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

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1. Statistical Analysis Plan: I4C-MC-JTBF: 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 I4C-MC-JTBF]
[Phase 1b/2]

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

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3. Revision History

This is the second version and was written to include a new cohort of NSCLC in Part B and provide further statistical justification in Section 5.2 Determination of Sample Size. SAP version 2 is approved before any interim analyses in Part B are conducted.

The key changes of the second version are:

- In Section 5.2, sample size is updated due to the addition of NSCLC cohort. Weighted average power is calculated to further justify the clinical utility of the biomarker. Table JTBF 5.3 is added to show the operating characteristics of Simon's optimal two-stage design, which provides details when further patients may be added to enroll up to approximately 45 patients per cohort.
- More details about the definition of PFS are provided in Section 6.12.

4. Study Objectives

4.1. 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).

4.2. 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.

4.3. Exploratory Objectives

The exploratory objectives of this study are:

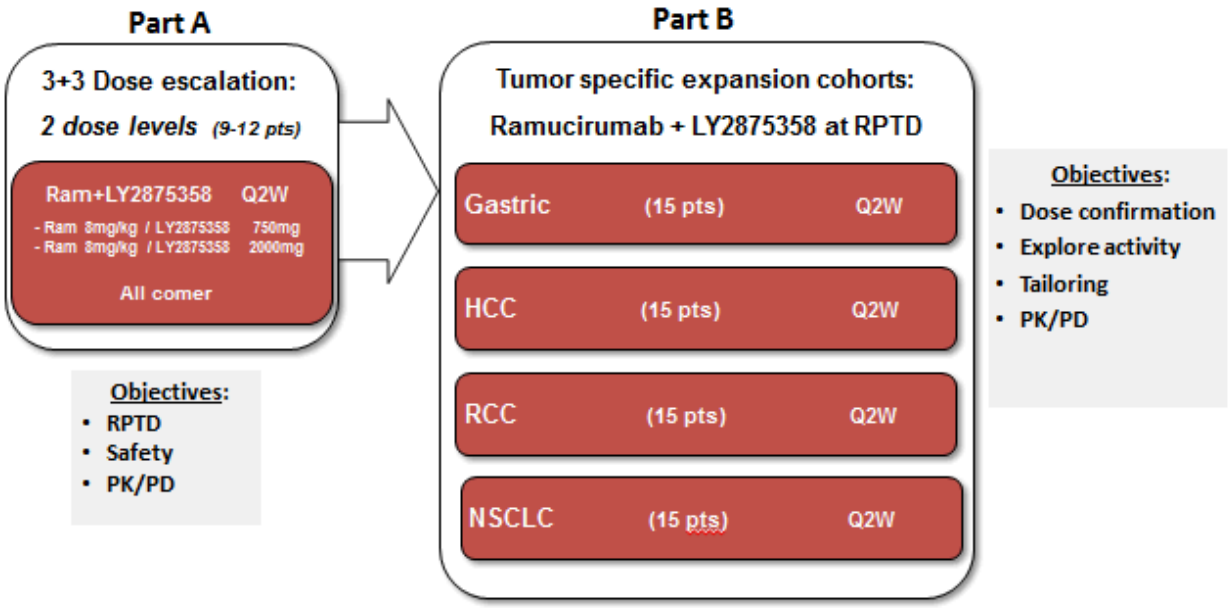
- To evaluate tumor tissue and blood for biomarkers related to the VEGF and MET signaling pathway and tumor biology of the respective tumor types enrolled in the study, which may include but are not necessarily limited to tumor expression (eg, MET and VEGFR-2) and circulating biomarker (eg, VEGF-A, HGF, 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.

5. Study Design

5.1. 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: 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 non-small cell lung cancer (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.5.1).



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

Figure JTBF.5.1. 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. 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.

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. 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 3 tumor-specific expansion cohorts (approximately 15 patients each):

- Part B1: Advanced gastric or GEJ adenocarcinoma
- Part B2: Advanced hepatocellular carcinoma (excluding fibrolamellar carcinoma)
- Part B3: Advanced renal cell carcinoma (all histologies)
- Part B4: Advanced non-small cell lung cancer (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 and/or PK/PD data, the recommended schedule and dose of LY2875358 in Part B might be individually adjusted for each tumor cohort.

