressed in the majority of human cancers. Treatment with anti-VEGF or VEGFR-2 monoclonal antibodies (mAbs) delays progression and prolongs the survival of patients (Ferrara and Kerbel 2005; Ellis and Hicklin 2008; Fuchs et al. 2013). However, inhibition of VEGF signaling is accompanied by increased invasiveness and metastasis in some preclinical models (Rubenstein et al. 2000; Casanovas et al. 2005; Ebos et al. 2009; Paez-Ribes et al. 2009). The mechanism of the exaggerated aggressiveness is unknown, but contributing factors could be vessel pruning, hypoxia, and increased expression of the mesenchymal epithelial transition factor (MET), the tyrosine kinase receptor for the hepatocyte growth factor (HGF) (Bottaro and Liotta 2003; Pennacchietti et al. 2003). The HGF/MET pathway promotes tumor cell motility, proliferation, survival, invasion, and metastasis (Benvenuti and Comoglio 2007; Trusolino et al. 2010). Mesenchymal epithelial transition factor is overexpressed, activated, amplified, or mutated in a wide variety of solid tumors (Graveel et al. 2009; Ponzo et al. 2009; Trusolino et al. 2010), is correlated with poor prognosis (Ghoussoub et al. 1998; Lengyel et al. 2005; Sawada et al. 2007; Kong et al. 2009), and is thought to contribute to a tumor's aggressiveness and resistance to therapy (Lai et al. 2009; Xu et al. 2010).

Preclinical animal studies recently demonstrated that MET expression is upregulated in response to anti-angiogenic treatment (Piao et al. 2013). The highest upregulation was seen in tumors that become resistant to anti-angiogenic therapy. Invasion and metastasis promoted by selective inhibition of VEGF signaling can be reduced by the concurrent inhibition of MET. Inhibition of VEGF signaling by function-blocking antibodies slows tumor growth but increases intratumoral vascular pruning, hypoxia, HIF-1α accumulation, MET activation, and change to a more mesenchymal tumor cell phenotype favoring a more aggressive tumor biology. In particular, hypoxia is known to increase MET expression in tumor cells through HIF-1α binding sites on the c-Met promoter (Pennacchietti et al. 2003). This phenotype of heightened tumor aggressiveness did not occur when MET inhibitors were co-administered with an anti-VEGF antibody or with sunitinib. The simultaneous pharmacological inhibition of MET and VEGF signaling not only slowed tumor growth but also reduced invasion and metastasis (Sennino et al. 2012). Concurrent inhibition of MET and VEGF signaling substantially prolonged the survival of mice over vehicle or anti-VEGF antibody alone (Sennino et al. 2012).

Similar to the reported literature, preclinical studies with the murine equivalent of the VEGFR-2 targeting antibody ramucirumab, DC-101, and the MET targeting humanized antibody LY2875358 resulted in statistically significant increases in antitumor activity in a gastric cancer

xenograft model (data on file). This cumulative evidence from preclinical models provides a clear rationale for simultaneous inhibition of MET and VEGF signaling as a potential therapeutic strategy, and fosters the hypothesis that the addition of LY2875358 to ramucirumab (LY3009806, IMC-1121B; hereafter referred to as ramucirumab) might counteract the emergence of a more aggressive phenotype induced by MET upregulation in response to anti-angiogenic treatment by ramucirumab.

This Phase 1b/2 study (I4C-MC-JTBF [JTBF]) will evaluate a recommended schedule and dose range for LY2875358 that may be safely administered in combination with ramucirumab to patients with advanced and/or metastatic cancer (Part A), followed by tumor-specific expansion cohorts for gastric or gastroesophageal junction (GEJ) adenocarcinoma, hepatocellular carcinoma (HCC), renal cell cancer or non-small cell lung cancer (NSCLC) patients for dose confirmation and exploration of clinical activity (Part B). The tumor types for expansion cohorts were selected based on clinical activity observed in Phase 2 or 3 trials for ramucirumab monotherapy in these tumor types, as outlined in Section 5.2.1; these tumors are also ones in which there exists preclinical and clinical evidence indicating that VEGFR-2 and MET signaling contribute to cancer pathogenesis.

5.2. Introduction to Study Drugs

Both ramucirumab and LY2875358 have been previously evaluated as monotherapy in separate clinical studies, and a recommended schedule and dose range for monotherapy has been determined for each of the 2 antibodies. Detailed information about the characteristics of ramucirumab and LY2875358 are provided in the respective Investigator's Brochures (IBs). The following sections provide a summary of the information most relevant to this Phase 1b/2 study (JTBF).

5.2.1. Ramucirumab

Ramucirumab is a recombinant human immunoglobulin G, subclass 1 mAb that specifically binds to the extracellular domain of VEGFR-2 with high affinity. This antibody potently blocks the binding of VEGF ligands to VEGFR-2, inhibits VEGF-stimulated activation of both VEGFR-2 and p44/p42 MAP kinases, and neutralizes VEGF-induced proliferation and migration of human endothelial cells.

The results of these preclinical pharmacodynamic studies supported the initial investigation of ramucirumab in the treatment of solid tumors.

Clinical investigations with ramucirumab in solid tumors have resulted in 4 positive Phase 3 trials, with 2 in gastric cancer (REGARD and RAINBOW), 1 in NSCLC (REVEL), and 1 in metastatic colorectal cancer (CRC; RAISE). Ramucirumab (Cyramza®) is approved in the United States as a single agent or in combination with paclitaxel as a treatment for people with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose cancer has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy, and in combination with docetaxel as a treatment for people with metastatic NSCLC whose cancer has progressed on or after platinum-based chemotherapy. In addition, the European Commission

approved ramucirumab (Cyramza) in combination with paclitaxel and as a single agent when combination therapy is not appropriate, for people with advanced gastric cancer after prior chemotherapy.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of ramucirumab may be found in the IB. Information on AEs expected to be related to ramucirumab may be found in Section 7 (Development Core Safety Information [DCSI]) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

5.2.1.1. Ramucirumab and Gastric or GEJ Adenocarcinoma

Study I4T-IE-JVBD (JVBD; also known as REGARD) was the pivotal study comparing ramucirumab plus best supportive care (BSC) versus placebo plus BSC in the treatment of advanced gastric or GEJ adenocarcinoma following disease progression during or following first-line platinum- or fluoropyrimidine-containing combination therapy (Fuchs et al. 2013). Study JVBD was a global, Phase 3, multicenter, randomized, double-blind, placebo-controlled study that examined single-agent ramucirumab 8 mg/kg given every 2 weeks (Q2W) in combination with BSC in patients with histologically or cytologically confirmed metastatic or locally recurrent, unresectable gastric or GEJ adenocarcinoma. A total of 355 patients were randomized in a 2:1 ratio to receive ramucirumab plus BSC or placebo plus BSC. The study met its primary endpoint of overall survival (OS), demonstrating a statistically significant and clinically relevant improvement with ramucirumab. Ramucirumab, as a single agent, reduced the risk of death in this population by 22% (hazard ratio [HR] = 0.776; 95% confidence interval [CI], 0.603-0.998; p=0.0473), resulting in a 37% longer median OS in the ramucirumab arm than in the placebo arm (5.2 months vs. 3.8 months, respectively). Improvement in OS with ramucirumab was accompanied by statistically significant improvements over placebo in median progression-free survival (PFS) and PFS at 12 weeks. Treatment with ramucirumab significantly reduced the risk of disease progression or death by 52% (HR = 0.483; 95% CI, 0.376-0.620; p<0.0001), resulting in a 62% longer median time to disease progression in the ramucirumab arm than in the placebo arm (2.1 months vs. 1.3 months, respectively). Progression-free survival at 12 weeks was 40.1% in the ramucirumab arm and 15.8% in the placebo arm (p<0.0001). No difference in terms of response rate (RR) were observed between the 2 treatment arms (3% RR for both arms). Rates of hypertension were higher in the ramucirumab arm than in the placebo arm (16% vs. 8%, respectively), whereas rates of other AEs were mostly similar between treatment arms (94% vs. 88%, respectively). Ramucirumab is the first biological treatment given as a single drug that has survival benefits in patients with advanced gastric or GEJ adenocarcinoma progressing after first-line chemotherapy.

5.2.1.2. Ramucirumab and Hepatocellular Cancer

In the Phase 2 Study I4T-IE-JVBQ (JVBQ), patients with unresectable HCC who had not received prior systemic anticancer therapy were enrolled to assess the efficacy and safety of ramucirumab as first-line therapy (Zhu et al. 2013). A total of 42 adult patients received

ramucirumab 8 mg/kg Q2W until disease progression or limiting toxicity in this single-arm study. The primary endpoint was PFS; secondary endpoints included objective RR and OS. The median PFS was 4.0 months (95% CI, 2.6-5.7]). The RR was 9.5% (95% CI, 2.7-22.6) (4/42 patients had a partial response [PR]), and the median OS was 12.0 months (95% CI, 6.1-19.7). For patients with Barcelona Clinic Liver Cancer stage C disease, the median OS was 4.4 months (95% CI, 0.5-9.0) for patients with Child-Pugh B cirrhosis versus 18.0 months (95% CI, 6.1-23.5) for patients with Child-Pugh A cirrhosis. Treatment-related Grade ≥3 toxicities included hypertension (14%), gastrointestinal (GI) hemorrhage and infusion-related reactions (7% each), and fatigue (5%). There was 1 treatment-related death (GI hemorrhage). After treatment with ramucirumab, there was an increase in serum VEGF and placental growth factor (PlGF) and a transient decrease in soluble VEGFR-2.

A randomized, controlled Phase 3 trial (Study I4T-IE-JVBF; Study JVBF, also known as REACH) of ramucirumab monotherapy versus placebo in a second-line setting (post-sorafenib) for advanced HCC is currently ongoing (NCT01140347). Study JVBF is a global, randomized, double-blind Phase 3 study of ramucirumab plus BSC compared to placebo and BSC as a second-line treatment in patients with HCC who have been previously treated with sorafenib in the first-line setting. The study did not meet its primary endpoint of OS; although the OS results favored the ramucirumab arm, they were not statistically significant. Encouraging single-agent ramucirumab activity was observed, with meaningful improvements in key secondary endpoints of PFS, objective response rate (ORR), and time to progression (TTP).

5.2.1.3. Ramucirumab and Renal Cell Carcinoma

Multi-targeted tyrosine kinase inhibitors (TKIs) have antitumor activity in metastatic renal cell carcinoma. Resistance to these agents develops frequently and their use is often limited by intolerance (Sternberg et al. 2010; Rini et al. 2011). Study I4T-IE-JVBP (JVBP) investigated the clinical efficacy and safety of ramucirumab in patients with TKI-resistant/intolerant metastatic renal cell carcinoma (Garcia et al. 2013). In this single-arm Phase 2 trial, patients received ramucirumab 8 mg/kg Q2W until disease progression or intolerable toxicity. The majority of patients (89.7%) had received prior sunitinib, either as the only prior TKI or prior to/following sorafenib. The primary endpoint was RR. Thirty-nine renal cell carcinoma patients received ramucirumab monotherapy. The RR was 5.1% (95% CI, 0.6%-17.3%). The 12-week disease control rate (DCR) was 64.1% (95% CI, 47.2%-78.8%). Median PFS and OS were 7.1 months (95% CI, 4.1-9.7) and 24.8 months (95% CI, 18.9-32.6), respectively. Grade 3 or higher AEs occurring in ≥5% of patients included Grade 3 hypertension (7.7%) and proteinuria (5.1%). There was 1 on-study death from multi-organ failure. Although the study did not meet its primary endpoint of ≥15% RR, ramucirumab was associated with evidence of antitumor activity in patients with TKI-resistant/intolerant metastatic renal cell carcinoma. Ramucirumab was safe and well tolerated in the study.

5.2.1.4. Ramucirumab and Non-Small Cell Lung Cancer

Ramucirumab was studied in a pivotal randomized, double-blind, Phase 3 study for NSCLC patients (Study JVBA; also known as REVEL). The REVEL study evaluated the efficacy and safety of ramucirumab plus docetaxel versus placebo plus docetaxel in the second-line treatment

of Stage IV nonsquamous and squamous NSCLC following disease progression after one prior platinum-based therapy (Perol et al. 2014). A total of 1,253 patients (26.2% squamous) were randomized in a 1:1 ratio to receive docetaxel 75 mg/m^2 in combination with either ramucirumab 10 mg/kg or placebo on day 1 of a 21-day cycle until disease progression, unacceptable toxicity, or death. The study met its primary endpoint of OS, demonstrating a statistically significant and clinically relevant improvement for the ramucirumab combination arm. The OS HR was 0.857 (95% CI 0.751, 0.98; P=0.0235) with a median OS of 10.5m for ramucirumab plus docetaxel versus 9.1m for docetaxel. The OS was longer for ramucirumab plus docetaxel in most patient subgroups, including squamous and non-squamous histology. Secondary efficacy endpoints included PFS and ORR. The HR for PFS was 0.762 (P<0.0001) with a median PFS of 4.5 months for ramucirumab plus docetaxel versus 3.0 months for docetaxel. The ORR was 22.9% for ramucirumab plus docetaxel and 13.6% for docetaxel (p<0.001). The patient characteristics were balanced between both arms. Grade ≥3 AEs occurring in >5% of patients on ramucirumab plus docetaxel were neutropenia (34.9% vs. 28.0%), febrile neutropenia (15.9% vs. 10.0%), fatigue (11.3% vs. 8.1%), leukopenia (8.5% vs. 7.6%), hypertension (5.4% vs. 1.9%), and pneumonia (5.1% vs. 5.8%). Grade 5 AEs were comparable between arms (5.4% vs. 5.8%), as was pulmonary hemorrhage (any grade; all patients: 2.1% vs. 1.6%; squamous patients: 3.8% vs. 2.4%). In conclusion, REVEL demonstrated a statistically significant improvement in ORR, PFS, and OS for ramucirumab in combination with docetaxel versus docetaxel in NSCLC patients with Stage IV NSCLC as second-line treatment after platinum-based therapy.

5.2.2. LY2875358

LY2875358 is a humanized immunoglobulin G, subclass 4 bivalent mAb that can block signaling of the HGF/MET pathway via 2 modes of action. LY2875358 blocks ligand-dependent and ligand-independent MET signaling as demonstrated in preclinical studies described in the IB. Ligand-dependent activation of the MET pathway is impaired upon binding of LY2875358 to MET by limiting HGF interaction with the receptor. In addition, binding of LY2875358 to MET causes receptor internalization and degradation of MET resulting in suppression of ligand-independent activation of MET.

LY2875358 has been evaluated in the first-in-human Phase 1 Study I4C-MC-JTBA (JTBA) and the Phase 1 Study I4C-JE-JTBD (JTBD) in Japanese patients, with the primary objective being to determine a recommended Phase 2 dose (RP2D) range of LY2875358 as monotherapy and in combination with erlotinib. In both studies, LY2875358 was administered intravenously (IV) Q2W using a flat dosing scheme at doses of up to 2000 mg as monotherapy and in combination with erlotinib. As of 18 March 2014, cumulatively 184 subjects have received LY2875358 in the 6 ongoing clinical trials, including 123 patients receiving LY2875358 monotherapy. No dose-limiting toxicities (DLTs) have been reported for either LY2875358 monotherapy or for combination therapy with erlotinib in in the dose escalation Studies JTBA and JTBD. The most frequently reported treatment-emergent adverse events (TEAEs) possibly related to LY2875358 monotherapy across all studies within the LY2875358 clinical program include fatigue (16.3%), nausea (9.8%), diarrhea (5.7%), and peripheral edema (5.7%). A total of 7 possibly related TEAEs (≥Grade 3) for LY2875358 monotherapy were reported: 2 events of fatigue and 1 event

each of peripheral edema, pancreatitis, anemia, nausea, and hyponatremia. A total of 87 SAEs have been reported in the Lilly Safety System (LSS) database in Studies JTBA and JTBD as of 18 March 2014. Of these SAEs, 5 were considered possibly related to LY2875358 by either the investigator or the sponsor, including 1 event each of thrombocytopenia, pancreatitis, dyspnea, pyrexia, and peripheral edema in a patient with pre-existing edema.

The RP2D range of LY2875358 was determined in Study JTBA and JTBD to be between 700-2000 mg IV Q2W for monotherapy. For Phase 2 studies, a dose of 750 mg Q2W was selected because this dose is predicted to saturate MET receptors in patients with cancer and achieve exposures sufficient to yield maximal MET inhibition and tumor growth inhibition in vivo.

In Study JTBA, a durable confirmed PR according to Response Evaluation Criteria in Solid Tumors (RECIST) has been observed for LY2875358 monotherapy in a patient with metastatic transitional cell carcinoma enrolled at 700 mg LY2875358 in the dose-escalation segment (data on file). Five additional patients (21.7%) demonstrated stable disease (SD) as their best overall response for LY2875358 monotherapy in the dose escalation portion of Study JTBA.

