Statistical Analysis Plan I4T-MC-JVCZ (b)

Randomized Phase 2 Trial Evaluating Alternative Ramucirumab Doses in Combination with Paclitaxel in Second-Line Metastatic or Locally Advanced, Unresectable Gastric or Gastroesophageal Junction Adenocarcinoma

NCT02514551

Approval Date: 15-Nov-2017

1. Statistical Analysis Plan
I4T-MC-JVCZ: Randomized Phase 2 Trial Evaluating Alternative Ramucirumab Doses in Combination with Paclitaxel in Second-Line Metastatic or Locally Advanced, Unresectable Gastric or Gastroesophageal Junction Adenocarcinoma

Ramucirumab (LY3009806) Gastric or Gastroesophageal Junction Adenocarcinoma

An open-label, randomized Phase 2 study comparing alternative ramucirumab dose levels in combination with paclitaxel in approximately 240 patients with advanced gastric or gastroesophageal junction adenocarcinoma with disease progression during or following prior combination chemotherapy. Treatment will continue until a discontinuation criterion is met.

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[Protocol I4T-MC-JVCZ]
[Phase 2]

Statistical Analysis Plan V1 electronically signed and approved by Lilly: 26 September 2015
Statistical Analysis Plan V2 electronically signed and approved by Lilly on date provided below

Approval Date: 15-Nov-2017 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

3. Revision History

Statistical Analysis Plan Version 1 was approved prior to the first patient visit.

Version 2 was approved prior to the primary progression-free survival (PFS) analysis to update the components listed below:

- Revised censoring rules to match with the censoring rules in RAINBOW study.
- Revised PFS sensitivity analysis criteria in Table 5.2 due to the censoring rules changes.
- Modified the definition and analysis of important protocol deviations prior to database lock.
- Changed the wording "30-day post 30-day post treatment follow-up visit" to "30-day post treatment discontinuation.
- Modified Section 5.6.2 Important Protocol Violation to match with the criteria team discussed.
- Added two additional exploratory analyses for the PFS and OS data in Section 5.10.2.3.
- Modified Section 5.12.3. The summary will be provided separately for 1) all deaths, 2) deaths up to 30 days after treatment discontinuation, and 3) deaths after 30-day post treatment discontinuation.

4. Study Objectives

Objectives	Endpoints
Primary	
• Evaluate the efficacy of ramucirumab 12 mg/kg versus placebo, both in combination with paclitaxel, in terms of PFS	• PFS, as determined by investigator assessment per RECIST 1.1
Secondary	
• Evaluate the efficacy of ramucirumab 12 mg/kg versus ramucirumab 8 mg/kg, both in combination with paclitaxel, in terms of PFS	• PFS, as determined by investigator assessment per RECIST 1.1
• ORR	• ORR
• DCR	• DCR
• PK of ramucirumab in combination with paclitaxel	• Minimum ramucirumab concentration in serum (C_{min})
• Safety and tolerability	The safety endpoints evaluated will include but are not limited to the following: • TEAEs, AESIs, SAEs, and hospitalizations • Clinical laboratory tests, vital signs, and physical examinations
• Immunogenicity	• Blood samples for immunogenicity testing will be collected to determine antibody production against ramucirumab.
• **Exploratory**	•
• OS Assess the relationship between biomarkers with clinical outcome	• OS Biomarker research on genetic and circulating factors may be assessed from whole blood and plasma samples, unless precluded by local regulations.

Abbreviations: AESIs = adverse events of special interest; DCR = disease control rate; ERB = ethical review board; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria In Solid Tumors; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.

5. A Priori Statistical Methods

5.1. Determination of Sample Size

Estimation of the sample size for this study was performed to ensure adequate statistical power for both a conventional analysis of PFS, with a log-rank test for ramucirumab doses of 12 mg/kg versus 8 mg/kg using data from Study JVCZ alone (denoted as PFS analysis 2), and a network meta-analysis with RAINBOW for comparing ramucirumab dose of 12 mg/kg with placebo (denoted as PFS analysis 1).