To explore potential biomarkers predicting clinical activity for the combination of ramucirumab and LY2875358, availability of tumor samples after progression 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 was amended prior to commencement of Part B, which may include respecification of the selected tumor types for Part B. Based 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, Part B4 for NSCLC was 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 (Protocol 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 (Protocol Section 8.2.1).

5.2. Determination of 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 (i.e., 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 2-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 the REGARD trial, Table JTBF.5.2), then there is a 36.7% chance of incorrectly concluding that the regimen merits further study. Table JTBF.5.1 demonstrates chance of observing at least 1 patient with clinical response for the combination of ramucirumab and LY2875358. For instance, .if the true clinical RR is 10% across all four expansion cohorts in part B, there is 49.3% probability of observing

>=1 responder in all four cohorts. On the other hand, if the true clinical RR is 3%, there is 74.64% probability of still observing at least 1 cohort with >=1 responder. 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 I 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.

Table JTBF.5.1. Multiple cohorts testing characteristics: Comparions of chance of observing at least 1 patient with a clinical response between combination of ramucirumab and LY2875358 and ramucirumab monotherapy cohorts

	Response Rate	Number of cohort(s) where at least 1 patient has a clinical response				
		0	1	2	3	4
Combination	**10%**	0.19%	2.93%	16.51%	41.42%	38.95 %
Monotherapy	**3%**	16.06%	37.23%	32.38%	12.52%	1.81%

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 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 I 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 5.2 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 (Fuchs et al. 2013). The uninteresting RR of NSCLC is based on the average RR of squamous and nonsquamous groups 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 5.3 summarizes landmark disease control and landmark disease control considered of interest to enroll up 45 pateints per cohort. Such decisions will be documented in writing, and a written notification will be sent to the IRB prior to enrollment of further patients.

Table JTBF.5.2. Simon's Optimal Two-stage Design Parameters for Each Cohort

Tumor Type	Uninteresting RR	Favorable RR	1-sided Type I 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	1	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.5.3. Previously Obeserved Antitumor activities of Ramucirumab Monotherapy on Gastric or GEJ adenocarcinoma, Hepatocellular carcinoma, and Renal cell cancer

Tumor Type	Study	n	mPFS	mOS	ORR	DCR	Landmark	Secondary CSF
Gastric/GEJ	JVBD	355	2.1mos	5.2 mos	3%	49%	12-wks PFS 40%	60%
HCC	JVBQ	42	4 mos	12 mos	10%	N/A	4-mos PFS 50%	75%
RCC	JVBP	39	7.1mos	24.8mos	5%	64% (12 week)	7.1-mos PFS 50%	75%
NSCLC	Scagliotti et al. 2011	288	3 mos	7.7 mos	8.6%	N/A	3-mos PFS 50%	75%

Abbreviations: n: number of patients; mPFS: progression free survival in months; mOS: overall survival in months; ORR: overall response rate; DCR: disease control rate; CSF: critical success factor;

In summary, 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 4 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.

5.3. 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.

6. A Priori Statistical Methods

6.1. 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 Clinical Research Physician (CRP), pharmacokineticist, statistician and clinical development associate. The Lilly CRP and statistician will also be responsible for the appropriate conduct of an internal review process for both the final study report and any study-related material to be authorized for publication by Lilly.

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 (SD), standard error (SE), minimum, and maximum. Categorical endpoints will be summarized using N, frequency, percentages, and associated SE.

Exploratory analyses of the data that are not described in the protocol will be conducted as deemed appropriate.

In Part A, all data will be summarized by cohort (and all patients combined when appropriate), unless stated otherwise. In Part B, all data will be summarized by tumor-specific cohort.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the clinical study report.