Study JTBA has been amended and is currently enrolling patients in 5 different tumor-specific expansion cohorts for dose confirmation of LY2875358 monotherapy at 2000 mg Q2W, including cohorts for renal cancer and HCC patients (approximately 15 patients each). In the renal cell cancer cohort, 3 out of 15 evaluable patients demonstrated SD as their best response, including a papillary renal cancer patient who has been on study for 12 months as of October 2013 (data on file). Further durable, confirmed PRs for LY2875358 monotherapy have been observed in a patient enrolled in the HCC cohort and for a patient in the uveal melanoma with liver metastases cohort. No data are so far available for LY2875358 monotherapy in gastric cancer patients, as the Asian gastric cancer patient study for LY2875358 monotherapy (Study I4C-JE-JTBE) is pending analysis.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) for ramucirumab and LY2875358 may be found in the respective molecule IBs. Information on AEs expected to be related to the investigational products may be found in Section 7 DCSI of the respective IBs. Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the respective IBs.

5.3. Rationale for Study I4C-MC-JTBF

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. Given these requirements, the rationale for this study is based on the following:

- Published preclinical data supporting the concept of blocking MET signaling to counteract the emergence of a more aggressive phenotype induced by MET upregulation in response to anti-angiogenic treatment
- The clinical efficacy observed for ramucirumab in gastric, hepatocellular, renal cell and non-small cell lung cancers

- in Phase 2 and/or Phase 3 studies
- The initial clinical activity of LY2875358 monotherapy with PRs and SDs in advanced/metastatic cancer patients in Phase 1 studies
- The favorable safety profile of ramucirumab and LY2875358 as monotherapies in clinical studies.

Study I4C-MC-JTBF (JTBF) will test the hypothesis of whether LY2875358 may be safely administered in combination with ramucirumab. It will further explore the antitumor activity of the combination in specific tumor types. To this end, advanced and/or metastatic cancer patients will receive increasing doses of LY2875358 (750-2000 mg Q2W) to determine a recommended schedule and dose range for LY2875358 in combination with a fixed regimen of ramucirumab 8 mg/kg Q2W (Part A), followed by tumor-specific expansion cohorts for gastric or GEJ adenocarcinoma, hepatocellular carcinoma, renal cell or non-small cell lung cancer patients for dose confirmation and exploration of clinical activity (Part B). Given the safety profile of ramucirumab and LY2875358 as monotherapies, the potential benefits of this study are expected to outweigh the potential risks.

5.3.1. Rationale for Amendment (a)

The primary rationale for amendment (a) is to add a further expansion cohort for NSCLC to Part B of study JTBF as outlined in Section 8.1 of the initial protocol. Ramucirumab demonstrated clinical benefit in NSCLC patients in a recently published Phase 3 study when combined with docetaxel (Perol et al. 2014; see Section 5.2.1.4). Since the rationale of a more aggressive phenotype induced by MET upregulation in response to anti-angiogenic treatment is also pertinent to NSCLC, the documented clinical efficacy of ramucirumab in NSCLC supports the addition of a further expansion cohort to evaluate the combination of ramucirumab and LY2875358 in NSCLC.

In addition, some minor editorial changes have been made throughout the protocol to improve clarity and practicability of the protocol and secure alignment with the intended study design.

5.3.2. Rationale for Amendment (b)

The rationale for amendment (b) is to modify Exclusion Criterion [28] and allow patients previously treated with ramucirumab to enroll in Part B1 (Gastric or GEJ adenocarcinoma) and Part B4 (NSCLC) cohorts reflecting the approval of ramucirumab for those tumors since initiation of the study.

Minor editorial changes have been made throughout the protocol to improve clarity and practicability of the protocol, secure alignment with the intended study design, and update information available for study drugs.

6. Objectives

6.1. Primary Objective

The primary objective of this study is to determine a recommended schedule and dose range for LY2875358 that may be safely administered in combination with a fixed regimen of ramucirumab to patients with advanced and/or metastatic cancer.

As a co-primary objective for Part B, this study will evaluate preliminary antitumor activity observed with LY2875358 in combination with a fixed regimen of ramucirumab, in tumor-specific expansion cohorts, in terms of overall response rate (ORR).

6.2. Secondary Objectives

The secondary objectives of this study are:

- To characterize the safety and toxicity profile of LY2875358 in combination with a fixed regimen of ramucirumab
- To evaluate the pharmacokinetics (PK) of ramucirumab and LY2875358 when given in combination
- To document any antitumor activity observed with LY2875358 in combination with a fixed regimen of ramucirumab
- To evaluate incidence and levels of antitherapeutic antibodies against ramucirumab and LY2875358 when given in combination.

6.3. Exploratory Objective

The exploratory objectives of this study are:

- To evaluate tumor tissue and blood for biomarkers related to the VEGF and MET signaling pathway and tumor biology of the respective tumor types enrolled in the study, which may include but are not necessarily limited to tumor expression (eg, MET and VEGFR-2) and circulating biomarker (eg, VEGF-A, HGF, extracellular cleaved domain of MET [MET ECD]) and their potential association with the objectives of the study (including PK/pharmacodynamic [PD] biomarker relationship)
- To evaluate antitumor activity based on functional tumor imaging examinations, including but not limited to 2-deoxy-2[F-18]fluoro-D-glucose positron emission tomography (FDG-PET) or other relevant modalities.

7. Study Population

Patients will undergo screening and baseline procedures per the Study Schedule (see Screening/Baseline Assessments, Attachment 1). Study inclusion and exclusion criteria will be applied per Sections 7.1 and 7.2. Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened as needed after discussion with the clinical research physician (CRP) or designee (Section 7.3). Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

7.1. Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria during screening prior to first dose of study drug.

[1] Patients must have histological or cytological confirmed diagnosis of the following tumor types that is advanced and/or metastatic cancer and must be, in the judgment of the investigator, an appropriate candidate for experimental therapy after available standard therapies have failed, or for whom standard therapy would not be appropriate.

- Part A:
  - Any type of solid tumor ("all comer")
- Part B:
  - Part B1: Gastric or GEJ adenocarcinoma
  - Part B2: Hepatocellular cancer (excluding fibrolamellar carcinoma)
  - Part B3: Renal cell carcinoma (any histology)
  - Part B4: Non-small cell lung cancer (squamous or non-squamous)

[2] Have at least 1 measurable lesion outside of the central nervous system (CNS) whose presence is assessable using standard techniques by RECIST version 1.1 (Eisenhauer et al. 2009). For patients with prior radiation therapy, measurable lesions must be outside a previous radiotherapy field if they are the sole site of disease, unless disease progression has been documented at that site since radiation.

[3] Availability of a tumor sample taken prior to study treatment but **after progression (or discontinuation) on the most recent line of systemic tumor therapy** ("post-progression tumor sample") or willing to undergo a tumor biopsy pre-study treatment (mandatory). Tumor sample requirements are described in Section 10.2.1.

Tumor tissue (formalin-fixed paraffin-embedded [FFPE] blocks) or unstained slides from any time since diagnosis of the tumor disease (ie, archival tumor samples) will be requested but are not required (optional).

[4] Have a performance status of ≤2 on the Eastern Cooperative Oncology Group (ECOG) scale in Part A and ≤1 on the ECOG scale in Part B (Attachment 6).

[5] Have adequate organ function, as demonstrated by:

- Hematologic: Absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelets ≥75 x 10^9/L, and hemoglobin ≥8 g/dL. Transfusions are not allowed within 14 days of the first dose of study drug to reach defined platelets, or hemoglobin values
- Hepatic: Bilirubin ≤1.5 times upper limits of normal (ULN), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤2.5 times ULN. Patients with hepatic metastases or hepatocellular carcinoma: Bilirubin ≤3.0 mg/dL and ALT and AST ≤5 times ULN
- Renal: Serum creatinine, ≤1.5 times ULN or calculated creatinine clearance >30 mL/min
- Coagulation: Adequate coagulation function, as defined by International Normalized Ratio (INR) ≤1.5, prothrombin time (PT) and partial thromboplastin time/activated partial thromboplastin time (PTT/aPTT) ≤1.5 times ULN.

[6] Routine urinalysis showing ≤1+ protein or protein/creatinine ratio <0.5. For proteinuria ≥2+ or urine protein/creatinine ratio ≥0.5, 24-hour urine must be collected and the level must be <1 g of protein in 24 hours for patient enrollment.

[7] Have discontinued all previous cancer therapies and any agents that have not received regulatory approval for any indication, for at least 21 days or 5 half-lives prior to study enrollment, whichever is shorter, and recovered from the acute effects for therapy (toxic effects of prior locoregional therapy, surgery, or other treatment-related toxicity resolved to baseline or ≤Grade 1). Patients must have discontinued mitomycin-C or nitrosourea therapy for at least 42 days.

[8] Have given written informed consent prior to any study-specific procedures.

[9] Have an estimated life expectancy, in the judgment of the investigator, that will permit the patient to complete 8 weeks (2 cycles) of treatment.

[10] *Males and females with reproductive potential*: Must agree to use medically approved contraceptive precautions during the study and for at least 3 months following the last dose of study drug.

Females with childbearing potential must have had a negative serum pregnancy test ≤7 days before the first dose of study drug and must not be breast-feeding.

[11] Are ≥18 years of age

[12] Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

7.2. Exclusion Criteria

Potential study patients may not be included in the study if any of the following apply during screening.

[13] Have serious pre-existing medical conditions (at the discretion of the investigator, such as severe acute or chronic medical condition or laboratory abnormality that may increase the risk associated with study participation)

[14] Have a history of hypertensive crisis or hypertensive encephalopathy or current poorly controlled hypertension (blood pressure [BP] systolic ≥150 mmHg and/or diastolic ≥95 mmHg) despite standard medical management.

[15] Patient has experienced any arterial thromboembolic event (ATE), including myocardial infarction, unstable angina pectoris, cerebrovascular accident, or transient ischemic attack, within 6 months prior to receiving study drugs.

[16] Have a history of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolic event (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to receiving study drugs. Patients with chronic portal vein thrombosis who are asymptomatic and not considered to need anti-coagulation therapy are eligible.

[17] Are receiving therapeutic anticoagulation with warfarin, low-molecular-weight heparin, or similar agents. Patients receiving prophylactic, low-dose anticoagulation therapy are eligible provided that they are on low-molecular-weight heparin or oral Xa inhibitors or it is medically appropriate at the investigator's judgment that patients are switching to low-molecular-weight heparin or oral Xa inhibitors before initiation of study therapy.

Patients on prophylactic anticoagulation therapy with unresected primary tumors or luminal tumor recurrence following resection are eligible, provided that the tumor does not present a significant bleeding risk in the opinion of the investigator or consulting gastroenterologist.

[18] The patient is receiving chronic therapy with nonsteroidal anti-inflammatory drugs (NSAIDs; eg, indomethacin, ibuprofen, naproxen, or similar agents) or other antiplatelet agents (eg, clopidogrel, ticlopidine, dipyridamole, and anagrelide). Aspirin use at doses up to 325 mg/day is permitted.

[19] Have significant bleeding disorders, vasculitis, or had a significant bleeding episode from the GI tract within 3 months prior to receiving study drugs

[20] Have a history of GI perforation and/or fistulae within 6 months prior to receiving study drugs

[21] Have congestive heart failure (CHF) New York Heart Association class ≥3 or symptomatic or poorly controlled cardiac arrhythmia.

[22] Have undergone major surgery within 28 days prior to receiving study drugs, or have had a central venous access device placement within 7 days prior to receiving study drugs or major surgical procedures are planned.

[23] Have a serious or nonhealing wound, peptic ulcer, or bone fracture within 28 days prior to receiving study drugs.

[24] Have an known active fungal, bacterial, and/or known viral infection including:

- human immunodeficiency virus (screening is not required)
- viral hepatitis A (screening is not required)
- hepatitis B or C (screening is required-documentation of a negative test result within 6 months must be available for hepatitis B surface antigen and hepatitis C [antibodies or ribonucleic acid according to local standard]). Hepatocellular cancer patients with chronic viral (B or C) hepatitis are eligible if they retain adequate liver function determined by Child-Pugh Stage A.

[25] Have liver cirrhosis with a Child-Pugh Stage of B or C

[26] Have symptomatic CNS malignancy (with the exception of medulloblastoma) or metastasis (baseline contrasted computed tomography [CT] of the head or magnetic resonance imaging [MRI] of the brain required in all patients. For those patients with known CNS metastases, ongoing CNS surveillance using the same modality is required at half the frequency as extra-CNS imaging).

Patients with treated CNS metastases are eligible for this study if they were adequately treated and currently not requiring corticosteroids and/or anticonvulsants for its treatment, and their disease is asymptomatic and radiographically stable for at least 30 days. Patients with unequivocally documented leptomeningeal metastases are excluded.

[27] Have corrected QT (QTc) interval of >470 msec on screening electrocardiogram (ECG) at several consecutive days of assessment

[28] Have received previous treatment with ramucirumab or LY2875358, except for patients enrolled in Cohort B1 (Gastric or GEJ adenocarcinoma) and B4 (NSCLC) who may have received previous ramucirumab treatment.

[29] Known hypersensitivity to any of the treatment components of ramucirumab or LY2875358.

[30] Have a second primary malignancy that, in the judgment of the investigator and sponsor, may affect the interpretation of results.

[31] Are pregnant or breastfeeding.

[32] Have received treatment within 28 days of the initial dose of study drug with an investigational product or non-approved use of a drug or device (other than the study drug/device used in this study) for non-cancer indications or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[33] For Part B4 (NSCLC) only:

- The patient has radiologically documented evidence of major blood vessel invasion or encasement by cancer.

  For squamous cell histology or for centrally located mediastinal masses (<30 mm from the carina) identified by CT scan or chest X-ray, the patient must undergo an MRI of the chest or intravenous contrast CT scan prior to study treatment, to exclude major airway or blood vessel invasion by cancer.

- Patients with a history of gross hemoptysis (defined as bright red blood or ≥1/2 teaspoon) within 2 months prior to study treatment.

- The patient has radiographic evidence of intratumor cavitation, regardless of tumor histology.

7.3. Rescreening

A patient who fails screening is allowed to screen again after signing a new informed consent form (ICF) and being assigned a new patient number under the conditions specified in this section.

The following patients may be eligible for rescreening for any of the following circumstances:

- Patients who have become eligible to enroll in the study as the result of a protocol amendment
- Patients whose status has changed such that the eligibility criterion that caused the patient to screen fail, would no longer cause the patient to screen fail again (eg, unexpected surgery during the screening period that causes a screen failure but is no longer relevant following recovery from surgery)
- Patients who complete screening and meet all inclusion and exclusion requirements but are unable to be enrolled due to extenuating circumstances (eg, severe weather, death in family, child illness).

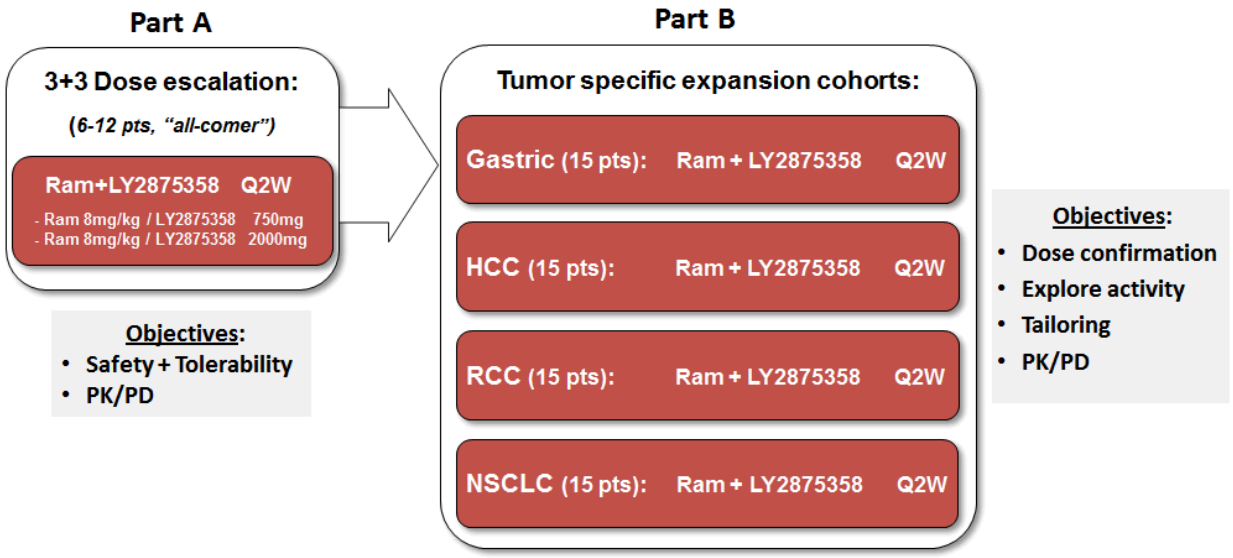
A patient for whom a tumor sample from prior to study treatment but after progression (or discontinuation) to the most recent line of systemic tumor therapy was available, but fails screening for other reasons, will not need to resubmit another tumor sample if screened again, provided the original sample was adequate to perform the protocol required tests.