The sample size to test PFS for the comparison of ramucirumab doses of 12 mg/kg and 8 mg/kg using data from Study JVCZ alone was determined based on the following assumptions:

- $\alpha = 0.05$ (2-sided)
- statistical power = 80%
- randomization 1:1
- hazard ratio (HR)=0.667, targeting a 2-month increase in median PFS from 4 months (ramucirumab 8 mg/kg) to 6 months (ramucirumab 12 mg/kg)
- Accrual rate: 0-1m: 2 pts; 1-2m: 4pts; 2-3m: 5pts; >3m: 7.5pts/m

Under these assumptions, approximately 191 PFS events from 228 patients will be needed. Assuming 5% early drop outs (such as patients withdrawing consent or lost to follow-up), 240 patients will be randomized in this study. With the assumed accrual rate, the estimated study duration is 36 months.

The sample size to test PFS for the comparison of the ramucirumab dose of 12 mg/kg in Study JVCZ with placebo in RAINBOW using meta-analysis with RAINBOW was determined based on the following assumptions:

- $\alpha = 0.05$ (2-sided)
- statistical power = 90%
- HR=0.635*0.667=0.424, where:
    - 0.635 is the observed HR (ramucirumab 8 mg/kg compared with placebo) in RAINBOW, and
    - 0.667 is the assumed HR (ramucirumab 12 mg/kg compared with 8 mg/kg) in Study JVCZ.

Denote:

- HR_1 = hazard ratio from RAINBOW (8 mg/kg compared with placebo), and $Z_1 = -\ln(HR_1)$
- HR_2= hazard ratio from this study (12 mg/kg compared with 8 mg/kg), and $Z_2 = -\ln(HR_2)$

then, the number of events can be determined based on the test statistic $Z = Z_1 + Z_2$ with variance $Var(Z) = Var(Z_1) + Var(Z_2)$. Specifically, given a true HR ω (new ramucirumab dose compared with placebo), the number of events is determined by:

$$Var(Z) = \left(\frac{\ln(\omega)}{z_{\alpha/2} + z_{\beta}}\right)^2$$

Given Var(Z_1)= 0.007 from RAINBOW and Var(Z_2) = 4/(number of events), 64 PFS events from JVCZ are required to compare the ramucirumab 12 mg/kg with placebo based on network meta-analysis. Therefore, the 191 events, as determined by the test for ramucirumab 12 mg/kg compared with ramucirumab 8 mg/kg, is also sufficient for the meta-analysis.

This number of events is also adequate for safety and PK analysis.

5.2. General Considerations

This document describes the statistical analyses planned prior to final treatment assignment unblinding of the aggregate database. 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 CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

All tests of treatment effects will be conducted at a two-sided alpha level of 0.05, and all confidence intervals (CIs) will be given at a two-sided 95% level, unless otherwise stated. Statistical analysis will be performed using SAS software (SAS, Version 9.1.2 or higher).

The following general terms will be used globally in the SAP:

- Unless otherwise specified, summary statistics stand for n, mean, standard deviation, median, minimum, and maximum for continuous variables; and frequency and percentage for categorical variables.
- **Study Treatment Period:** begins on the day the first dose of study treatment is administered and ends when the patient and the investigator agree that the patient will no longer continue study treatment. The date of this agreement is to be reported on the case report form (CRF) as the Date of Discontinuation from study treatment.
- **Postdiscontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.

  Short-term follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (±7 days) (until the short-term 30-day safety follow-up visit is completed).

  Long-term follow-up begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion (whichever is earlier).

5.2.1. Definitions of Analysis Variables

Definitions of efficacy and safety analysis variables are listed in Section 5.2.1.1 and Section 5.2.1.2, respectively. Other variables are listed below alphabetically.

- **Age (years):** (Informed Consent Date – Date of Birth + 1)/365.25.
  Note: Average days in a year = 365.25, reflecting the Julian Year of three years with 365 days each and one leap year of 366 days. Birth month and day are imputed to be 01 July because only birth year is collected through CRF.
- **Baseline measurement** is the last non-missing measurement prior to first dose for safety analyses; and the last non-missing measurement prior to randomization for demographic and efficacy analyses.
- **Duration** is calculated as:
  - Duration (days): (End Date – Start Date + 1)
  - Duration (weeks): (End Date – Start Date + 1)/7
  - Duration (months): (End Date – Start Date + 1)/30.4375
    Note. Days in months = (1/12)*average number of days in a year
  - Duration (years): (End Date – Start Date + 1)/365.25
- **Duration of disease** is defined as months from first diagnosis of cancer to randomization.
- **Measurable disease (Yes/No)** is defined as yes for patients with at least one target lesion and no otherwise, based on radiographic assessment data collected at baseline.
- **Study Day** indicates the number of days the patient has been receiving study treatment. It is calculated as assessment date – randomization date + 1 day, if the assessment is done on or after the randomization day. If the assessment is done prior to the randomization day, the study day will be calculated as assessment date – randomization date. Date of randomization is defined as Study Day 1.