Table JTBF.6.1. explains the data handling conventions and rules used in the analysis:

Table JTBF.6.1. Data Handling Conventions and Rules

Term	Definition or Rule
Study Day	If assessment is on or after date of first dose then (date of assessment) – (date of first study drug dose) +1
	If assessment precedes first dose of drug then (date of assessment) – (date of first study drug dose)
	There is no study day 0. Study day 1 is the date of first dose and study day -1 is the day before the first dose.
Cycle Day	If assessment is on or after date of first dose in the cycle then (date of assessment) – (date of first study drug dose in cycle) +1
	If assessment precedes first dose of drug in a cycle then (date of assessment) – (date of first study drug dose in cycle)
	There is no cycle day 0. Cycle day 1 is the date of first dose in the

	cycle and cycle day -1 is the day before the first dose.
Baseline	For change from baseline analyses, baseline value is defined as the last reported measure on or before the first dose (prior to the dose administration). For change from baseline within a cycle, the measure prior to the first dose of that cycle is baseline. If more than one pre-dose measure is available, they may be averaged if appropriate.
Entered	Patients who sign the informed consent document.
Enrolled	Patients who have been assigned to a treatment (assigned means they received ≥1 dose for this study).

6.2. Adjustments for Covariates

Adjustment for covariates is not applicable. However, the following variable are of interest and analysis with respect to these variables will be discussed in section 6.14 Subgroup Analyses:

- Age (<= 65 years vs. > 65 years)
- Sex (male vs. female)
- Tumor types (Part B1: Gastric or GEJ adenocarcinoma; Part B2: Hepatocellular cancer (HCC); Part B3: Renal cell carcinoma (RCC, any histology); Part B4: Non-small cell lung cancer (NSCLC, squamous or non-squamous))
- ECOG performance status (0,1 vs 2 in part A and 0 vs 1 in part B)

6.3. Handling of Dropouts or Missing Data

Missing data will not be imputed.

In Part B, patients with response that is deemed non-evaluable will be included in the denominator for the purpose of calculating ORR. Non-evaluable patients are pateints who do not have a measuarable disease at baseline or patients who do not have any post-baseline assessment performed.

6.4. Multicenter Studies

This is a multicenter, non-randomized, open-label study. Enrollment by center and population will be summarized. Because of the limited sample size, endpoint analyses will not be conducted by enrollment center. The investigative center is potentially a prognostic cofactor for efficacy or safety. Therefore, secondary sensitivity analyses using centers or group of centers as a covariate may be performed on selected endpoints to explore whether center have an effect on the efficacy or safety parameters.

6.5. Multiple Comparisons/Multiplicity

No adjustments will be made for multiple comparisons unless otherwise specified.

6.6. Population for Analysis

Safety analyses will be conducted on all patients who have received at least one dose of ramucirumab and/or LY2875358.

Pharmacokinetic analyses will be conducted on patients who have received at least one dose of ramucirumab and/or LY2875358 and have sufficient samples collected to allow the estimation of ramucirumab and/or LY2875358 PK parameters.

Pharmacodynamic analyses will be conducted on patients who who have received at least one dose of ramucirumab and/or LY2875358 and have undergone PD assessments.

Efficacy analyses will be conducted on patients who have received at least one dose of ramucirumab and/or LY2875358.

6.7. Patient Disposition

A detailed description of patient disposition will be provided. It will include summaries of the following:

- The number and percentage of patients entered into the study, treated, as well as the number and percentage of patients completing study.
- All patient discontinuations will be documented, and the extent of each patient's participation in the study will be reported. Data on patient discontinuation from study drug and study (overall and by reason for discontinuation) will be listed. If known, a reasons for patients discontinuation will be given.
- All clinically relevant protocol deviations will be listed by pre-determined categories (for example, inclusion/exclusion criteria, non-compliance with protocol procedures, drug dosage/intervention, use of excluded treatments, informed consent/assent process, continuing after meeting withdrawal criteria, or other).

All patients entered into the study will be accounted for in the summary disposition tables. Patients entered into study are patients who signed main informed consent. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins will be specified.

Screening failures will be listed and summarized: Information includes number of times of screen failures, subject ID(s) from each screen failure and reason for screen failure. Patients that are deemed eligible that were previously screen failures will also be summarized.

6.8. Patient Characteristics

Patient characteristics for the treated population will include a listing and/or summary of the following:

- Patient demographics, including age, sex, screening height and weight, and screening body mass index, reported using descriptive statistics
- Baseline disease characteristics, including initial diagnosis and ECOG performance status, summarized by presenting frequency counts and percentages
- Prior disease-related therapies if known, including dose, best response, duration of response, date of progression and etc.
- Concomitant medications.