8. Investigational Plan

8.1. Summary of Study Design

Study JTBF is a nonrandomized, open-label, dose-escalation, multicenter Phase 1b/2 study that consists of 2 parts:

- Part A: Dose escalation part with increasing doses of LY2875358 (750-2000 mg Q2W) to determine a recommended schedule and dose range for LY2875358 that may be safely administered in combination with a fixed regimen of ramucirumab 8 mg/kg Q2W to patients with advanced and/or metastatic cancer.
- Part B: Tumor-specific expansion cohorts in patients with gastric or GEJ adenocarcinoma, hepatocellular carcinoma, renal cell cancer or NSCLC (approximately 15 patients each) for dose confirmation of LY2875358 in combination with a fixed regimen of ramucirumab 8 mg/kg Q2W and exploration of clinical antitumor activity (Figure JTBF.1).



Abbreviations: HCC = hepatocellular carcinoma; NSCLC = non-small cell lung cancer; PD = pharmacodynamics; PK = pharmacokinetics; pt = patient; Q2W = every 2 weeks; Ram = ramucirumab; RCC = renal cell cancer.

Figure JTBF.1. Study design for I4C-MC-JTBF.

In **Part A**, dose escalation of LY2875358 will follow a 3+3 dose escalation scheme to determine a recommended schedule and dose of LY2875358 in combination with a fixed regimen of ramucirumab 8 mg/kg Q2W. The dose of ramucirumab 8 mg/kg Q2W has been used for ramucirumab Phase 2 and 3 studies in gastric/GEJ, hepatocellular carcinoma, and renal cell cancer patients. Patients will be enrolled in cohorts of at least 3 patients. Eligible patients will receive ramucirumab as a 60-minute IV infusion followed by LY2875358 as a 90-minute IV infusion on Days 1 and 15 of a 28-day cycle. LY2875358 will be administered after a minimum

of a 60-minute observation period (minimum of 30-minute observation period in Cycle 2 and beyond) after the end of the ramucirumab infusion on Days 1 and 15 of a 28-day cycle. If it is determined that a reduced LY2875358 infusion time is safe and feasible, the investigators will be notified in writing and the pharmacy manual updated to reflect the change. Both LY2875358 dose levels intended to be evaluated in Part A (ie, 750 and 2000 mg LY2875358 flat-dose) have been determined in the Phase 1 Study JTBA to be safe and biologically active, and are further studied in currently ongoing Phase 2 studies as monotherapy or in combination regimens.

Dose escalation of LY2875358 will be guided primarily by safety assessments during Cycle 1 (28 days); available PK and PD biomarker data may also be used as a secondary consideration. Blood samplings are being performed at expected time of maximal plasma concentration of ramucirumab and LY2875358, and up to 24 hours after the end of infusion of both antibodies to evaluate the PK profile of ramucirumab and LY2875358 when given in combination. The sponsor and the investigators will review and discuss all available patient safety data prior to dose escalation. If appropriate, intermediate LY2875358 dose level (or below the LY2875358 starting dose of 750 mg) may be explored after discussion between the sponsor and the investigator. The decision will be documented in writing.

Part B is intended to confirm safety and tolerability of LY2875358 in combination with a fixed regimen of ramucirumab 8 mg/kg Q2W and to explore preliminary efficacy of the combination treatment in 4 tumor-specific expansion cohorts (approximately 15 patients each):

- Part B1: Advanced gastric or GEJ adenocarcinoma
- Part B2: Advanced hepatocellular carcinoma
- Part B3: Advanced renal cell carcinoma (all histologies).
- Part B4: Advanced NSCLC (squamous or non-squamous)

Part B will be opened after an interim analysis of Part A data. The dose and schedule of LY2875358 in Part B for combination with the fixed regimen of ramucirumab 8 mg/kg Q2W will be defined based upon safety, PK/PD, and antitumor activity observed in Part A. The sponsor, in collaboration with the investigators, will review Part A results prior to determining the recommended schedule and dose of LY2875358 to be studied in Part B. The decision will be documented in writing and a written notification will be sent to the Institutional Review Board (IRB) prior to enrollment of patients into Part B. No amendment will be required. If indicated by safety, PK/PD and/or emerging clinical data, the recommended schedule and dose of LY2875358 and ramucirumab in Part B might be individually adjusted for each tumor cohort following written notification by the sponsor. For patient enrolled in Part B4 (that is NSCLC), careful patient selection, based on anatomical factors of large size, vessel encasement and tumor cavitation, and continuous patient monitoring is required.

To explore potential biomarkers predicting clinical activity for the combination of ramucirumab and LY2875358, availability of tumor samples taken prior to study treatment but after progression (or discontinuation) on the most recent line of systemic tumor therapy (or willingness to undergo a pre-study treatment tumor biopsy) will be mandatory for patients in Parts A and B. This “post-progression tumor sample” may be evaluated for biomarkers related

to the VEGF and MET signaling pathway and tumor biology of the respective tumor types enrolled in the study, which may include but is not necessarily limited to MET expression/amplification and VEGFR-2. In addition, tumor tissue from any time since diagnosis of the tumor (ie, archival tumor samples) will be requested (optional) to explore any relationship between clinical activity and biomarker status based on the archival tissue versus the mandatory "post-progression tumor sample." The analysis of both type of tumor samples is expected to critically inform any tailoring strategy for the further development of a ramucirumab and LY2875358 combination treatment.

Moreover, blood samples for exploratory biomarker analysis will be collected throughout this study which may be assessed for circulating biomarker (ie, VEGF-A, HGF, MET ECD) and their potential association with the objectives of the study.

The protocol for Study JTBF may be amended (eg, prior to commencement of Part B, which may include respecification of the selected tumor types for Part B. Depending on the safety and tolerability of ramucirumab in Part A, and the results of ongoing clinical and preclinical studies for ramucirumab and LY2875358 in combination with standard of care therapies, further treatment arms in Part B may be added by a protocol amendment.

The planned duration of treatment is not fixed. At the end of the first treatment cycle, each patient will be clinically evaluated for safety by the investigator before being permitted to receive the next treatment cycle. Eligible patients will receive 2 cycles of ramucirumab and LY2875358, unless 1 or more of the criteria for discontinuation (per Section 8.2.1) are met. Patients who have completed 2 cycles and are receiving clinical benefit may remain on study, provided they have not met any criteria for discontinuation (per Section 8.2.1).

Refer to Attachment 1 for the Study Schedule.

The sponsor, monitor, and investigators will perform this study in compliance with the protocol, GCP and International Conference on Harmonisation (ICH) guidelines, and applicable regulatory requirements.

8.1.1. Sample Size

To determine a recommended schedule and dose range of LY2875358 in combination with ramucirumab that may be safely administered to patients with advanced and/or metastatic cancer, an adequate patient sample size is required. A sufficient sample size will allow for an accurate evaluation of the relationship between exposure and toxicity, as well as an evaluation of the relationship between exposure and pharmacological effects using descriptive statistics and appropriate modeling techniques, if data warrant. This sample size is estimated to be a total of approximately 70 patients (6-12 [Part A] + 60 [Part B]).

For Part A, following a 3+3 dose escalation scheme, the sample size calculation assumes that cohorts will include 3 to 6 patients. If 2 cohorts for the intended 2 dose levels for LY2875358 (ie, 750 and 2000 mg) are needed to determine a recommended dose range for LY2875358 in combination with ramucirumab, then approximately 6-12 patients will be enrolled in Part A. To ensure accurate evaluation of safety, tolerability, or PK/PD biomarkers, additional patients may

be enrolled during Part A if deemed appropriate based on agreement between the investigators and the sponsor.

For Part B, the sample size of approximately 15 patients per expansion cohort was selected to allow adequate confirmation of safety and tolerability of LY2875358 in combination with ramucirumab and to identify evidence of preliminary clinical activity worthy of further investigation in Phase 2, analogous to the first stage of a Simon's two-stage design. If the true clinical RR according to RECIST for the combination of ramucirumab and LY2875358 in 1 of the tumor types selected is 10%, then there is a 79% chance of observing at least 1 patient with a clinical response, which might warrant further study of the regimen. On the other hand, if the true RR is close to the RR of ramucirumab monotherapy (for example, 3% in REGARD), then there is a 36.7% chance of incorrectly concluding that the regimen merits further study. In addition, variable response to treatment due to genetic variation can be measured based on patients' post-progression tumor samples. It is assumed that 50% of the study population is expected to be biomarker positive, and the true response rates are 40% and 3% in the biomarker positive and biomarker negative group respectively. Since the observed number of biomarker positive patients can vary, the sample size of 15 would give us a weighted average power of 40% (i.e. each power is weighted by its associated probability of observed number of biomarker positive patients) based on 2-sided type 1 error rate of 20% to detect statistically significant dependence between biomarker status and clinical response, suggesting the potential clinical utility of the biomarker for identifying the most appropriate target population.

In case of significant clinical activity in any of the tumor-specific expansion cohorts, further patients may be added to enroll up to approximately 45 patients per cohort to further characterize the safety and explore preliminary clinical activity of LY2875358 in combination with a fixed regimen of ramucirumab treatment, if deemed appropriate after discussion and mutual agreement between the investigators and the sponsor. A sample size of 45 would give us a weighted average power of 83% based on 2-sided type 1 error rate of 5% to detect the significant dependence between biomarker status and clinical response as above. The criterion of significant clinical activity may vary based on tumor-specific response rates or landmark disease control. Table JTBF.1 summarizes the parameters of Simon's optimal two-stage design for each cohort. The uninteresting RR of Gastric/GEJ, HCC, RCC are referenced from previous trials JVBD, JVBQ and JVBP. The uninteresting RR of NSCLC is based on the RR in the second-line docetaxel arm (Scagliotti et al. 2011). Alternatively, disease control may be considered in order to proceed with enrollment up to 45 patients per cohort if deemed appropriate. Table JTBF.2 summarizes landmark disease control and landmark disease control considered of interest to enroll up 45 patients per cohort. Such decisions will be documented in writing following discussions between the investigators and the sponsor, and a written notification will be sent to the IRB prior to enrollment of further patients.

Table JTBF.1. Simon's Optimal Two-stage Design Parameters for Each Cohort

Tumor Type	Uninteresting RR	Favorable RR	1-sided type 1 error rate	Power	n_1	n	r_1	r
Gastric/GEJ	3%	10%	0.15	0.7	14	45	1	3
HCC	10%	22%	0.1	0.75	14	42	2	7
RCC	5%	12%	0.15	0.7	13	45	1	4
NSCLC	8.5%	22%	0.1	0.8	14	41	2	6

Abbreviations: GEJ = gastroesophageal junction; HCC = hepatocellular carcinoma; n_1 = number of patients enrolled in the first stage; n = total number of patients enrolled; NSCLC = non=small cell lung cancer; r_1 = number of responses required to proceed to the second stage; r = total number of responses required for further investigation of the drug; RCC = renal cell carcinoma; RR = response rate.

Table JTBF.2. Previously Observed Landmark Disease Control for Each Cohort

Tumor Type	Observed Landmark	Landmark of Interest
Gastric/GEJ	12-weeks PFS 40%	60%
HCC	4-mos PFS 50%	75%
RCC	7.1-mos PFS 50%	75%
NSCLC	3-mos PFS 50%	75%

Abbreviations: GEJ = gastroesophageal junction; HCC = hepatocellular carcinoma; mos = months; NSCLC = non-small cell lung cancer; PFS = progression-free survival; RCC = renal cell carcinoma

8.1.2. Rationale for Selection of Dose

In this study, ramucirumab will be administered at a fixed regimen of 8 mg/kg in combination with LY2875358 at a dose range of 750-2000 mg, both administered Q2W.

The ramucirumab dose and schedule of 8 mg/kg Q2W IV infusion is the same as those for which safety and clinical efficacy have been demonstrated in Phase 2 and/or Phase 3 studies in gastric and GEJ adenocarcinoma, hepatocellular carcinoma, and renal cell cancer patients.

The LY2875358 dose range of 750-2000 mg administered as an Q2W IV infusion combination with ramucirumab was selected based on the safety and PK profile established for LY2875358 monotherapy in the Phase 1 Study JTBA and in preclinical in vivo efficacy studies. A Target-Mediated Drug Disposition (TMDD) model adequately fit the human PK data from the Study JTBA dose escalation and was used to simulate the dose range of 700-2000 mg Q2W. In this dose range, non-receptor-mediated clearance predominates, suggesting that receptors (MET) are saturated. Also, based on the simulations of LY2875358 PK of 750 mg Q2W, 100% of the population is predicted to have a minimum concentration at steady state (Css,min) ≥50 μg/mL, which is the Css,min associated with maximal tumor growth inhibition in the ligand-independent xenograft model MKN45. Furthermore, based on in vivo target inhibition studies, MET

inhibition at the level of the tumor would be maximized at a dose of 750 mg Q2W. In addition, PRs were observed in Study JTBA in the 700- to 2000-mg dose range. Two patients who received doses of 700 mg and 2000 mg as monotherapy achieved a PR (data on file). Two patients who received LY2875358 in combination with erlotinib achieved a PR, 1 each at doses of 700 mg and 2000 mg. Therefore, LY2875358 exposures achieved by 700-2000 mg Q2W are expected to be sufficient to prevent HGF binding and signaling, reduce expression of MET, and inhibit MET-driven growth of solid tumors.

Patients enrolled in this study will be closely monitored for safety and tolerability of the combination of ramucirumab and LY2875358. Dose escalation following a 3+3 dose escalation scheme in Part A will be only allowed after evaluation of all safety data. In addition, available PK/PD results will be reviewed prior to dose escalation.

8.1.3. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final analysis. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient.

8.2. Discontinuations

8.2.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor CRP/clinical research scientist (CRS) and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the Lilly CRP/CRS agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without investigational product if the Lilly CRP/CRS does not agree with the investigator's determination that it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

Patients will be discontinued from the study drug(s) in the following circumstances:

- The patient has evidence of progressive disease.
    - NOTE: In select cases, after discussion with the sponsor, treatment beyond progression may be permissible if the patient is thought to be deriving ongoing benefit from the study therapy. For instance, local therapies, such as radiation treatment to control isolated areas of CNS progression, may be permissible provided study drugs are held on the days of local therapy. Additional systemic therapy, however, is not allowed. This option is contingent upon study drug

availability. Patients may continue until they fulfill another one of the criteria for study discontinuation.

- The patient experiences unacceptable toxicity that is deemed related to study drug(s) (eg, a persistent moderate toxicity that is intolerable to the patient).
- The patient experiences a Grade 3 or 4 infusion-related reaction related to study drug(s) The patient should be permanently discontinued from ramucirumab for any of the following events (see Section 9.2.3.2):
    - Grade 4 hypertension or persistent/recurrent hypertension
    - Grade 4 proteinuria or persistent/recurrent proteinuria >3 g/24 hours
    - Grade 3 or 4 ATE
    - Grade 3 or 4 venous thromboembolic event (VTE) considered by the investigator to be life-threatening, or symptomatic and not adequately treated by anticoagulation therapy.
    - Pulmonary embolism/deep vein thrombosis occurs or intensifies during anticoagulant therapy
    - Grade 3 or 4 bleeding or hemorrhagic event
    - GI perforation
    - Grade 3 or 4 events consistent with CHF
    - New occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis
    - Reversible posterior leukoencephalopathy syndrome (RPLS)
    - Any event which would warrant ramucirumab to be modified by >2 dose reductions or to be held for >2 consecutive doses (approximately 28 days; see definition in Section 9.2.3). In situations where >2 consecutive doses have been missed, events related to the missed doses have resolved, and there is evidence of ongoing disease control, continuation of ramucirumab and/or LY2875358 may be considered and must be discussed with the Lilly clinical team.
- The patient should be permanently discontinued from LY2875358 for any of the following events (see Section 9.2.3.3):
    - Concomitant elevation of AST/ALT and bilirubin that is deemed related to LY2875358, as defined in Section 9.2.3.3
    - Any event, which would warrant LY2875358 to be held for >2 consecutive doses (approximately 28 days; see definition in Section 9.2.3).