5.2.1.1. Efficacy Analysis Variables

Definition of efficacy analysis variables are listed below.

Progression-free survival (PFS) is defined as the time measured from the date of randomization to the date of radiographic documentation of progression (as defined by RECIST v.1.1) or the date of death due to any cause, whichever is earlier. The detailed censoring rule is provided in Table JVCZ.5.1.

PFS (day) = Date of progression / censor - Date of randomization + 1

Table JVCZ.5.1. Censoring Rule of Progression-Free Survival Analysis

Situation	Event / Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate radiological assessment or date of randomization (whichever is later)
unless		
No baseline radiological tumor assessment available	Censored	Date of randomization
No adequate post baseline radiological tumor assessment available and no death reported	Censored	Date of randomization
No tumor progression or death prior to new anticancer therapy	Censored	Date of adequate radiological assessment prior to (start of new therapy) or date of randomization (whichever is later)
Tumor progression or death documented immediately after 2 or more consecutive missing scan intervals following last adequate radiological tumor assessment or randomization (whichever is later)	Censored	Date of last adequate radiological assessment prior to the missing assessment or date of randomization (whichever is later)

Abbreviation: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Note:

Adequate radiological tumor assessment refers to an assessment with one of the following responses: CR, PR, SD or PD.

If there are multiple dates associated with one assessment, the assessment date will be set to the first date when the overall response is PD and the last date otherwise.

Table JVCZ.5.2 lists censoring rules for sensitivity analysis (SA) definitions.

Table JVCZ.5.2. Censoring Rules for Progression-Free Survival Sensitivity Analysis Definitions

Sensitivity Analysis (SA) Definition #	Situation	Date of Progression or Censor	Progressed / Censored
SA 1: Count symptomatic deterioration as progression	Radiographic documented progression or symptomatic deterioration	Date of documented progression or date of symptomatic deterioration, whichever occurred first.	Progressed
SA 2: Ignore new anticancer treatment	New anticancer treatment (systemic therapy) started before radiographicdomumented progression or death	last adequate radiological assessment prior to new anticancer treatment or date of randomization whichever is later	Progressed
SA 3: Ignore missing tumor assessment	Radiographic documented progression or death occur immediately after 2 or more scan intervals	last adequate radiological assessment prior to missed tumor assessment or date of randomization whichever is later	Progressed

Sensitivity Analysis (SA) Definition #	Situation	Date of Progression or Censor	Progressed / Censored
SA 4: Treat lost to follow up as progression	Patient is lost to follow-up without radiographic documented progression or death	Date of next scheduled post baseline radiological assessment at or after becoming lost to follow-up	Progressed

Objective response rate (ORR) is defined as the proportion of randomized patients achieving a best overall response of PR or CR per RECIST v.1.1. Patients who do not have any post baseline tumor response assessments are considered non-responders and are included in the denominator when calculating the response rate.
Note: Tumor assessments performed after initiation of new anticancer treatment (systemic therapy) will be excluded from evaluating the best overall response.

Disease control rate (DCR) is defined as the proportion of randomized patients achieving a best overall response of CR, PR, or SD per RECIST v.1.1. Patients who do not have any post baseline tumor response assessments for any reason are considered non-responders and are included in the denominator when calculating the response rate.
Note: Best overall response is the best response recorded from randomization until disease progression, in the order of CR, PR, and SD. Refer to Attachment 5 of the protocol for definitions of CR, PR, and SD.

Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause. If the patient was alive at the cutoff for analysis (or was lost to follow-up), OS data will be censored for analysis on the last date the patient was known to be alive.

5.2.1.2. Safety Analysis Variables

Definitions of variables for safety analysis are listed by category and alphabetically within category.

Adverse event (AE)-related variables are listed below:

- **Adverse event (AE)** is defined as any untoward medical occurrence in a patient administered a pharmaceutical product, without regard to the possibility of a causal relationship.