6.9. 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.

Potential discontinuation of a patient due to study noncompliance (not attending the scheduled visits; see Protocol Attachment 1) will be presented overall as well as for each cycle.

6.10. Concomitant Therapy

Concomitant medications will be summarized for the safety population using the World Health Organization preferred nomenclature. The numbers and percentages of patients reporting concomitant therapies will be provided overall, by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug name.

Prior therapies, including systemic, radiotherapy, and cancer surgeries will be listed and summarized by cohort and overall for all enrolled patients. The Lilly World Health Organization [WHO] Drug Version Dec 2012 B2 or higher will be used to code therapy.

6.11. 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 delays and dose adjustments

- Laboratory values
- Vital signs
- DLTs at each dose level
- ECG readings
- Deaths on treatment and within 30 days of treatment discontinuation

Hospitalizations and transfusions during the study treatment period or during the 30-day postdiscontinuation follow-up period will be summarized by study parts.

Dose Limiting Toxicity and Equivalent Toxicity

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.

Maximum Tolerated Dose

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.

6.11.1. Extent of Exposure

LY2875358
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.

Ramucirumab
Ramucirumab will be dosed prior to the administration of LY2875358 on Days 1 and 15 of a 28-day cycle in Part A and B of this study.

LY2875358 in combination with Ramucirumab
A patient is said to have received a cycle if they received some of the scheduled/planned dose of study treatment in the cycle. A patient is said to have completed a cycle if they received all of study treatment planned for this cycle. The number of patients receiving/completing a given number of cycles will be presented by dose level and overall in a summary table, as well as listed by patient.

The number of dose reductions, dose delays, and number of cycles received will be summarized for all treated patients by parts and by cohorts. The number of patients with any dose reductions and delays will be presented overall as well as for each cycle by parts and cohorts.

6.11.2. Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be used to report AEs. Any minor version of CTCAE Version 4.0 (for example, CTCAE Version 4.03) may be used for this study. Minor updates to the CTCAE Version 4.0 from the NCI will not necessitate a protocol amendment, and the use of an updated CTCAE Version 4.0 will not be considered a protocol violation. For AEs without matching terminology within the NCI-CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. The verbatim text for these AEs will be coded according to the available version of the Medical Dictionary for Regulatory Activities (MedDRA). For analysis and reporting of AEs, the MedDRA coded terms corresponding to these CTCAE "other-specify" AEs will be used.

A treatment-emergent adverse event (TEAE) is defined as (i) adverse event that occurred after the administration of at least one dose of study therapy, regardless of causality; or (ii) adverse events already present during screening that worsen following exposure to the treatment,

regardless of causality. Event worsen in severity is supported by higher CTCAE grade observed after first dose of study treatment for the corresponding MedDRA lower level term.

The CTCAE term (or MedDRA Lower Level Term (LLT) for cases of CTCAE "other-specify") will be used in the treatment-emergent determination.

The number of patients who experienced a TEAE, SAE, TEAE related to study drug, died, or discontinued from the study due to an AE will be summarized by treatment. Treatment-emergent adverse events will be summarized by System Organ Class (SOC), by decreasing frequency within SOC, and by maximum CTCAE severity grade, including the total of patients with maximum severity grade ≥3.

Historical illnesses (coded according to the MedDRA dictionary) and pre-existing conditions (using CTCAE terms and severity grades) will be listed by part and by cohort. Historical illnesses are events in the past that ended before the Screening Visit. Pre-existing conditions are events that are present at screening and continue. The pre-existing conditions will be presented by patient and can be combined with the adverse event listing, so that the history of the pre-existing conditions/adverse events can be traced.

6.11.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

Deaths and other serious adverse events will be listed and summarised. Summaries for patients on therapy will include:

- Listing of Patients who Discontinued due to Adverse Events or Death
- Listing of Deaths Reported
- Listing of Serious Adverse Events

Reasons for death will be summarized separately for on-therapy and within 30 days of last dose of study drug/last visit. All SAEs will be summarized by preferred term.