NOTE: If 1 of the 2 investigational study drugs need to be discontinued permanently due to treatment-related toxicity specifically attributable to one of the study drugs (eg, ramucirumab-related hypertension), the patient may continue treatment with the other study drug at the investigator´s discretion and following a discussion with the Lilly clinical team, as long as the patient is receiving therapeutic benefit in the opinion of the investigator and is not fulfilling any of the criteria for study discontinuation. This option is contingent upon study drug availability

Patients will be discontinued from the study in the following circumstances:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Investigator/Physician Decision
    - The investigator/physician decides that the patient should be discontinued from the study or study drug(s)
    - If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug(s) must occur prior to introduction of the other agent
- Patient Decision
    - The patient requests to be discontinued from the study or study drug
- Sponsor Decision
    - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- The patient is significantly noncompliant with study procedures and/or treatment (Section 9.6).

The reason for and date of discontinuation will be collected for all patients. The Date of Discontinuation (for any of the above reasons) from study treatment is to be reported on the electronic case report form (eCRF). Patients who discontinue will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

8.2.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges it necessary for any scientific, medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

8.2.3. Discontinuation of the Study

The study will be discontinued if Lilly, while considering the rights, safety, and well-being of the patient(s), judges it necessary for any scientific, medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

9. Treatment

9.1. Materials and Supplies

9.1.1. Ramucirumab

Ramucirumab, provided by Lilly, is a sterile, preservative-free solution for infusion formulated in an aqueous solution at a concentration of 10 mg/mL (500 mg/50 mL vial). The buffer contains 10 mM histidine, 75 mM sodium chloride, 133 mM glycine, and 0.01% polysorbate 80. Ramucirumab is a clear or slightly opalescent and colorless or pale yellow liquid without visible particles. The pH is 6.0. The osmolality is 285 mmol/kg.

Ramucirumab must be stored under refrigeration at 2°C to 8°C with protection from direct light. DO NOT FREEZE AND/OR SHAKE RAMUCIRUMAB. Stability studies have demonstrated that the drug product can withstand transient excursion to room temperature without adverse effect; however, storage at this temperature is not recommended.

9.1.2. LY2875358

LY2875358 will be provided by Lilly as investigational product. LY2875358 for injection is a lyophilized product supplied in glass vials containing 75 mg of LY2875358. This product is reconstituted with 3.2 mL of sterile water for injection, resulting in 25 mg/mL of LY2875358. The reconstituted formulation is stable for up to 6 hours at room temperature. For further instructions, please refer to the pharmacy binder.

LY2875358 should be stored within the temperature range stated on the label.

Clinical study materials will be labeled according to the country's regulatory requirements.

9.2. Study Drug Administration

The investigator or designee is responsible for:

- explaining the correct use of the investigational agents and planned duration of each individual's treatment to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensation, destruction, and collection, and
- returning or destroying all unused medication to Lilly or its designee at the end of the study.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drugs so that the situation can be assessed.

Eligible patients will receive 2 cycles of study drugs, unless 1 or more of the criteria for discontinuation (per Section 8.2.1) are met. Patients who have completed 2 cycles and are receiving clinical benefit may remain on study provided they have not met any criteria for study

discontinuation (per Section 8.2.1). If tolerated, ramucirumab and LY2875358 infusions should be administered on the same day to keep the schedule of both study drugs synchronized.

9.2.1. Ramucirumab Dosing Schedule

Ramucirumab will be dosed at 8 mg/kg and administered as a 1-hour IV infusion prior to the administration of LY2875358 on Days 1 and 15 of a 28-day cycle in Part A and B of this study. The infusion rate of ramucirumab should not exceed 25 mg/min.

9.2.1.1. Premedication for Ramucirumab

Premedication is recommended prior to infusion of ramucirumab. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride 50 mg (or equivalent). Additional premedication may be provided at the investigator's discretion. Premedication must be provided in the setting of a prior Grade 1-2 infusion-related reaction, as detailed in Section 9.2.3.1. All premedication administered must be adequately documented on the eCRF.

9.2.2. LY2875358 Dosing Schedule

LY2875358 will be administered after a minimum of a 60-minute observation period (minimum of 30-minute observation period in Cycle 2 and beyond) following the end of the ramucirumab infusion on Days 1 and 15 of a 28-day cycle. LY2875358 will be administered as an IV infusion using either a central or a peripheral venous line. No in-line, sterile, nonpyrogenic filter should be used. To ensure that the total dose of LY2875358 will be administered, the line should be flushed at the end of the infusion (see pharmacy instructions). The LY2875358 infusion, including the flushing of the line, should be administered over a period of approximately 90 minutes. If it is determined that a reduced LY2875358 infusion time is safe and feasible, the investigators will be notified in writing and the pharmacy instructions will be updated to reflect the change.

No premedication is recommended prior to infusion of LY2875358. Premedication may be provided at the investigator's discretion. Premedication must be provided in the setting of a prior Grade 1-2 infusion-related reaction, as detailed in Section 9.2.3.1. All premedication administered must be adequately documented on the eCRF.

9.2.2.1. Dose Escalation of LY2875358 in Part A

In Part A, dose levels of LY2875358 previously tolerated as monotherapy and in combination with erlotinib in Study JTBA will be administered following the proposed dose escalation scheme below:

Dose level 1: LY2875358 750-mg flat dose as a 90-minute IV infusion after a minimum of a 60-minute observation period (minimum of 30-minute observation period in Cycle 2 and beyond) following the end of the ramucirumab 8-mg/kg infusion on Days 1 and 15 of a 28-day cycle

Dose level 2: LY2875358 2000-mg flat dose as a 90-minute IV infusion after a minimum of a 60-minute observation period (minimum of 30-minute observation period in Cycle 2 and beyond) following the end of the ramucirumab 8-mg/kg infusion on Days 1 and 15 of a 28-day cycle

Dose escalation will be guided primarily by safety assessments, in particular AEs, during Cycle 1. By nature of being a dose escalation study, data will be evaluated on an ongoing basis to determine a recommended schedule and dose range of LY2875358 that may be safely administered in combination with ramucirumab on Days 1 and 15 of a 28-day cycle.

The sponsor and investigators will review and discuss all patient safety data prior to dose escalation. In addition, if available at the time of dose escalation decision, PK results will be used as secondary/supporting data for dose escalation. Intermediate dose levels for LY2875358 (or a dose below the starting dose) may be considered based on appearance of toxicity or PK/PD modeling, if deemed appropriate by agreement between the investigators and the sponsor. If during the dose escalation, a new sequence of drug administration (eg, inverse order of administration or sequential dosing of the study drugs on separate days) should be indicated for safety or PK reasons, or preclinical data suggest that this may pose a better regimen, then the investigators together with the sponsor will decide on this change and inform the ERBs in writing. No protocol amendment will be required.

No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly CRP/CRS; the decision will be documented in writing. Based on the ongoing safety reviews, modifications to the dose escalation strategy or other design elements may be made via protocol amendment to ensure patient safety. Intrapatient dose escalation will not be permitted in this study.

For assessment of toxicity the standard scoring system, Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, established by the National Cancer Institute (NCI) (NCI 2010) will be used. A minor version of CTCAE Version 4.0 (eg, CTCAE Version 4.03) may be used for this study. Minor updates to CTCAE Version 4.0 will not necessitate a protocol amendment, and the use of an updated CTCAE Version 4.0 will not be considered a protocol violation. Any AEs related to study drugs will be considered as toxicities.

9.2.2.2. Dose-Limiting Toxicity Determination

Dose-limiting toxicity is defined as an AE during Cycle 1 that is possibly, probably, or definitely related to treatment with LY2875358 in combination with a fixed regimen of ramucirumab and fulfills any 1 of the following criterion using the NCI CTCAE Version 4.03:

- ≥Grade 3 non-hematological toxicity. Exceptions will be made for:
  - nausea, vomiting, diarrhea, constipation, or skin rash that persists for ≤3 days following appropriate supportive care intervention
  - Grade 3 hypertension in which systolic BP ≥160 mmHg and/or diastolic BP ≥100 mmHg persist <7 days after intensified antihypertensive therapy is initiated
- Grade 4 hematological toxicity of ≥7 days duration
- ≥Grade 3 thrombocytopenia with ≥Grade 2 bleeding
- Any febrile neutropenia

- Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose-limiting (eg, any toxicity that is possibly related to the study medication that requires the withdrawal of the patient from the study during Cycle 1).

Infusion-related reactions (including hypersensitivity reactions and anaphylaxis) should not be considered as DLTs unless the investigator or Lilly medical monitor provides compelling rationale to support their inclusion as a DLT.

Patients in Part A (Cycle 2 or greater) and Part B will be evaluated on an ongoing basis for AEs. In these patients, a DLT-equivalent toxicity will be defined based on trends of any clinical significant toxicity deemed by the study investigators and Lilly clinical research personnel to be dose-limiting and related to study drug(s)s. The investigators and Lilly CRP/CRS will have to agree as to whether such AEs are considered as DLT-equivalent.

9.2.2.3. Dose Escalation Method and Maximum Tolerated Dose Definition

In this study, a 3+3 dose-escalation paradigm will be utilized. If 1 patient, at any dose level, experiences a DLT during the DLT period (Cycle 1), then up to 3 additional patients will be enrolled at that dose level. If a DLT is observed in ≥2 out of 6 patients at any dose level, dose escalation will cease and either the previous dose level will be declared the maximum tolerated dose (MTD) or, following discussions between the investigators and the sponsor, additional patients may be treated at intermediate doses between the previous and the current dose levels.

The first patient enrolled in Part A in this study will be observed for a DLT (as defined in Section 9.2.2.2) during the first 14 days of Cycle 1, before subsequent patients are treated at that dose level. If the first patient does not experience a DLT during this period, subsequent patients may be concurrently enrolled at the initial cohort. In subsequent cohorts, all patients may be enrolled concurrently.

9.2.2.4. Dose Confirmation of LY2875358 in Part B

Once a recommended schedule and dose range of LY2875358 that may be safely administered in combination with ramucirumab on Days 1 and 15 of a 28-day cycle has been determined in Part A, the tumor expansion portion of the study (Part B) will be opened. Approximately 15 patients in each of the 4 specified tumor types will be enrolled (approximately 60 patients in total). The dose and schedule of LY2875358 in Part B for combination with the fixed regimen of ramucirumab 8 mg/kg Q2W will be defined based upon safety, PK/PD, and antitumor activity observed in Part A. The sponsor, in collaboration with the investigators, will review Part A results prior to determining the recommended schedule and dose of LY2875358 to be studied in Part B. The decision will be documented in writing and a written notification will be sent to the IRB prior to enrollment of patients into Part B. No amendment will be required. If indicated by safety, PK/PD, and/or emerging clinical data, the recommended schedule and dose of LY2875358 and ramucirumab in Part B might be individually adjusted for each tumor cohort following written notification by the sponsor.

9.2.3. Dose Adjustments and Delays

In Cycle 1, no dose adjustments, or delays of ramucirumab and/or LY2875358 will be allowed (ie, DLT assessment period), except in case of any DLT.

In Cycle 2 or beyond, if a patient experiences a toxicity warranting a dosing delay in the investigator´s opinion, ramucirumab and/or LY2875358 dosing may be held for up to 2 consecutive doses (approximately 28 days) to allow sufficient time for recovery from the toxicity. This approximate 28-day time period begins on the day that the next dose of study treatment should have been administered but was withheld for toxicity. If both study drugs were held due to a toxicity, study treatment with both study drugs should be resumed as soon as that toxicity is resolved, provided that the patient did not meet any discontinuation criteria.

In case the toxicity is specifically attributable to 1 of the 2 experimental study drugs in the opinion of the investigator (eg, ramucirumab-related hypertension), the patient may continue to receive the other study drug following the regularly scheduled Q2W treatment time points (eg, LY2875358). In this setting, treatment of the withheld study drug (eg, ramucirumab) should be resumed at the next regularly scheduled Q2W treatment time point of the continued study drug (eg, LY2875358) following the resolution of the event causing the hold. Make-up doses of the withheld study drug occurring between regularly scheduled Q2W treatment time points are not permitted in order to keep the administration of both study drugs synchronized to the same study days (ie, Day 1 or 15 of a cycle). In situations where >2 consecutive doses have been missed, events related to the missed doses have resolved, and there is evidence of ongoing disease control, continuation of ramucirumab and/or LY2875358 may be considered and must be discussed with the Lilly clinical team.

It is recognized that, in the course of clinical cancer care, it is not always possible to schedule therapeutic infusions precisely 2 weeks following a prior infusion (ie, because of holidays, travel difficulties, or other circumstances). Accordingly, study drug infusions administered within the timing window as indicated in the Study Schedule (see Attachment 1) relative to the regularly scheduled Q2W treatment time point will be considered acceptable. Moreover, in Cycle 3 or beyond, ramucirumab and LY2875358 dosing may be delayed for up to approximately 14 days because of holidays, weekends, inclement weather, or other justifiable events, and not counted as a protocol violation. This approximate up to 14-day time period begins on the day that the next dose of study treatment should have been administered. In order to keep the administration of both study drugs synchronized, the next dose of ramucirumab and LY2875358 should be administered at the same study day to continue the regularly scheduled Q2W treatment time points.

In the event of dosing delays or missed doses, disease assessment and imaging studies should be undertaken according to the original study schedule, regardless of the actual number of on-study treatments received.

9.2.3.1. Infusion-Related Reaction

As with other mAbs, infusion-related reactions may occur during or following ramucirumab and/or LY2875358 administration. Patients should be closely monitored for signs and symptoms

indicative of an infusion-related reaction, starting with the initiation of the infusion until at least 30 minutes after the infusion. Monitoring should be performed in an area where resuscitation equipment and other agents (eg, epinephrine, corticosteroids) are readily available (Table JTBF.3).

Any treatment-related infusion-related reactions are defined according to the NCI-CTCAE Version 4.03 definition ("General disorders and administration site conditions" section). Symptoms occurring during or following infusion of investigational product may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome ("Immune system disorders" section). In the setting of symptoms occurring during or following infusion of the study drugs, investigators are encouraged to use the AE term "infusion-related reaction" and any additional terms (including those not listed here) that best describe the event.

Table JTBF.3. NCI-CTCAE Version 4 Infusion-Related Reactions[a]

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Allergic reaction	Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.					
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilator support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					

Abbreviations: IV = intravenous; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03; NSAID = nonsteroidal anti-inflammatory drug.

a Premedication must be provided in the setting of a prior Grade 1-2 infusion-related reaction.

Consistent with usual medical practice, selected parenteral medications may be utilized for Grade 2 allergic/hypersensitivity reaction as detailed below. The sponsor physician or designee should be contacted immediately if questions arise concerning the grade of the reaction. The following are treatment guidelines for infusion-related reactions:

Grade 1

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

Grade 2

- Stop the infusion.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally for fever, and oxygen.
- Resume the infusion at 50% of the prior rate for the duration of the infusion and all subsequent infusions once the infusion-related reaction has resolved or decreased to Grade 1; the infusion duration should not exceed 2 hours for each of the study drugs
- Monitor for worsening of condition.
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion.
- For a second Grade 1 or 2 infusion-related reaction, administer dexamethasone 8-10 mg IV (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally, and dexamethasone 8-10 mg IV (or equivalent).

Grade 3

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 8-10 mg IV (or equivalent), bronchodilators for bronchospasm, and other medications/treatment as medically indicated.
- Patients who have a Grade 3 infusion-related reaction will not receive further investigational product causing this infusion-related reaction.

Grade 4

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 8-10 mg IV (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-related reaction will not receive further investigational product causing this infusion-related reaction.

If a patient should have an infusion-related reaction to the study drugs, all attempts should be made to obtain blood samples for both immunogenicity and PK analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event.

9.2.3.2. Treatment Guidelines and Dose Modifications for Ramucirumab-specific Adverse Events

Dose modifications of ramucirumab are permitted in the setting of non-life-threatening, reversible Grade 3-4 clinical AEs (eg, fever) considered to be at least possibly related to ramucirumab.

- For toxicities that resolve to Grade ≤1 or baseline, ramucirumab may be re-administered at a dose of 8 mg/kg
- If a second instance of such an event occurs, ramucirumab should be subsequently re-administered at a dose of 6 mg/kg Q2W.
- A second dose reduction to 5 mg/kg Q2W is permitted for this level of event (Grade 3-4).

Any further dose reduction of ramucirumab below 5 mg/kg is not permitted, and if the criteria for a ramucirumab dose reduction are met for patients at 5 mg/kg ramucirumab Q2W, ramucirumab must be discontinued. If the dose of ramucirumab is reduced, subsequent dose increases are not permitted. If a patient's dose is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

Patients who enter the study with symptoms or laboratory values equivalent to NCI-CTCAE Version 4.03 Grade 1-2 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 investigator. Asymptomatic Grade 3-4 laboratory abnormalities should not result in dose interruptions, modifications, or discontinuation of study therapy unless determined to be clinically significant by the investigator (or unless otherwise specified in the study protocol).