- **AEs of special interest (AESIs)** include arterial thromboembolic events (ATE)*, bleeding/hemorrhage (also gastrointestinal [GI] hemorrhage as a subcategory)*, congestive heart failure (CHF)*, fistula (GI* and non-GI), gastrointestinal perforation (non-fistula)*, healing complication, hypertension*, infusion related reaction (IRR), liver injury/failure*, proteinuria*, renal failure*, reversible posterior leukoencephalopathy syndrome (RPLS), thrombotic microangiopathy and venous thromboembolic events (VTE)*.
  Notes: Categories of AESI may be modified as the understanding of the safety of the investigational drug increases. The final list of categories will be maintained at both the compound and study level and reported in the CSR.

- **Consolidated AEs** are composite AE terms consisting of synonymous preferred terms (PTs) to allow meaningful interpretation of the AE data. Consolidated AE categories and PTs will be maintained at compound and/or study level and reported in the CSR.

- **Serious adverse event (SAE)** is any AE that results in one of the following outcomes:

  - death

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

- **Treatment-emergent adverse event (TEAE)** is defined as any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.

Exposure-related variables are listed below:

- **Number of dose level reductions:** Sum of the number of dose level reductions as reported in the eCRF
- **Dose delays:** As reported in the eCRF
- **Dose withheld (Not Administered):** As reported in the eCRF.

Ramucirumab or placebo treatment:

- Duration of treatment (weeks; 14 days added to duration of treatment because administration is every 2 weeks [on day 1, 15 of each 4-week cycle]) = [(Date of last dose − date of first dose) + 14] ÷ 7
- Cumulative dose, dose intensity, relative dose intensity:
  - Cumulative dose (mg/kg) = Sum of (Dose administered at each infusion [mg] ÷ Last available weight [kg])
  - Weekly dose intensity (mg/kg/week) = (Cumulative dose) ÷ (Duration of Treatment[week])
  - Planned weekly dose intensity (mg/kg/week) = 2 x 8mg/kg / 3 weeks = 5.3 mg/kg/week
  - Relative dose intensity (%) = (Weekly dose intensity) ÷ (Planned weekly dose intensity) x 100

Paclitaxel treatment:

- Duration of treatment (weeks; 14 days added to duration of treatment because last administration of each cycle is for 2 weeks [on day 1, 8, 15 of each 4-week cycle]) = [(Date of last dose – date of first dose) + 14] ÷ 7
- Cumulative dose, dose intensity, relative dose intensity:
  - Cumulative dose (mg/m2) = Sum of all (total dose administered [mg] ÷ BSA using last available weight [m²])
  - Weekly dose intensity (mg/m2/week) = (Cumulative dose) ÷ (Duration of treatment)
  - Planned weekly dose intensity (mg/m²/week) = 3x 80mg/m2 / 4 weeks = 60 mg/m2/week

- Relative dose intensity (%) = (Weekly dose intensity) ÷ (Planned weekly dose intensity) x 100

5.2.1.3. PK Analysis Variables

Definition of PK analysis variables are listed below:

- Minimum concentration (C_{min}): Serum concentrations of ramucirumab prior to infusion
- Approximate maximum concentration (C_{max}): Serum concentrations of ramucirumab at 1-hour post-end of ramucirumab infusion

5.3. Adjustments for Covariates

As supportive analysis, the primary and secondary efficacy endpoints will also be analyzed adjusting for pre-specified potential prognostic factors chosen from the variables listed below. Detailed description as for which factors to be used will be provided for relevant analyses in later sections.

- Randomization stratification factors:
  - ECOG performance status (0 versus 1)
- Other factors of interest:
  - Sex (males versus females)
  - Age (< 65 versus ≥65 years)
  - Race (White versus Asian versus all others)
  - Geographic region
  - primary tumor location (gastric versus GEJ)
  - disease measurability (measurable versus nonmeasurable)
  - Prior first-line treatment (doublet versus triplet)
  - Time to progression on first-line therapy
  - Previous gastrectomy (Y/N)
  - Histologic subtype (diffuse versus intestinal versus mixed/unknown)
  - Peritoneal metastases (Y/N)
  - Weight loss (≥10% over the 3 months prior to study entry versus <10%)
  - Number of metastatic sites (≤2 versus ≥3)
  - Liver metastasis (Yes versus No)
  - Presence of ascites (Yes versus No)

- Tumor differentiation (Well, Moderately, Poorly, Unknown[1])
- Primary tumor present (Y/N)

5.4. Handling of Dropouts or Missing Data

Rules for handling dropouts or missing data are listed by type of analysis alphabetically. Unless otherwise specified, observed data will be used and missing data will not be imputed or carried forward.