6.11.4. Clinical Laboratory Evaluation

Laboratory data (including chemistry, hematology, coagulation, and urinalysis) will be listed for all patients on therapy. Relevant hematology and chemistry laboratory values will be graded according to CTCAE v4.0. The grades will be included on the listing and summarized by the maximum grade at each cycle over the entire study for all patients on therapy.

Abnormal laboratory results will be listed for all patients on therapy by cycle. To the extent that they can be assessed according to CTCAE v4.0 specific grades, these abnormal lab results will be summarized by cohort and cycle independent of clinical findings determined by the investigator. International System of Units (SI units) will be presented in all outputs.

6.11.5. Vital Signs and Other Physical Findings

Vital sign data including blood pressure (BP), pulse rate (PR), temperature (T), respiratory rate (RR), height and weight will be listed and summarized for all patients on therapy. Patients with abnormal vital signs will be listed and summarized.

6.11.6. Electrocardiograms

For each patient, 12-lead ECGs will be obtained according to the Study Schedule (Protocol Attachment 1). All ECG´s will be analyzed for safety and categorical analysis will be provided including:

1. Number and percentage of individuals with abnormal ECG findings.
2. Number and percentage of individuals with AEs that could be associated with prolongation of cardiac repolarization or proarrhythmia, e.g., palpitations, dizziness, syncope, cardiac arrhythmias and sudden death.

Categorical analysis of the following ECG parameter will be performed at day 1 and day 15 of each cycle and the short term follow up visit at the time points outlined in the protocol and changes will be compared to baseline (i.e. Cycle 1, Day 1 pre-dose). The analysis will include the number and percentage of individuals with:

1. Absolute QT/QTc values > 450 ms, > 480 ms, and > 500 ms; as well as the number and percentage of individuals with change from baseline > 30 ms and > 60 ms.
2. PR changes from baseline ≥ 50% if baseline value is < 200 ms and ≥ 25% of baseline value is ≥ 200 ms.
3. QRS changes from baseline ≥ 50% if baseline value is < 110 ms and ≥ 25% of baseline value is ≥ 110 ms.

6.11.7. Transfusion Data

Transfusion data will be listed for all patients on therapy by cohort.

6.11.8. X-Ray Data

Chest x-ray data will be listed for all patients on therapy by cohort.

6.12. Efficacy Analyses

As a coprimary objective for Part B, this study will evaluate preliminary antitumor activity observed with ramucirumab in combination with LY2875358 in the tumor-specific expansion cohorts.

Overall Response Rate (ORR): ORR is defined as the proportion of patients who exhibit a confirmed CR or PR relative to baseline as defined by RECIST 1.1 (Eisenhauer et al. 2009).

ORR is computed as the number of responders divided by the total number of treated patients. A responder is defined as any patient who exhibits a confirmed CR or PR relative to baseline

assessment, done on or up to 7 days prior to Cycle 1 Day 1. Patients with response that is deemed not evaluable will be considered non-responders and will be included in the denominator for the purpose of calculating ORR. ORR will be assessed within each cohort, ORR with 95% CIs will be estimated using the Clopper-Pearson method.

Progression-Free Survival (PFS): The PFS time is measured from the date of receiving the first dose of study drug to the date of first objective progression as assessed by the investigator or the date of death due to any cause, whichever is earlier. Table 6.2 provides additional details. The censoring is taken in the following order:

- If a patient does not have a complete baseline disease assessment, then the PFS time will be censored at the enrollment date, regardless of whether or not objectively determined disease progression or death has been observed for the patient; otherwise,
- If a patient is not known to have died or have objective progression as of the data inclusion cutoff date for the analysis, the PFS time will be censored at the last evaluable objective progression-free disease assessment date.

If a patient has a missed visit prior to an event (progression or death), then the PFS time will be censored at the last evaluable assessment prior to the event.