9.2.3.2.1. Hypertension

The following are treatment guidelines for hypertension that develops during the study.

Grade <3

- If the hypertension is not associated with symptoms, continue ramucirumab and initiate antihypertensive therapy.
- If the 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 investigational product should be reduced upon re-treatment to 6 mg/kg Q2W. A second

dose reduction to 5 mg/kg Q2W should be undertaken if an additional postponement of ramucirumab is required.

Grade 3 (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg; 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 mmHg or diastolic BP remains ≥100 mmHg >3 weeks after initiation of additional antihypertensive therapy, hold ramucirumab while continuing appropriate antihypertensive therapy.
- If the hypertension is associated with symptoms, hold ramucirumab while continuing appropriate 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 upon re-treatment to 6 mg/kg Q2W. A second dose reduction to 5 mg/kg Q2W should be undertaken if an additional postponement of investigational product is required.

Grade 4 or refractory

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

9.2.3.2.2. Proteinuria

If, while receiving ramucirumab, a patient has proteinuria ≥2+ per a dipstick or routine urinalysis test, ramucirumab will continue as scheduled, and a 24-hour urine collection will be conducted prior to the subsequent scheduled treatment cycle. If the protein level is <2 g/24 hours, the patient will continue on ramucirumab at the same dose without interruption. If the protein level is 2 to 3 g/24 hours, ramucirumab for the subsequent cycle will be held for 2 weeks and a 24-hour urine collection will be repeated. Treatment with ramucirumab will resume at a reduced dose level (6 mg/kg Q2W) once the protein level returns to <2 g/24 hours. A second dose reduction of ramucirumab to 5 mg/kg every 2 weeks is permitted if proteinuria >2 g/24 hours recurs. Ramucirumab will be discontinued if the protein level is >3 g/24 hours, if there is a third occurrence of proteinuria >2 g/24 hours, or if the protein level does not return to <2 g/24 hours within 2 weeks.

9.2.3.2.3. Thromboembolic Events

Investigators should perform all testing required to fully characterize arterial or venous thromboembolic/vascular events. The incidence and type of thromboembolic/vascular events will be collected and reported. Ramucirumab should be discontinued in the event of any Grade 3-4 ATE or VTE that is considered by the investigator to be life-threatening, or symptomatic and not adequately treated by anticoagulation therapy. Ramucirumab may be continued in the setting

of an incidentally diagnosed, asymptomatic deep vein thrombosis or pulmonary embolism, or following these events when symptoms have resolved with the institution of anticoagulation therapy. Ramucirumab should also be discontinued in the setting of a deep vein thrombosis or pulmonary embolism that occurs or intensifies while the patient is receiving therapeutic anticoagulation therapy.

9.2.3.2.4. Bleeding (Hemorrhagic) Events

Serious bleeding (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 ramucirumab IB, the incidences of hemorrhagic events to date, significant background incidence of bleeding in some malignancies, and use of concomitant antiplatelet therapy in some of the reported cases preclude any definitive association between bleeding and ramucirumab, although ongoing surveillance and identification (and exclusion) of patients with high bleeding risk remain essential. Ramucirumab should be discontinued in the event of any Grade 3 or 4 bleeding (hemorrhagic) event.

9.2.3.2.5. Gastrointestinal Perforations

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

9.2.3.2.6. Congestive Heart Failure in Patients Who Received Ramucirumab in Combination With Mitoxantrone or Following Prior Anthracycline Therapy

An increased risk of CHF has been associated with some anti-angiogenic therapeutic agents, particularly in patients with metastatic breast cancer previously 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 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. Ramucirumab should be discontinued in the event of any Grade 3-4 events consistent with CHF.

9.2.3.2.7. Surgery and Impaired Wound Healing

Surgery and impaired wound healing have been observed with some anti-angiogenic agents. Ramucirumab will not be administered to patients who have undergone major surgery within 28 days prior to initiation of study treatment or who have undergone central venous access device placement within 7 days prior to receiving study drugs. Patients with postoperative and other nonhealing wound complications are excluded, as are patients for whom major surgical procedures are planned.

9.2.3.2.8. Liver Injury/Liver Failure

An independent data monitoring committee (IDMC) for Study I4T-IE-JVBF (JVBF) a randomized, blinded study evaluating ramucirumab versus placebo in hepatocellular carcinoma following prior sorafenib therapy recommended modifications following an 02 August 2012 meeting. This was the fifth meeting of the IDMC for this study (the prior meetings had concluded with recommendations to continue this study without modifications), and occurred at the request of the sponsor to investigate a potential association of liver failure and other events of severe liver injury with ramucirumab. The IDMC reviewed unblinded safety data from 400 patients who had been treated with either ramucirumab or placebo. The data cut-off date of this safety review was 18 July 2012. In review of the safety data, the IDMC noted that death rates related to study medication were in the expected range for patients with hepatocellular carcinoma and cirrhosis. However, the IDMC observed a numeric imbalance of liver-related AEs, specifically for hepatic encephalopathy, between the 2 treatment arms. Based on this safety finding, the IDMC specifically addressed hepatic encephalopathy, hepatorenal syndrome, and ascites in the context of cirrhosis, exclusive of other etiologies of these diagnoses.

The IDMC recommended continuing Study JVBF with modifications. These modifications included: (a) exclusion of patients with Child-Pugh B cirrhosis (or worse), (b) exclusion of patients with cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis, and (c) an additional criteria for discontinuation of study drug (ramucirumab or placebo) for patients with new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis. Although the IDMC's recommendations are specific to Study JVBF, Lilly has chosen to implement these recommendations for ongoing Lilly-sponsored studies in which patients are receiving ramucirumab. Ramucirumab should be discontinued following a new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis.

9.2.3.2.9. Reversible Posterior Leukoencephalopathy Syndrome

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 (Hinchey et al. 1996). 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 (Hinchey et al. 1996; Garg 2001; Lee et al. 2008). Magnetic resonance imaging represents the most reliable method for the diagnosis (Lee et al. 2008). Clinical symptoms and MRI abnormalities usually recover within days to weeks with proper

management, although permanent neurologic dysfunction has been reported (Hinchey et al. 1996; Tajima et al. 1999; Garg 2001; Lee et al. 2008). 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 (Garg 2001; Marinella and Markert 2009). More recently, RPLS has been associated with the use of the anti-VEGF agent bevacizumab, as described in the prescribing information for this agent (Marinella and Markert 2009; Avastin package insert, 2011).

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 (Schwartz 1996). 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 (Marinella and Markert 2009).

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 (Stott et al. 2005). As of 31 December 2012, 1 SAE of RPLS has been reported in the double-blind, randomized, placebo-controlled Phase 3 colorectal cancer Study I4T-MC-JVBB (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, investigators should control BP in accordance with the guidelines in the ramucirumab IB and in relevant sections of the study protocol (Section 9.2.3.2.1). In addition, investigators 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. If the diagnosis of RPLS is confirmed, ramucirumab should be permanently discontinued.

9.2.3.3. Treatment Guidelines for LY2875358-Specific Adverse Events

Intrapatient dose adjustments of LY2875358 will not be permitted in this study.

In Cycle 2 or beyond, patients who experience any Grade 3 or greater toxicity related to LY2875358 therapy should have LY2875358 therapy held for up to 2 consecutive doses (approximately 28 days) to allow sufficient time for recovery from the toxicity. This approximate 28-day time period begins on the day that the next dose of LY2875358 should have been administered but was withheld for toxicity. Patients who do not recover within this time period from this LY2875358-related toxicity to a level that, in the opinion of the investigator, is reasonable to allow for continuation of LY2875358 treatment, should discontinue further LY2875358 treatment.

Patients who experience a concomitant elevation of AST/ALT >3 times ULN and bilirubin >2 times ULN related to LY2875358 and who lack a natural disease state known to cause liver

enzyme elevation (eg, hepatic metastases) should be permanently discontinued from LY2875358 treatment. Only patients who have experienced a clinical benefit from study therapy may, at the discretion of the investigator, be re-challenged with LY2875358 after recovery from concomitant elevation of AST/ALT >3 times ULN and bilirubin >2 times ULN related to LY2875358.

Patients enrolled in Part B will undergo ongoing safety monitoring per tumor-specific expansion cohorts. If DLT-equivalent toxicities (Section 9.2.2.2) have been identified for a particular tumor-specific expansion cohort, LY2875358 dose de-escalation for all patients in this tumor-specific expansion cohort (or, if appropriate, in all cohorts) will be discussed between the investigators and the sponsor. The decision will be documented in writing and provided to IRBs/ERBs in writing. No amendment will be required.

9.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive ramucirumab and LY2875358 in this study. Before each patient's enrollment into the study, an eligibility check must be conducted between the investigational site and the Lilly clinical research personnel to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor will confirm the dose and identification number assignment and cohort for each patient. No dose escalations (ie, to the next cohort) can occur without prior discussion and agreement with the responsible Lilly CRP or CRS.

If investigators have eligible patients who have consented concurrently to Part A, more than 3 patients may be entered at a particular dose level, provided that accrual has not ceased due to excessive toxicity. This enrollment procedure is allowed because of the advanced disease state of this patient population and the screening involved in defining eligibility. This event should be approved by the sponsor following discussions with the investigators.

9.4. Blinding

This is an open-label study.

9.5. Concomitant Therapy

No other chemotherapy, radiotherapy, immunotherapy, cancer-related hormone therapy, or experimental drugs will be permitted while the patients are on this study, with the following exceptions:

- Palliative radiotherapy of ≤14 calendar days in Cycles 2 and beyond following discussions between the investigators and the sponsor (eg, a solitary [non-skull] skeletal metastasis), as long as the patient has not developed another reason for study discontinuation
- Patients on stable doses of bisphosphonates or denosumab are allowed to continue. These agents should not be initiated within the 4 weeks prior to study enrollment or at any point while on the study

- In select cases, after discussion with the sponsor, local therapies (such as radiation treatment to control isolated areas of CNS progression) may be permissible provided study drugs are held on the days of local therapy).

In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the eCRF. Replacement hormonal therapy initiated before study entry will be allowed.

Patients should receive full supportive care. The routine use of granulocyte colony stimulating factors (G-CSF) is not permitted during this study. If clinically indicated, the use of G-CSF is permitted during investigational therapy at the discretion of the investigator. G-CSF or similar agents are recommended following Grade 3 or 4 neutropenia of duration >5 days or following any incidence of febrile neutropenia (ANC $<1.0 \times 10^9$/L with temperature ≥38.5°C).

If clinically indicated at any time during the study, erythropoietin and packed red blood cell transfusions may be used according to American Society of Clinical Oncology guidelines (Rizzo et al. 2008).

The use of analgesic agents is permitted at the discretion of the investigator. The chronic use of antiplatelet therapy (eg, clopidogrel, ticlopidine, prasugrel, dipyridamole, picotamide, indobufen, anagrelide, triflusal, or similar agents) and NSAIDs with a high risk of bleeding (for example, indomethacin, ibuprofen, naproxen, or similar agents) is strongly discouraged unless at the discretion and responsibility of the investigator after careful assessment of the individual bleeding risk of the patient. Chronic use of analgesic agents with no or low bleeding risk (for example, paracetamol/acetaminophen, metamizole, dipyrone, or propyphenazone) is acceptable.

Patients receiving therapeutic anticoagulation with warfarin, low-molecular-weight heparin, or similar agents are excluded from participation. Anticoagulant therapy may be instituted during the course of treatment on study as detailed in Section 9.2.3.2.3 (following an asymptomatic or treatable deep vein thrombosis or pulmonary embolism), provided that no evidence of portal hypertension (including splenomegaly) or any prior history of variceal bleeding exists.

All concomitant medications should be recorded throughout the patient's participation in the study.

9.6. Treatment Compliance

Ramucirumab and LY2875358 will be administered IV at the investigational site, under the direction of the investigator. As a result, patient's compliance with study drug administration is ensured. Patients should attend scheduled clinic visits and must comply with study criteria under their control. Deviation(s) from the prescribed dosage regimen should be recorded on the eCRF. Potential discontinuation of a patient due to study noncompliance (not attending the scheduled visits; see Attachment 1) will be discussed between the investigator and the Lilly CRP/CRS before the final determination is made to discontinue the patient.

9.6.1. Evaluable Patients

Patients who withdraw from the study before receiving study drugs will be replaced and will not be included in the safety or efficacy assessments. Safety analyses will be conducted on all patients who have received at least 1 dose of study drug, regardless of whether they are deemed evaluable for the assessment of a dose level.

Any patient who is discontinued from the study before completing the first cycle of ramucirumab and LY2875358 treatment will be deemed non-evaluable for assessment of a dose level, unless it can be documented whether the patient did or did not experience a DLT during Cycle 1.

If a patient is noncompliant during Cycle 1 due to reasons other than drug-related toxicity, he or she will be considered nonevaluable and may be replaced. Nonevaluable patients may be replaced to ensure that at least 3 patients complete 1 cycle of therapy at each dose level, unless accrual to that cohort has stopped due to a DLT. Patients who are not evaluable for PK, but who complete 1 cycle of therapy, may be replaced upon consultation with the investigator(s) and the Lilly CRP/CRS to ensure adequate PK data, unless accrual to that cohort has stopped due to a DLT.

10. Safety, Pharmacokinetic, Pharmacodynamic, and Efficacy Data Collection

10.1. Safety Evaluations

The safety and tolerability of ramucirumab and LY2875358 have been separately assessed in clinical studies, and the results from these studies are detailed in the respective IBs. This Phase 1b/2 study contains detailed safety monitoring that will permit initial characterization of the safety profile of the combined administration of ramucirumab and LY2875358 in patients with advanced or metastatic cancer. Study procedures and their timing, including collection of blood, urine, and tumor samples, are described in the Study Schedule (Attachment 1).

Standard laboratory tests, including chemistry, hematology, coagulation, and urinalysis panels, will be performed. A urine or serum pregnancy test will be administered if applicable. Other clinical laboratory tests will also be collected. Attachment 2 lists the specific tests that will be performed for this study.

10.1.1. Safety Data Collection and Review

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

The investigator is responsible for the appropriate medical care of the patient during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JTBF.4 presents a summary of AE and SAE reporting guidelines. Table JTBF.4 also shows which database or system is used to store AE and SAE data.

10.1.2. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any clinically significant findings from labs, vital sign measurements, and so on, that occur should also be reported to Lilly or its designee as

an AE. Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

The investigator, monitor, and sponsor will review the collected data regularly for evidence of AEs. All patients will be assessed routinely for AEs as outlined in the study schedule. All AEs observed will be graded using NCI-CTCAE Version 4.03.

The NCI-CTCAE Version 4.03 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. Any minor version of NCI-CTCAE Version 4.03 (eg, Version 4.0X) may be used for this study. Minor NCI-CTCAE Version 4.03 updates will not necessitate a protocol amendment. For AEs without matching terminology within the NCI-CTCAE Version 4.03 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the eCRF. This collection is in addition to verbatim text used to describe the AE.

In addition to collecting the AE verbatim, the CTCAE term, and the CTCAE severity grade, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

Cases of pregnancy that occur during maternal or paternal exposures to study drugs should be reported. Data on fetal outcome and breastfeeding should be collected, if feasible, for regulatory reporting and drug safety evaluation.

Upon documentation of pregnancy, the patient must be removed from the study and treatment with study drug(s) must be stopped immediately.

For all enrolled patients, study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. While the patient is on study, site personnel will record any change in these preexisting condition(s) and the occurrence and nature of any AEs. In addition all AEs related to protocol procedures are reported to Lilly or designee.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure and/or study drug via eCRF. The investigator decides whether he or she interprets the observed AEs as related to either study disease, study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terminologies are defined:

- **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.
- **Unrelated**: without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures, all "related" and "possibly related" AEs and SAEs will be defined as related to study drug.

10.1.2.1. Serious Adverse Events

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalizations or elective procedures for underlying 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.

An SAE is any AE during this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization (except for study drug administration)
- a life-threatening experience (ie, immediate risk of dying)
- persistent or significant disability/incapacity
- 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 on 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 events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study drug.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

If an investigator becomes aware of SAEs occurring to a patient after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol

procedure or study drug, the investigator should report the SAEs to the sponsor, and the SAEs will be entered in the LSS.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.1.2.1.1. Adverse Event and Serious Adverse Event Reporting

Data on SAEs that occur before the end of trial will be stored in the collection database and the LSS.

10.1.2.1.2. Prior to Administration of Study Drug(s)

During screening, all AEs and SAEs (regardless of relatedness to protocol procedures) are collected after the patient has signed the informed consent form. For patients who do not enroll in the trial (ie, have not received at least 1 dose of ramucirumab and/or LY2875358), only AEs and SAEs related to protocol procedures are required to be collected.