General rules for imputing dates related to AE or concomitant therapy:

- Onset date of an AE or start date of a concomitant therapy:
  - If only the day is missing, the date will be set to:
    - First day of the month that the event occurred, if the onset yyyy-mm is after the yyyy-mm of first study treatment.
    - The day of the first study treatment, if the onset yyyy-mm is the same as yyyy-mm of the first study treatment.
  - If both the day and month are missing, the complete date will be set to:
    - 01 January of the year of onset, if the onset year is after the year of the first study treatment.
    - The date of the first dose, if the onset year is the same as the year of the first study treatment.
- Resolution date of an AE or end date of a concomitant therapy:
  - If only the day is missing, the date will be set to the last day of the month of the occurrence, or to the date of death if the patient died in the same month.
  - If both the day and month are missing, the date will be set to 31 December of the year of occurrence or to the date of death if the patient died in the same year.

If a date is completely missing, then the AE will be considered treatment emergent. In case of additional therapies, if the start date is completely missing, the therapy will be considered concomitant.

General rule for imputing other dates: If a date variable is needed for an analysis, use the following general rule to impute incomplete date:

- If the date has no missing year and month but the day is missing, then assign Day 1 to the day.

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[1] In Cox PH model, the grouping of tumor differentiation is Well/Moderately versus Poorly/Unknown.

- If the date has no missing year, but has missing month, then assign January to the month.

After imputation, the imputed date should be logically consistent with other relevant date variable(s). For example, if a visit start date was 10 May 2008 and a tumor assessment date was xx May 2008 (missing day) but it was known that it occurred after that visit, then after imputation, the tumor assessment date became 01 May 2008. In this case, the imputed tumor assessment date should be compared to the visit start date and then corrected to be the visit start date, 10 May 2008.

Safety analysis: The following rule for missing data processing will apply for safety analysis:

- Missing classifications concerning study medication relationship will be considered as related to study medication.
- If the AE onset date is missing or partial, the date will be compared as far as possible with the date of first dose of study medication when determining whether or not the AE is present at baseline. In this case, the AE will be assumed to be treatment emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first dose of study medication.

Time-to-event analysis: All censored data will be accounted for using appropriate statistical methods. See Section 5.2.1 and Section 5.10 for details.

5.5. Multicenter Studies

This is a multicenter, randomized, open-label study. Investigative center was not a stratification factor because the large number of investigative centers would breakdown the intended balance within each combined stratification level by the stratified randomization method. It will not be included as a covariate in any covariate-adjusted analysis because the large number of investigative centers in this study cannot be practically incorporated into such analysis.

5.6. Study Patients

The following summaries (frequency and percentage) and listings for patient disposition will be performed:

- Patient disposition by investigator site and country and overall: patients entered (i.e., signed informed consent), entered but not randomized, randomized (i.e., ITT population), randomized but not treated, treated (i.e., safety population), in Per-Protocol population (PPP).
- Reasons for discontinuation for the following patients groups:
    - all treated patients as well as patients continuing on the study
    - randomized patients who did not receive any study treatment
- Reason for screen failure for patients who entered but not randomized
- Listings of
    - primary reason for discontinuation

- date of randomization, first dose administration, last dose administration, and treatment discontinuation.

5.6.1. Analysis Populations

Table JVCZ.5.3 lists analysis population definitions and associated data type for analysis.

Table JVCZ.5.3. Analysis Populations

Population	Definition	Analysis Type / Variable	Note
Intention-to-treat (ITT) Population	All randomized patients	Baseline characteristics, concomitant medication, all efficacy analyses	Patients will be grouped according to randomized treatment.
Safety Population (SP)	All randomized patients who received any quantity of study drug	Safety, e.g. dosing/exposure, AE and resource utilization	Patients will be grouped according to treatment received as defined by the first dose received.
Per-Protocol Population (PPP)	ITT patients who received at least one cycle of study therapy and did not have any major protocol violations that could potentially affect the efficacy conclusion. These major protocol violations are detailed in Section 5.6.2.	PFS analysis 2 on PPP as a sensitivity analysis of PFS; other efficacy endpoints may also be analyzed as needed	PPP will only be performed if there are significant numbers of patients with major protocol violations (≥5% of total ITT population).

Abbreviations: AE = adverse event; OS = overall survival; PFS = progression-free survival.