Table 6.2. Definition of PFS

Situation	Outcome	Date of Progression or Censoring
Death before first objective PD assessment	Progressed	Date of death
Objective PD	Progressed	Date of first radiologic assessment showing progressive disase
No evaluable baseline tumor assessments	Censored	Enrollment date
No progression	Censored	Date of last radiologic assessment of measured lesions showing no progression
New systemic anticancer treatment started	Censored	Date of last radiologic assessment of measured lesions showing no progression prior to the commencement of new systemic anticancer treatment
Death or progression after more than one missed visit (after 3 months since last assessment)	Censored	Date of last radiologic assessment of measured lesions showing no progression prior to the missed visit

The date of first documented objective disease progression must be recorded on the CRF even if it occurs after the patient has started a new therapy.

Disease Control Rate (DCR): The proportion of patients in the analysis population who exhibit an SD or confirmed CR or PR relative to baseline during the study. Response is defined by RECIST 1.1 (Eisenhauer et al. 2009).

Change in Tumor Size (CTS): The change in tumor size from baseline to the measurement with the smallest tumor size during the study period. Change in tumor size will be assessed in each patient using radiographic imaging. The tumor size of target lesions will be determined as defined by RECIST 1.1 (Eisenhauer et al. 2009).

6.13. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

6.13.1. PK/PD 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 Target-mediated drug disposition (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, ORR, 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.

6.13.2. Biomarker Analyses

Protocol 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 4.3. 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, B2, B3, and B4 of the study, tumor-specific (gastric, hepatocellular, or renal cell cancers) 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.

6.14. Subgroup Analyses

As subgroup analyses, co-primary endpoints for Part B will be analyzed for the potential prognostic factors such as

- Tumor types (Part B1: Gastric or GEJ adenocarcinoma; Part B2: Hepatocellular cancer (HCC); Part B3: Renal cell carcinoma (RCC, any histology)); Part B4: Non-small cell lung cancer (NSCLC, squamous or non-squamous))
- Age (<= 65 years vs. > 65 years)
- Sex (male vs. female)
- ECOG performance status (0,1 vs 2 in part A and 0 vs 1 in part B)

6.15. Protocol Violations

All significant protocol deviations will be listed by parts (Part A, Part B1, B2, B3 and B4) and by reasons (e.g., inclusion/exclusion criteria, noncompliance with protocol procedures, informed consent/assent process etc.).

6.16. Interim Analyses and Data Monitoring

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

For Part B, both safety and efficacy data will be assessed. Interim analyses will be conducted after approximately 15 patients have completed 3 cycles in Parts B1,B2 and B4 (gastric, hepatocellular cancers and non-small cell lung cancer) and 6 cycles in Part B3 (renal cell cancer).

6.17. Planned Exploratory Analyses

Exploratory analysis will be performed 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. Exploratory analyses may include but are not necessarily limited to tumor expression (eg, MET and VEGFR-2) and circulating biomarkers (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).

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)) will also be analized exploratorily.

In the event of emergence of importantand relevant scientific findings, SAP may be updated to allow further analyses on biomarkers and antitumor activities.

6.18. Annual Report Analyses

The following reports are needed as requested for annual reporting purposes

Clinical Investigator Brochure:

- Summary of SAE (patients on therapy).
- Summary of deaths reported (patients on therapy).
- Summary of Patient disposition.
- Summary of primary reason for treatment discontinuation.
- Listing and summary of treatment-emergent adverse events –by CTCAE category and term.

Development Safety Update Report:

- Cumulative Subject Exposure by Age Group and Sex
- Cumulative Subject Exposure by Racial Group
- Estimated Cumulative Subject Exposure

- Subject Exposure by Gender
- Listing of Patients Who Discontinued Due to Adverse Event
- Listing of Deaths

6.19. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by treatment group, by MedDRA preferred term.

- An adverse event is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

A participant flow summary will also be produced. This participant flow will describe how many patients in each study part completed the study, and for those who did not, the frequency of each reason for not completing.

- At the time of database lock, the following patients will be considered to have completed the study:
    - any patient enrolled in Part A who completed one cycle of treatment or discontinued due to an adverse event and completed the required safety and full set of PK assessments during cycle 1.
    - any patient enrolled in Parts B1, B2, B3 and B4 who was treated until disease progression (objective or symptomatic) or death, or discontinued due to an

adverse event and completed the required safety assessments during follow up; patient must have measurable disease at baseline and at least one post treatment radiographic assessment per RECIST.

7. References

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