10.1.2.1.3. On Therapy

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring while the patient is receiving study drug must be reported to Lilly or its designee. A patient is considered to be receiving study drug from the time he/she receives the first dose of study drug to when he/she receives the last dose of study drug.

10.1.2.1.4. Follow-Up Visit

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring during the follow-up visit (Visit 801) must be reported to Lilly or its designee. The initial follow-up period (V801) starts following the last dose of LY2875358. At the follow-up visit (V801) (30 ± 3 days after last dose of LY2875358) the patient will be required to have specific safety assessments (Attachment 1).

Following the safety assessments, which mark the end of the follow-up visit (Visit 801), the patient will be discontinued from the study, unless there is an ongoing AE or SAE that is possibly related to study drug(s). In this instance, the patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up.

If it is deemed to be in the best interest of the patient to start a new anticancer treatment prior to the scheduled end of the follow-up visit, the follow-up visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

After the follow-up visit (Visit 801), AEs are not required to be reported unless the investigator feels the AEs were related to either study drug(s) or a protocol procedure. If an investigator becomes aware of an SAE believed to be related to protocol procedures or study drug(s), the investigator should report the SAE to the sponsor, and the SAE will be entered in the LSS.

10.1.2.1.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are not listed in the DCSI of the IB and that the investigator identifies as related to study drug or procedure. The US 21 CFR 312.32, the EU Clinical Trial Directive 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 regulatory regulations and the associated detailed guidances.

10.1.2.2. Summary of Adverse Event/Serious Adverse Event Reporting Guidelines

The AE and SAE reporting guidelines are summarized in Table JTBF.4.

Table JTBF.4. Adverse Event and Serious Adverse Reporting Guidelines for Study JTBF

Timing	Types of AEs/SAEs Reported	Collection Database	Lilly Safety System
Prestudy (baseline assessments) (Starts at the signing of informed consent and ends just before the first dose of study drug)	Pre-existing conditions All AEs All SAEs regardless of relatedness	x x x	 x
On therapy (Starts at first dose of study drug[s] and ends at last dose of study drug[s])	All AEs All SAEs regardless of relatedness	x x	 x
Follow-up Visit (Visit 801) (Starts just after the last dose of study drug[s] and ends when end of study safety assessments are completed 30 ± 3 days after last dose of study drug[s])	All AEs All SAEs regardless of relatedness	x x	 x
Subsequent follow-up visits, if necessary for patient monitoring	Ongoing AEs possibly related to study drug(s), or protocol procedures All SAEs related to protocol procedures or study drug(s)	x x	 x
Patient no longer on study	All SAEs related to protocol procedures or study drug of which the investigator becomes aware		x

Abbreviations: AE = adverse event; SAE = serious adverse event.

10.1.3. Other Safety Measures

10.1.3.1. Electrocardiograms

For each patient, single 12-lead ECGs will be obtained according to the Study Schedule (Attachment 1). The patient must be supine for approximately 5 to 10 minutes before ECG

collection and remain supine during ECG collection. Electrocardiograms must be recorded before collecting any blood for safety or PK tests. Electrocardiograms may be obtained at additional times, when deemed necessary (eg, for safety reasons). All recorded ECGs should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant finding is identified (including but not limited to changes in QT/QTc interval from baseline), the investigator will determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

10.1.4. Safety Monitoring

The Lilly CRP or CRS will monitor safety data throughout the course of the study.

Representatives from Lilly Global Patient Safety will specifically monitor SAEs. Lilly will review SAEs within time frames mandated by company standard operating procedures. The Lilly CRP/CRS will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or CRS, and periodically review:

- trends in safety data
- laboratory analytes
- AEs
- If a study patient experiences elevated ALT $\geq$5 X ULN and elevated total bilirubin $\geq$2 X ULN, clinical and laboratory monitoring should be initiated by the investigator. For patients entering the study with ALT $\geq$3 X ULN, monitoring should be triggered at ALT $\geq$2 X baseline.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3).

10.1.5. Complaint Handling

Lilly collects complaints on study drugs used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

Complaints related to concomitant drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the complaint process in accordance with the instructions provided for this study:

- recording a complete description of the complaint reported and any associated adverse events using the study-specific complaint forms provided for this purpose
- faxing the completed complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.2. Sample Collection and Testing

Attachment 1 lists the schedule of study evaluations in this study.

Attachment 2 lists the specific laboratory tests that will be performed for this study.

Attachment 4 lists the schedule for PK and PD sample collections in this study.

Attachment 7 provides a summary of the estimated maximum number and volume of invasive samples, for all sampling, during the study.

10.2.1. Samples for Study Qualification and Health Monitoring

Tumor tissue, blood, and urine samples will be collected at the times specified in the Study Schedule (Attachment 1). Attachment 7 summarizes volumes for all invasive sampling (screening, safety evaluations, and bioanalytical markers).

Investigators must document their review of each laboratory safety report.

To meet study eligibility criteria, patients must have available a FFPE tumor specimen taken by core needle biopsy or surgical biopsy prior to study treatment but after progression (or discontinuation) to the most recent line of systemic tumor therapy ("post-progression tumor sample") or be willing to undergo a tumor biopsy of a pre-study treatment by core needle biopsy or surgical biopsy. Tumor specimen samples may be of any type of tissue, with the exception of bone or CNS metastases. Cytological samples and fine-needle aspiration specimens are not acceptable. Tumor tissue specimens must have adequate evaluable tumor cells. Due diligence should be used to make sure that tumor specimens (not a normal adjacent or a tumor margin sample) are provided. An associated pathology report may also be requested to be sent with the samples. Tumor samples will be labeled with patient number and tissue of origin.

For the "post-progression tumor sample", submission of a tissue block is preferred. Alternatively, approximately 15 serially cut unstained sections from the FFPE block can be submitted. If the requested amount of tumor samples from the "post-progression tumor sample" are not available, the patient may still be eligible, upon discussion with the Lilly study team, with the assumption that the patient can provide sufficient tumor tissue specimen for assessment of at least MET expression and VEGFR-2 status.

Blood and urine samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm

that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

The tumor tissue samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drugs. Tumor specimens submitted as a FFPE tissue block will be returned to the sites by end of study or upon request.

10.2.2. Samples for Biomarker Research

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to ramucirumab and LY2875358. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

Collection of samples for biomarker research and PK/PD analyses is an integral part of this study. Assessments may include analysis of tumor tissue and blood for exploratory biomarkers related to the VEGFR-2 and HGF/MET signaling pathways as well as to biology of the respective tumor types in this study and potential resistance mechanisms. The association of biomarkers with the objectives of the study (including PK/PD biomarker relationship) may be assessed. The exploratory biomarker sampling times are listed in Attachment 1. The exploratory biomarker analysis may be performed by the sponsor or at a laboratory selected by the sponsor.

Samples for exploratory biomarker research to be collected from patients in this study are the following:

- Tumor tissue samples: Mandatory "post-progression tumor samples" and optional tumor samples from any time since diagnosis of the tumor disease (ie, archival tumor samples) may be analyzed for, including but not necessarily limited to, VEGFR-2, MET expression, MET and EGFR amplification, and HGF expression.
  Optional tissue samples for biomarker research from patients willing to consent to additional on study biopsies should be collected at any time during the study if safe and feasible and upon notification of the sponsor (preferably core tumor biopsies; alternatively, cytology or fine-needle aspiration). In particular, biopsies from patients

progressing on study therapy are encouraged to be performed, provided no other cancer treatment has been started and the procedure does not impede or delay planned cancer treatment.

- Blood samples: Blood samples may be analyzed for, including but not necessarily limited to, circulating levels of VEGF-A, soluble VEGFR-2, PlGF, HGF, and MET-ECD. Blood biomarker levels from the study treatment period may be compared with baseline (screening). In addition, the time course of blood biomarker levels during the study and PK/PD biomarker relationship may be evaluated.

Details for the handling and shipping of tumor biopsy samples will be provided in a separate document. Instructions and supplies required for the collection, processing, and shipment of the patients' tissue and blood samples will be provided by the sponsor.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Samples will be destroyed according to a process consistent with local regulation.

10.2.3. Samples for Drug Concentration Measurements Pharmacokinetics

Pharmacokinetic samples will be collected as specified in the Pharmacokinetic and Pharmacodynamic Sampling Schedule (Attachment 4).

10.2.3.1. Pharmacokinetic Samples

Blood samples will be collected for the analysis of ramucirumab and LY2875358 levels to estimate the PK parameters of both compounds when administered in combination. Furthermore, PK parameters will be assessed for evaluation of PK/PD relationship, and to inform dose escalation.

The PK sampling times are listed in Attachment 4. Up to 5 additional PK samples may be drawn during the study if warranted and agreed upon by both the investigator and sponsor.

Instructions for the collection and handling of blood samples will be provided by the sponsor or central lab. The actual date and time (24-hour clock time) of each sampling will be recorded.

These samples will be analyzed at a laboratory designated by the sponsor. Serum concentrations of LY2875358 and ramucirumab will be assayed using validated enzyme-linked immunosorbent assay methods.

The PK samples will be stored at a facility designated by the sponsor.

The remaining serum from the samples collected for PK may be pooled and used for exploratory biomarker work as deemed appropriate.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last patient visit for the study.

10.2.4. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against study drugs (ramucirumab and LY2875358). Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of study drugs. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of study drugs.

Samples may be stored for a maximum of 15 years following last patient visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to study drugs. The duration allows the sponsor to respond to regulatory requests related to study drugs.

10.3. Efficacy Evaluations

A secondary objective of the study is to document any antitumor activity. Refer to Attachment 1 for details regarding the timing of specific efficacy measures. Efficacy measures include:

- ORR: The proportion of patients who exhibit a confirmed complete response (CR) or PR relative to baseline as defined by RECIST 1.1 (Eisenhauer et al. 2009)
- DCR: The proportion of patients in the analysis population who exhibit a SD or confirmed CR or PR relative to baseline during the study
- PFS: The time from the date of study enrollment to the date of first observation of objective progression or death from any cause
- Change in tumor size: The change in tumor size from baseline measurement to the measurement with the smallest tumor size during the study.

Each patient will be assessed by one or more of the following radiologic tests for tumor measurement:

- CT scan
- MRI
- Chest x-ray.

Each patient's full extent of disease will also be assessed with:

- Tumor measurement by RECIST 1.1 (Eisenhauer et al. 2009)
- Evaluation of tumor markers, if indicated
- Evaluation of ECOG performance status (refer to Attachment 6).

Consistent with RECIST, all patients may undergo alternative imaging studies consistent with institutional guidelines to assess tumor response. This may include, but is not limited to, FDG-PET, dynamic contrasted-enhanced MRI, or other modalities.

To confirm objective responses, all lesions should be radiologically assessed, and the same radiologic method used for the initial response determination should be repeated at least 4 weeks following the initial observation of an objective response, using the sample method that was used at baseline. If a patient is discontinued from the study, repeat radiology assessments may be omitted if clear clinical signs of progressive disease are present.

10.4. Procedure/Sampling Compliance

Every attempt will be made to enroll patients who have the ability to understand and comply with instructions. Noncompliant patients may be discontinued from the study.

The collection times of safety assessments, PK and PD samples, and efficacy measurements are given as targets, to be achieved within reasonable limits. The scheduled time points may be subject to minor alterations; however, the actual collection time must be correctly recorded.

The scheduled collection times may be modified by the sponsor based on analysis of the safety and PK information obtained during the study. Any major modifications that might affect the conduct of the study, patient safety, and/or data integrity will be detailed in a protocol amendment.

11. Data Management Methods

11.1. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable IRB/ERBs with direct access to the original source documents.

11.2. Data Capture Systems

11.2.1. Case Report Form

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome measures (eg, a rating scale), a daily dosing schedule, or an event diary.

For data handled by a data management third-party organization (TPO), CRF data and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to the Lilly data warehouse, using standard Lilly file transfer processes.

For data handled by the sponsor internally, CRF data and some or all data that are related will be managed by the sponsor and stored electronically in the sponsor's system.

11.2.2. Ancillary Data

Data managed by a central vendor will be stored electronically in the central laboratory's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system and/or TPO's system.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to the Lilly generic labs system and/or TPO's system.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Data Analyses

12.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly.

The interpretation of the study results will be the responsibility of the investigator with the Lilly CRP and/or CRS, pharmacokineticist, and statistician. The CRP and/or CRS and statistician will also be responsible for the appropriate conduct of an internal review for both the final study report and any study-related material to be authorized by Lilly for publication.

The analyses for this study will be descriptive, except for possible exploratory analyses as deemed appropriate. Data analyses will be provided by dose levels and for all patients combined wherever appropriate. For continuous variables, summary statistics will include number of patients (N), mean, median, standard deviation, standard error (SE), minimum, and maximum. Categorical endpoints will be summarized using N, frequency, percentages, and associated SE. Missing data will not be imputed. Exploratory analyses of the data that are not described in the protocol will be conducted as deemed appropriate.

Up to approximately 70 patients may be enrolled in this multicenter Phase 1b/2 study with an open-label, dose escalation design. Patients will be enrolled into cohorts sequentially without randomization to dose level. During dose escalation (Part A), the total samples size per cohort will be determined by DLTs (up to 6 patients per cohort before establishing the MTD). For the tumor-specific expansion cohorts (Part B), additional patients will be enrolled within 3 cohorts for specified tumor types (approximately 15 patients per group). The sample size of approximately 15 patients for the tumor-specific expansion cohorts was selected to allow adequate assessment of safety at the recommended dose and to identify evidence of activity worthy of further investigation in Phase 2.

12.2. Patient Disposition

All patient discontinuations will be documented, and the extent of each patient's participation in the study will be reported. If known, a reason for their discontinuation will be given.

12.3. Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics including age, sex, screening height and weight, and screening body mass index
- Baseline disease characteristics
- Prior disease-related therapies
- Concomitant medications.

Other patient characteristics will be summarized as deemed appropriate.

12.4. Safety Analyses

All patients who receive at least 1 dose of ramucirumab and/or LY2875358 will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using NCI CTCAE Version 4.03.

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drugs
- Dose adjustments
- Laboratory values
- Vital signs
- DLTs at each dose level
- ECG readings.

12.5. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of study drug(s) and have had samples collected.

Population PK models for LY2875358 and ramucirumab may be developed using nonlinear mixed effect modeling. The LY2875358 PK data from this study may be added to data available from other studies, such as the Phase 1 Study JTBA, and the base model for LY2875358 will be the previously developed TMDD model. Noncompartmental methods may also be used if warranted by the data.

The parameters for ramucirumab will include steady-state maximum (Css,max) and steady-state minimum (Css,min) and area under the concentration-time curve during the dosing interval at steady state ($AUC_{\tau,ss}$).

The parameters for LY2875358 may include systemic clearance (CL), volume of distribution (V), Css,min, or TMDD model parameters, such as receptor-mediated clearance, non–receptor-mediated clearance, volume of the central compartment, and volume of the peripheral compartment.

Additional exploratory analyses will be performed if warranted by data. These exploratory analyse may include:

- Evaluating the relationship between PK and antitherapeutic antibodies
- Evaluating the relationship between PK and biomarkers, such as MET ECD
- Evaluating the relationship between exposure and response in terms of safety and efficacy (eg, incidence of adverse reactions, PFS, OS, change in tumor size).

The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation. It is possible that other validated equivalent PK software programs may be used if appropriate, warranted, and approved by Global Pharmacokinetic Management.

12.6. Efficacy

The study was not designed to make a comparative efficacy assessment. However, as a co-primary objective for Part B, this study will evaluate preliminary antitumor activity observed with ramucirumab in combination with LY2875358 in the tumor-specific expansion cohorts in terms of ORR. Any tumor response data will be tabulated for Part A and Part B.

12.7. Biomarker Analyses

Section 10.2.2 provides a description of the biomarker samples that may be used to carry out biomarker-specific exploratory analyses as mentioned in Section 6.3. Planned exploratory analyses will include, but are not limited to, known or hypothesized biomarkers that are related to VEGF and MET signaling pathways, or tumor biology of the respective tumor types enrolled or associated with sensitivity/resistance to the study drugs.

Across all parts of the study, blood and tissue samples specified (including post-progression- and/or archived tumor samples) may be analyzed to explore potential biomarker(s) associated with response to treatment. Somatic mutation status and/or copy number variations of genes that are targets of the study drug(s), known to be risk factors for cancer, or associated with resistance to anticancer therapies will be analyzed at a laboratory designated by the sponsor. This analysis may employ targeted or whole-exome sequencing approaches.

In Parts B1-4 of the study, tumor-specific biomarker results based on immunohistochemical (IHC), fluorescence in-situ hybridization (FISH), polymerase chain reaction (PCR), or other means for detection and quantitation of cancer-associated protein or nucleic acid changes may be investigated with the aim of identifying genetic variation(s) and/or variations in protein expression that are associated with favorable clinical response within each tumor type or more broadly across multiple tumor types.

All biomarkers will be specifically investigated with the aim of developing a patient stratification strategy that will enable defining a target patient population that is more likely to respond to the treatment regimen being investigated and/or less likely to suffer from TEAEs.

Where applicable, the above associative/correlative assessments involving clinical response and biomarker data may be extended or adjusted to include relevant safety, toxicity, and PK/PD endpoints.

12.8. Interim Analyses

An interim analysis will be performed after completion of Part A.

Since this is a dose-finding study, data will be reviewed on a cohort-by-cohort basis during the study until the MTD is determined. The purpose of these cohort-by-cohort reviews is to evaluate the safety data at each dose level and to determine if a DLT has been observed that would suggest MTD has been met or exceeded. Based on these interim results, modifications to the dose escalation strategy or other design elements may be made via protocol amendment to ensure patient safety. The investigators and the Lilly study team will make the determination regarding

dose escalation based upon their review of the safety and tolerability data as described in this protocol.

For Part B, interim analyses will be conducted approximately 3 months after the 15th patient in Parts B1, B2, and B4 (that is gastric, hepatocellular, and non-small cell lung cancers) and approximately 6 months after the 15th patient in Part B3 (renal cell cancer) starts study therapy. Further interim analysis may be considered if deemed appropriate by the sponsor.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study in a timely manner.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study and to document that the patient is satisfied with his or her understanding of the potential risks and benefits of participating in the study and desires to participate in the study.

The investigator is ultimately responsible for ensuring that informed consent is given by each patient before the study is started. 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 study drug.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites. All ICFs must be compliant with the ICH guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative sites. The ERBs will review the protocol as required.

The study site's ERBs should be provided with the following:

- the current IB, Patient Information Leaflet, or Package Insert, and updates during the course of the study
- ICF
- relevant curricula vitae.

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines

2) the ICH GCP Guideline [E6]

3) applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERBs.

Some of the obligations of the sponsor will be assigned to a TPO.

An identification code assigned by the investigator to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other study-related data.

13.3.1. Investigator Information

Site-specific contact information may be provided in a separate document.

13.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The final report coordinating investigator or designee will sign the clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most qualified and evaluable patients will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol JTBF Study Schedule

Screening/Baseline Assessments

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤7	Comments
Informed Consent	X			Informed consent MUST be signed before performing any protocol procedure
Radiological Tumor Assessment (including head-contrasted CT or brain MRI)	X			These scans can be performed locally and may be from prior to consent if taken within 28 days of Day 1, Cycle 1. PET/CT allowed if CT portion is of diagnostic quality
Chest X-Ray	X			May be omitted in patients having a chest CT for their radiological tumor assessment
Functional Tumor Imaging	X			FDG-PET mandatory in Part B1 (gastric). Further functional tumor imaging (including but not limited to DCE-MRI, FLT-PET) is permitted in all patients if appropriate for the respective tumor type at the discretion of the investigator and considered institutional standard of care or is part of an appropriate imaging study open at the site.
Hepatitis B and C Screening	X			Screening is required (see Attachment 2); may be from prior to consent if done within 6 months of Day1, Cycle 1; Hepatitis B surface antigen and hepatitis C (antibodies or RNA according to local standard)
"Post-Progression Tumor Sample" (baseline)	X			Mandatory (see Section 10.2.1); may be from prior to consent if taken within 8 weeks of Day 1, Cycle 1. If this is not available, patient must undergo a tumor biopsy pre-study treatment
Archival Tumor Sample	X			Optional (see Section 10.2.2)
Medical History		X		Including alcohol/tobacco use/other relevant habits
Physical Examination		X		Including height and body weight
Vital Signs		X		Temperature, blood pressure (seated), heart rate, and respiration rate
Performance Status		X		Per ECOG scale (see Attachment 6)
CTCAE Version 4.03 Grading (Preexisting Conditions)		X		To be reported only after study eligibility is confirmed. Refer to Section 10.1.2 for reporting expectations.
Concomitant Medications		X		See Section 9.5
Local 12-Lead Electrocardiogram		X		Single ECG
Hematology		X		See Attachment 2
Serum Chemistry including calculated creatinine clearance		X		See Attachment 2
Coagulation		X		See Attachment 2
Urinalysis		X		See Attachment 2
Immunogenicity		X		
Sampling for Exploratory Blood Biomarkers		X		See Section 10.2.2
Serum Pregnancy Test			X	Negative serum pregnancy test result required prior to dosing for women of child-bearing potential

Abbreviations: CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DCE-MRI = dynamic contrasted-enhanced magnetic resonance imaging; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FDG-PET = 2-deoxy-2[F-18]fluoro-D-glucose positron emission tomography; FLT-PET = 3-deoxy-3[F-18]fluorothymidine positron emission tomography; PET = positron emission tomography; RNA = ribonucleic acid.

During- and Post-study Assessments

	Cycle 1					Cycle 2			Cycle 3–n		Short Term Follow-Up Visit 801[a]	Comments
Relative Day Within a Cycle	**1**	**2**	**8** (±1 day)	**15** (±1 day)	**22** (±1 day)	**1** (±2 days)	**8** (±2 days)	**15** (±2 days)	**1** (±3 days)	**15** (±3 days)		
Ramucirumab	X			X		X		X	X	X		
LY2875358	X			X		X		X	X	X		
Physical Examination	X		X	X		X		X	X		X	All physical examinations should include palpation of the thyroid
Weight	X		X	X		X		X	X	X	X	
Vital Signs	X	X	X	X		X	X	X	X	X	X	Temperature, blood pressure (seated), heart rate, and respiration rate
ECOG Performance Status	X					X			X		X	See Attachment 6
Local 12-Lead ECG[b]	X			X		X		X	X	X	X	Single ECG at each time point
Hematology [c]	X		X	X	X	X	X	X	X	X	X	Predose (see Attachment 2)
Serum Chemistry[c]	X		X	X	X	X	X	X	X	X	X	Predose (see Attachment 2)
Coagulation[c]	X		X	X	X	X	X	X	X	X	X	Predose (see Attachment 2)
Urinalysis[c,d]	X		X	X	X	X	X	X	X	X	X	Predose (see Attachment 2)
Pregnancy Test						X			X			Serum or urine. Females of childbearing potential only (see Attachment 2)
Tumor Marker	X					X			X		X	Depending on the respective tumor type (see Attachment 2)
Hormonal Panel (TSH and fT4)	X					X			X[e]		X	See Attachment 2
CTCAE Version 4.03 Grading	X					X			X		X	Collected throughout the study as needed. Refer to Section 10.1.2 for reporting expectations
Concomitant Medications	X					X			X		X	Throughout study as needed. See Section 9.5

	Cycle 1					Cycle 2			Cycle 3–n		Short Term Follow-Up Visit 801[a]	Comments
Relative Day Within a Cycle	**1**	**2**	**8** (±1 day)	**15** (±1 day)	**22** (±1 day)	**1** (±2 days)	**8** (±2 days)	**15** (±2 days)	**1** (±3 days)	**15** (±3 days)		
PK and PD Sampling[f]	Refer to Attachment 4 and Attachment 7											Refer to Attachment 4 and Attachment 7 for details. No further sampling after Cycle 9 but a sample is required at short term follow up visit (V801)
Immunogenicity[f]	X			X		X		X	X		X	See Section 9.2.3.1
Exploratory Blood Biomarker Sampling	X	X	X	X		X		X	X[e]		X	
Pharmacogenetic Sampling	X											This is a one-time sample which may be taken during Cycles 1 or 2
Optional Tumor Biopsy	X											Throughout study (see Section 10.2.1)
Radiological Tumor Assessment[g]	X											Every 6 weeks after initiation of study treatment; after Cycle 9 every 2-4 cycles as clinically indicated
Functional Tumor Imaging	X[h]											FDG-PET mandatory in Part B1 (gastric) 6 weeks after initiation of study therapy

Abbreviations: CNS = central nervous system; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DCE-MRI = dynamic contrasted-enhanced magnetic resonance imaging; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FDG-PET = 2-deoxy-2[F-18]fluoro-D-glucose positron emission tomography; FLT-PET = 3-deoxy-3[F-18]fluorothymidine positron emission tomography; fT4 = free thyroxine; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; TSH = thyroid-stimulating hormone; V = visit.

a Short-term follow-up begins on the day after the patient's last dose of study drug and ends approximately 30 days later. This visit should be scheduled 30 ± 3 days after last dose of study drug.

b Electrocardiograms must be recorded before any study drug is administered. In Cycle 1, Day 1 and 15 only, additional ECGs must be recorded pre- and post-LY2875358 infusion, immediately before collecting the corresponding PK samples.

[c] Local hematology, coagulation tests, and urinalysis may be done within 2 days prior to administration of study drugs (except Cycle 1, Day 1 [within 3 days]). An additional local chemistry panel according to local standard of care may be done and used for on-study dosing decisions; if done so, chemistry testing must also still be performed by the central laboratory at the regularly scheduled time points. The central chemistry laboratory results will be used for patient eligibility and subsequent safety analyses. In exceptional cases, patient may be enrolled based on local chemistry results after discussion with the sponsor if central laboratory samples results required for eligibility are not available in a timely manner (e.g., due to inclement weather conditions).

[d] If, while receiving the investigational product(s), a patient has proteinuria ≥2+ per a dipstick or routine urinalysis test, a 24-hour urine collection will be conducted prior to the subsequent scheduled treatment (see Section 9.2.3.2.2).

[e] Samples will be collected at Cycle 3, Cycle 5, Cycle 7, Cycle 9, and every 4 cycles thereafter while patient is on study treatment.

[f] If a patient experiences an infusion-related reaction (see Section 9.2.3.1), immunogenicity samples for anti-ramucirumab and anti-LY2875358 antibodies and PK samples will be taken as close to the onset of the event as possible, at the resolution of the event, and approximately 30 days following the event.

[g] The method of assessment used at baseline must be used consistently for tumor assessment and will be repeated approximately every 6 weeks (±7 days) during the study treatment period for lesions outside the CNS. For those patients with known CNS metastases, ongoing CNS surveillance using the same modality is required approximately every 12 weeks (±7 days). Positron emission tomography /CT is allowed if CT portion is of diagnostic quality.

[h] For patients in Part B1 (gastric), the mandatory FDG-PET approximately 6 weeks (±7 days) after initiation of study treatment should be performed only if the baseline FDG-PET demonstrated PET avid lesion(s). Further functional tumor imaging (including but not limited to DCE-MRI, FLT-PET) is permitted throughout the study in all patients if appropriate for the respective tumor type at the discretion of the investigator and considered as institutional standard of care or is part of an appropriate imaging study open at the site.

Attachment 2. Protocol JTBF Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]:	**Clinical Chemistry**[d]:
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Chloride
Neutrophils	Magnesium
Lymphocytes	Total bilirubin
Monocytes	Alkaline phosphatase
Eosinophils	Alanine aminotransferase (ALT)
Basophils	Aspartate aminotransferase (AST)
Platelets	Lactate Dehydrogenase (LDH)
	Total protein
Coagulation Tests[a]**:**	Albumin
Prothrombin time (PT/INR)	Blood urea nitrogen (BUN)
Partial thromboplastin time (PTT)	Creatinine
	Uric acid
Urinalysis[a]:	Calcium
Specific gravity	Glucose, random
pH	C-reactive protein
Protein[b]	Cholinesterase (CHE)
Glucose	
Ketones	**Calculated creatinine clearance**[d, e]
Blood	
Urine leukocyte esterase	**Hormone panel**[d]
	Thyroid stimulating hormone (TSH)
Hepatitis Tests[a]	Free thyroxine (fT4)
Hepatitis B surface antigen (HBSAg)	
Hepatitis C	**Tumor marker**[d]
	Carcinoembryonic antigen (CEA; all pts)
Pregnancy Test (female patients only)[a,c]	Alpha Fetoprotein (AFP; HCC pts only)
	CA19.9 (gastric cancer pts only)

Abbreviations: HCC = hepatocellular carcinoma; INR = International Normalized Ratio; pts = patients; RBC = red blood cells; WBC = white blood cells;

a Local or investigator-designated laboratory.

b If urine dipstick or routine urinalysis indicates proteinuria ≥2+ at screening and/or while receiving study drugs, a 24-hour urine collection must be obtained to locally assess urine protein concentrations.

c For women of child-bearing potential only. Serum test required at screening and within 7 days prior to initiation of study treatment. Urine or serum test may be performed prior to treatment at all other time points.

d Assayed by Lilly-designated laboratory.

e For screening/baseline assessment only.

Attachment 3. Protocol JTBF Hepatic Monitoring Tests for Treatment Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly clinical research physician/clinical research scientist.

Hepatic Monitoring Tests[a]

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferease; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = International Normalized Ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated or local laboratory.

b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 4. Protocol JTBF Pharmacokinetic and Pharmacodynamic Sampling Schedule

Pharmacokinetic and Pharmacodynamic Sampling Schedule

Study Period		Approximate Running Time (h)[a]	Unique Sample ID	Sample Description	LY2875358	Ram	MET ECD
Cycle 1	Day1	0	1	Pre-Ramucirumab Infusion	X	X	X
		1	2	End of Ramucirumab Infusion	X	X	X
		*Minimum of approximately **60** minutes between infusions*					
		2	3	Pre-LY2875358 Infusion[b]	X	X	
		3.5	4	End of LY2875358 Infusion (EOI)	X	X	X
		6.5	5	3 h Post-LY2875358 EOI	X	X	
		8.5	6	5 h Post-LY2875358 EOI	X	X	
		11.5	7	8 h Post-LY2875358 EOI	X	X	
	Day 2	24	8	21 h Post-LY2875358 EOI	X	X	X
	Day 8	168	9	Anytime on Day 8	X	X	X
	Day 15	0	10	Pre-Ramucirumab Infusion	X	X	X
		1	11	End of Ramucirumab Infusion	X	X	X
		*Minimum of approximately **60** minutes between infusions*					
		2	12	Pre-LY2875358 Infusion[b]	X	X	
		3.5	13	End of LY2875358 Infusion (EOI)	X	X	X
		6.5	14	3 h Post-LY2875358 EOI	X	X	
		8.5	15	5 h Post-LY2875358 EOI	X	X	
	Day 22	168	16	Anytime on Day 22	X	X	X
Cycle 2	Day 1	0	17	Pre-Ramucirumab Infusion	X	X	X
		1	18	End of Ramucirumab Infusion	X	X	X
		*Minimum of approximately **30** minutes between infusions*					
		1.5	19	Pre-LY2875358 Infusion[b]	X	X	
		3	20	End of LY2875358 Infusion	X	X	X
	Day 8	168	21	Anytime on Day 8	X	X	X
	Day 15	0	22	Pre-Ramucirumab Infusion	X	X	X
		1	23	End of Ramucirumab Infusion	X	X	X
		*Minimum of approximately **30** minutes between infusions*					
		1.5	24	Pre-LY2875358 Infusion[b]	X	X	
		3	25	End of LY2875358 Infusion	X	X	X

Study Period		Approximate Running Time (h)*	Unique Sample ID	Sample Description	LY2875358	Ram	MET ECD
Cycle 3	Day1	0	26	Pre-Ramucirumab Infusion	X	X	X
		1	27	End of Ramucirumab Infusion	X	X	X
		*Minimum of approximately **30** minutes between infusions*					
		1.5	28	Pre-LY2875358 Infusion[b]	X	X	
		3	29	End of LY2875358 Infusion (EOI)	X	X	X
	Day 15	0	30	Pre-Ramucirumab Infusion	X	X	X
		1	31	End of Ramucirumab Infusion	X	X	X
		*Minimum of approximately **30** minutes between infusions*					
		1.5	32	Pre-LY2875358 Infusion[b]	X	X	
		3	33	End of LY2875358 Infusion (EOI)	X	X	X
Cycle 5	Day1	0	34	Pre-Ramucirumab Infusion	X	X	X
		1	35	End of Ramucirumab Infusion	X	X	X
		*Minimum of approximately **30** minutes between infusions*					
		1.5	36	Pre-LY2875358 Infusion[b]	X	X	
		3	37	End of LY2875358 Infusion (EOI)	X	X	X
	Day 15	0	38	Pre-Ramucirumab Infusion	X	X	X
		1	39	End of Ramucirumab Infusion	X	X	X
		*Minimum of approximately **30** minutes between infusions*					
		1.5	40	Pre-LY2875358 Infusion[b]	X	X	
		3	41	End of LY2875358 Infusion (EOI)	X	X	X

Study Period		Approximate Running Time (h)*	Unique Sample ID	Sample Description	LY2875358	Ram	MET ECD
Cycle 7	Day1	0	42	Pre-Ramucirumab Infusion	X	X	X
		1	43	End of Ramucirumab Infusion	X	X	X
		*Minimum of approximately **30** minutes between infusions*					
		1.5	44	Pre-LY2875358 Infusion[b]	X	X	
		3	45	End of LY2875358 Infusion (EOI)	X	X	X
	Day 15	0	46	Pre-Ramucirumab Infusion	X	X	X
		1	47	End of Ramucirumab Infusion	X	X	X
		*Minimum of approximately **30** minutes between infusions*					
		1.5	48	Pre-LY2875358 Infusion[b]	X	X	
		3	49	End of LY2875358 Infusion (EOI)	X	X	X
Cycle 9	Day1	0	50	Pre-Ramucirumab Infusion	X	X	X
		1	51	End of Ramucirumab Infusion	X	X	X
		*Approximately **30** minutes between infusions*					
		1.5	52	Pre-LY2875358 Infusion[b]	X	X	
		3	53	End of LY2875358 Infusion (EOI)	X	X	X
	Day 15	0	54	Pre-Ramucirumab Infusion	X	X	X
		1	55	End of Ramucirumab Infusion	X	X	X
		*Approximately **30** minutes between infusions*					
		1.5	56	Pre-LY2875358 Infusion[b]	X	X	
		3	57	End of LY2875358 Infusion (EOI)	X	X	X
Follow-up Visit (Visit 801)			58	Anytime During Follow-up Visit	X	X	X

Abbreviations: EOI = end of infusion; MET ECD = mesenchymal epithelial transition factor – extracellular cleaved domain; Ram= ramucirumab.

[a] Approximate running time relative to start of each ramucirumab infusion.

[b] Sample should be obtained immediately prior to LY2875358 infusion.

Note: Samples are requested to be taken immediately before and immediately after the end of the study drug infusions. Aberrations to specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded. It is essential that the actual times of ramucirumab and LY2875358 doses and samples are recorded accurately on the appropriate forms.

Attachment 5. Protocol JTBF Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events (SAEs)

When contacting Lilly to report a SAE, please have the following information available:

Patient Demographics

- patient identification (number), sex, date of birth, origin, height, and weight

Study Identification

- full trial protocol number, investigator's name, investigator's number

Study Drug

- drug code or drug name, unit dose, total daily dose, frequency, route, start dose, cycle details, start date and last dose date (if applicable)

Adverse Event

- description, date of onset, severity, treatment (including hospitalization), action taken with respect to study drug, clinical significance, test and procedure results (if applicable)

Relationship to Study Drug & Protocol Procedures

Concomitant Drug Therapy

- indication, total daily dose, duration of treatment, start date, action taken

In Case of Death

- cause, autopsy finding (if available), date, relationship to study drug and protocol procedures.

Attachment 6. Protocol JTBF ECOG Performance Status

ECOG Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out performance of a light or sedentary nature, for example, light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken et al. 1982.

Attachment 7. Protocol JTBF Sampling Summary

This table summarizes the maximum number of samples, average volume amount per sample, and laboratory tests to be obtained during the study. The summary below provides estimates only. More samples could be required in case of retests, additional health monitoring (if needed), or for patients continuing treatment beyond the protocol-specified number of cycles in the study. Fewer samples may actually be taken (eg, patients who discontinue from the study).

Protocol I4C-MC-JTBF Sampling Summary[a]

Purpose	Sample Type	Average Amount per Sample	Maximum Number of Samples	Maximum Total Amount
Screening Tests[b]	Blood	6 mL	9	52 mL
Cycle 1 Health Monitoring Tests[a]	Blood	4.5 mL	12	54 mL
Cycle 2 Health Monitoring Tests[a]	Blood	4.5 mL	9	41 mL
Cycle 3-5 Health Monitoring Tests[a]	Blood	5.0 mL	9	87 mL
Visit 801 Health Monitoring Tests[a]	Blood	5.0 mL	3	16 mL
Exploratory Biomarkers[c]	Blood	5.5 mL	36	203 mL
Drug Concentration for Ramucirumab[c]	Blood	2 mL	42	84 mL
Drug Concentration for LY2875358[c]	Blood	2 mL	42	84 mL
Pharmacogenetic Sample	Blood	10	1	10 mL
Immunogenicity (for Ramucirumab and LY2875358)[c]	Blood	8.5 mL	8	68 mL
MET-ECD	Blood	3mL	29	87 mL
Hepatic Monitoring[c]	Blood	3 - 30 mL	-	-
Tumor Biopsy Tissue[d]	Tumor tissue FFPE block or unstained tumor tissue slides	N/A		1 FFPE block OR approximately 15, 4 micron unstained slides
Total	Blood			788 mL
Total	Tissue			1 FFPE block OR approximately 15, 4 micron unstained slides

Abbreviations: FFPE = formalin-fixed paraffin-embedded; MET-ECD = mesenchymal epithelial transition factor – extracelluar cleaved domain; N/A = not applicable.

[a] Additional samples may be drawn, if needed, for safety purposes.

[b] Covers all tests collected at screening.

[c] Covers Cycles 1 through 5 and Visit 801.

[d] This references only the required mandatory "post-progression tumor sample" collected at baseline. An optional archival biopsy tissue sample and/or optional tumor biopsy sample performed on study and/or at Visit 801 may also be collected.

Attachment 8. Protocol JTBF RECIST Criteria 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements.. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the CRF in millimeters (or decimal fractions of centimeters).

Nontarget Lesions

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (eg, multiple liver metastases recorded as one liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumour type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR). Specific guidelines for both prostate-specific antigen (PSA) response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

Pet Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

Partial Response (PR): At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Nontarget Lesions

Complete Response: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10mm short axis).

Non-CR/ non-PD: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The Best Overall Response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table 1. Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; PR = partial response; SD = stable disease.; PD = progressive disease; NE = inevaluable.

Table 2 is to be used when patients have *nonmeasurable* disease only.

Table 2. Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease ; NE = inevaluable.

[a] non-CR/non-PD is preferred over SD for nontarget disease.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6-8 weeks is reasonable. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from first dose.

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Independent Review of Response and Progression

When objective response (CR + PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Attachment 9. Protocol Amendment I4C-MC-JTBF(b) Summary: A Phase 1b/2 Study of Ramucirumab in Combination with LY2875358 in Patients with Advanced Cancer

Overview

The overall changes and rationale for the changes made to this protocol are as follows:

- The primary rationale for amendment (b) is to is to modify Exclusion Criterion [28] and allow patients that have been previously treated with ramucirumab may be included in Part B1.
- Updated Sections 5.2.1 and 5.2.1.2 (ramucirumab clinical information)
- Updated Section 5.2.2 (LY2875358 clinical information)
- Modified Section 9.2.3 (dosage adjustments and delays) to align with discontinuation criteria
- Clarified Section 9.5 (use of granulocyte colony stimulating factor)
- Corrected Section 12.1 (approximately 70 patients may be enrolled in this multicenter Phase 1b/2 study)
- Minor editorial changes have been made throughout the protocol to improve clarity and practicability of the protocol.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

5.2.1. Ramucirumab

~~Ramucirumab has been studied and/or continues to be investigated in ongoing clinical studies for multiple tumor indications. As of 31 December 2012, safety information was available for 1199 patients receiving ramucirumab in 7 Phase 1/1b studies, 16 open-label Phase 2 studies, and 1 Phase 3 study, including monotherapy and combination therapy with cytotoxic chemotherapy agents. In these studies, ramucirumab has demonstrated a favorable safety and clinical activity profile. The most frequently observed possibly related treatment-emergent adverse events (TEAEs) of special interest include adverse events (AEs) which have been associated with anti-angiogenic agents and therapeutic mAbs, and include the following categories: infusion-related reaction, hypertension, proteinuria, arterial thromboembolic events (ATEs), venous thromboembolic events (VTEs), bleeding/hemorrhagic events, gastrointestinal (GI) perforation, impaired wound healing, reversible posterior leukoencephalopathy syndrome (RPLS), and congestive heart failure (CHF) in patients who received ramucirumab following prior anthracycline therapy.~~

~~Data from Phase 1, 2, and 3 studies provide supporting evidence for ramucirumab activity in advanced solid tumors, including gastric or GEJ adenocarcinoma, hepatocellular carcinoma, renal cell cancer, and NSCLC.~~

The results of these preclinical pharmacodynamic studies supported the initial investigation of ramucirumab in the treatment of solid tumors.

Clinical investigations with ramucirumab in solid tumors have resulted in 4 positive Phase 3 trials, with 2 in gastric cancer (REGARD and RAINBOW), 1 in NSCLC (REVEL), and 1 in metastatic colorectal cancer (CRC; RAISE). Ramucirumab (Cyramza®) is approved in the United States as a single agent or in combination with paclitaxel as a treatment for people with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose cancer has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy, and in combination with docetaxel as a treatment for people with metastatic NSCLC whose cancer has progressed on or after platinum-based chemotherapy. In addition, the European Commission approved ramucirumab (Cyramza) in combination with paclitaxel and as a single agent when combination therapy is not appropriate, for people with advanced gastric cancer after prior chemotherapy.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of ramucirumab may be found in the IB. Information on AEs expected to be related to ramucirumab may be found in Section 7 (Development Core Safety Information [DCSI]) of the IB. Information on serious adverse events (SAEs) expected in the study

population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

5.2.1.2 Ramucirumab and Hepatocellular Cancer

~~A randomized, controlled Phase 3 trial of ramucirumab monotherapy versus placebo in a second-line setting (post-sorafenib) for advanced hepatocellular carcinoma is currently ongoing (NCT01140347).~~

A randomized, controlled Phase 3 trial (Study I4T-IE-JVBF; Study JVBF, also known as REACH) of ramucirumab monotherapy versus placebo in a second-line setting (post-sorafenib) for advanced HCC is currently ongoing (NCT01140347). Study JVBF is a global, randomized, double-blind Phase 3 study of ramucirumab plus BSC compared to placebo and BSC as a second-line treatment in patients with HCC who have been previously treated with sorafenib in the first-line setting. The study did not meet its primary endpoint of OS; although the OS results favored the ramucirumab arm, they were not statistically significant. Encouraging single-agent ramucirumab activity was observed, with meaningful improvements in key secondary endpoints of PFS, objective response rate (ORR), and time to progression (TTP).

5.2.2. LY2875358

As of ~~19~~18 March ~~2013~~2014, cumulatively ~~83~~184 subjects have received LY2875358 in the ~~2~~6 ongoing clinical trials, ~~Studies JTBA and JTBD~~including 123 patients receiving LY2875358 monotherapy. No dose-limiting toxicities (DLTs) have been reported for either LY2875358 monotherapy or for combination therapy with erlotinib in ~~these studies.~~in the dose escalation Studies JTBA and JTBD. The most frequently reported treatment-emergent adverse events (TEAEs) possibly related to LY2875358 monotherapy ~~in Study JTBA (N=60 patients) included~~across all studies within the LY2875358 clinical program include fatigue (~~13~~16.3%), nausea (9.8~~.3~~%), diarrhea (5.~~0%), and vomiting (5.0%) (all Grade 1~~ 7%), and ~~2). In this study, 3 Grade 3 AEs were considered~~peripheral edema (5.7%). A total of 7 possibly related ~~to~~TEAEs (≥Grade 3) for LY2875358~~: edema,~~ monotherapy were reported: 2 events of fatigue~~,~~ and 1 event each of peripheral edema, pancreatitis~~. In Study JTBD (N=9 patients), the only AE that study investigators have considered possibly related to LY2875358 monotherapy in >1 patient was hypoalbuminemia (n=2; 1 Grade 1 and 1 Grade 2). In this study, 1 Grade 3 AE was considered possibly related to LY2875358: ~~, anemia~~., nausea, and hyponatremia. A total of ~~45 serious adverse events (~~87 SAEs~~)~~ have been reported in the Lilly Safety System (LSS) database in Studies JTBA and JTBD as of ~~19~~18 March ~~2013~~2014. Of these SAEs, 5 were considered possibly related to LY2875358 by either the investigator or the sponsor, including 1 event each of thrombocytopenia, pancreatitis, dyspnea, pyrexia, and ~~pleural effusion in a patient with non-small cell lung cancer (NSCLC) and 2 events of~~ peripheral edema in ~~patients~~a patient with pre-existing edema.

Study JTBA has been amended and is currently enrolling patients in 5 different tumor-specific expansion cohorts for dose confirmation of LY2875358 monotherapy at 2000 mg Q2W, including cohorts for renal cancer and ~~hepatocellular carcinoma~~HCC patients (approximately 15

patients each). In the renal cell cancer cohort, 3 out of 15 evaluable patients demonstrated SD as their best response, including a papillary renal cancer patient who has been on study for 12 months as of October 2013 (data on file). ~~A further~~Further durable, confirmed ~~PR~~PRs for LY2875358 monotherapy ~~has~~have been observed in a patient enrolled in the HCC cohort and for a patient in the uveal melanoma with liver metastases cohort. No data are so far available for LY2875358 monotherapy in ~~hepatocellular carcinoma and~~ gastric cancer patients, as the ~~respective expansion cohort for hepatocellular carcinoma in JTBA and an~~ Asian gastric cancer patient study for LY2875358 monotherapy (Study I4C-JE-JTBE) ~~have been opened only recently~~is pending analysis.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) for ramucirumab and LY2875358 may be found in the respective molecule IBs. Information on AEs expected to be related to the investigational products may be found in Section 7 ~~(Development Core Safety Information [~~DCSI~~])~~ of the respective IBs. Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the respective IBs.

5.3.2. Rationale for Amendment (b)

The rationale for amendment (b) is to modify Exclusion Criterion [28] and allow patients previously treated with ramucirumab to enroll in Part B1 (Gastric or GEJ adenocarcinoma) and Part B4 (NSCLC) cohorts reflecting the approval of ramucirumab for those tumors since initiation of the study.

Minor editorial changes have been made throughout the protocol to improve clarity and practicability of the protocol, secure alignment with the intended study design, and update information available for study drugs.

7.2. Exclusion Criteria

[28] Have received previous treatment with ramucirumab or LY2875358, except for patients enrolled in Cohort B1 (Gastric or GEJ adenocarcinoma) and B4 (NSCLC) who may have received previous ramucirumab treatment.

9.2.3. Dose Adjustments and Delays

In case the toxicity is specifically attributable to 1 of the 2 experimental study drugs in the opinion of the investigator (eg, ramucirumab-related hypertension), the patient may continue to receive the other study drug following the regularly scheduled Q2W treatment time points (eg, LY2875358). In this setting, treatment of the withheld study drug (eg, ramucirumab) should be resumed at the next regularly scheduled Q2W treatment time point of the continued study drug (eg, LY2875358) following the resolution of the event causing the hold. Make-up doses of the withheld study drug occurring between regularly scheduled Q2W treatment time points are not permitted in order to keep the administration of both study drugs synchronized to the same study days (ie, Day 1 or 15 of a cycle). In situations where >2 consecutive doses have been missed, events related to the missed doses have resolved, and there is evidence of ongoing disease

control, continuation of ramucirumab and/or LY2875358 may be considered and must be discussed with the Lilly clinical team.

9.5. Concomitant Therapy

Patients should receive full supportive care~~, with the exception that the~~. The routine use of granulocyte colony stimulating factors (G-CSF) is not permitted during this study. ~~Patients should not receive G-CSF prophylactically in any cycle. Granulocyte colony stimulating factors may only be used for patients who have absolute neutrophil count $<0.5 \times 10^9$, neutropenic fever, or documented infections while neutropenic. Granulocyte colony stimulating factors or pegylated G-CSF must be discontinued at least 24 hours or 1 week before the start of the next cycle of treatment, respectively.~~ If clinically indicated, the use of G-CSF is permitted during investigational therapy at the discretion of the investigator. G-CSF or similar agents are recommended following Grade 3 or 4 neutropenia of duration >5 days or following any incidence of febrile neutropenia (ANC $<1.0 \times 10^9$/L with temperature ≥38.5°C).

12.1. General Considerations

Up to approximately ~~55~~70 patients may be enrolled in this multicenter Phase 1b/2 study with an open-label, dose escalation design. Patients will be enrolled into cohorts sequentially without randomization to dose level. During dose escalation (Part A), the total samples size per cohort will be determined by DLTs (up to 6 patients per cohort before establishing the MTD). For the tumor-specific expansion cohorts (Part B), additional patients will be enrolled within 3 cohorts for specified tumor types (approximately 15 patients per group). The sample size of approximately 15 patients for the tumor-specific expansion cohorts was selected to allow adequate assessment of safety at the recommended dose and to identify evidence of activity worthy of further investigation in Phase 2.

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