A patient listing of analysis population details will be provided. This listing will be presented by treatment group and will include: investigator site, patient identifier, inclusion/exclusion flag for each population and reason for exclusion from each population. All patients screened will appear on this listing.

5.6.2. Important Protocol Violations

The PPP is a subset of the ITT population and consists of the randomized and treated patients who do not have a major protocol violation (i.e. clinically important and potentially impact efficacy evaluations) as listed below:

- Patient does not have histologically- or cytologically-confirmed gastric carcinoma, including gastric adenocarcinoma or GEJ adenocarcinoma. In particular, patients with only squamous histology, but without any adenocarcinoma components
- No metastatic disease or locally recurrent, unresectable disease
- Had not experienced disease progression during first-line therapy or within 4 months after the last dose of first-line therapy for metastatic disease, or during or within 6 months after the last dose of neoadjuvant or adjuvant therapy.
- The patient did not receive combination chemotherapy prior to disease progression.

- Baseline ECOG performance status (ECOG PS) score of 2 or above or incorrect stratification factor values used for randomization.
- The patient has received more than one prior systemic chemotherapy regimen for the treatment of locally advanced and unresectable or metastatic gastric or GEJ (Siewert Types I-III) adenocarcinoma.
- Have documented brain metastases, leptomeningeal disease or uncontrolled spinal cord compression.
- Had received prior therapy with an agent that directly inhibits VEGF or VEGFR-2 activity (including bevacizumab and ramucirumab).
- Patient has received additional concurrent chemotherapy, biological response modifiers, other investigational agents and radiation therapy (except for palliation to symptomatic sites of disease) while receiving study treatment.
- Patient received incorrect study medication at least 25% of the times (i.e., Number of incorrect medication infusions/Total number of infusions patient received > =25%).

The list of patients (except for patients with incorrect study medication) included in this population will be identified prior to database lock for the final analysis.

The protocol violations described in this SAP are restricted to violations that can be assessed by analysis of data available in the clinical database.

5.7. Demographic and Other Baseline Characteristics

The following patient demographic and other baseline characteristics will be summarized:

- Patient demographics: age (years) and age group (<65versus ≥65), gender, race, ethnicity, height (cm), weight (kg), BSA (m2)
- Potential prognostic factors as listed in Section 5.3
- Baseline disease characteristics:
  - at initial diagnosis only: disease stage
  - at study entry only: current disease stage, duration of disease (months)
- Prior cancer therapies: type of therapy (surgery, radiotherapy, systemic therapy), type of prior surgery, type of prior radiotherapy, type of prior systemic therapy
- Historical illness (no versus at least one diagnosis) by Medical Dictionary of Regulatory Activities (MedDRA) PT, presented in decreasing frequency
  Note: Subjects reporting more than one condition/diagnosis within a PT will be counted only once for that PT.
- Comparison between the CRF and interactive voice response system (IVRS) values of the stratification factors

Patient listings of demographic data and baseline characteristics will be provided. Patient listings of prior cancer therapies (surgery, radiotherapy, and systemic therapy) will be provided.

5.8. Concomitant Medications

The following concomitant medications used in study treatment period or the 30-day post treatment discontinuation will be summarized by numbers and percentages by treatment group, presented in decreasing frequency of the World Health Organization (WHO) drug term across treatment arms:

- All concomitant medications
- Best supportive care (BSC) and select medications including growth factors (erythropoietin, G-CSF, granulocyte-macrophage colony-stimulating factor [GM-CSF])
  Note: Such drugs to be used for programming will be identified through reviewing of the unique drug terms collected in the study.
- Premedication for study drug.

The proportions of patients reporting use of concomitant medications will be compared between the treatment groups. Patient listing of all concomitant therapies and premedications will be provided.

5.9. Treatment Compliance

Ramucirumab/placebo and Paclitaxel will be intravenously administered only at the investigational sites. As a result, patient compliance is ensured.

5.10. Efficacy Analyses

A gatekeeping approach to test primary objective and key secondary objective will be applied in order to protect the study-wise Type I error rate and to enable inferential statements; each hypothesis is inferentially tested only if each of the preceding hypotheses were rejected. The sequential order of the confirmatory testing in the ITT population will be: 1) PFS analysis 1: PFS of ramucirumab 12 mg/kg plus Paclitaxel from JVCZ compared with placebo plus paclitaxel from RAINBOW using network meta-analysis; 2) PFS analysis 2: PFS of ramucirumab 12 mg/kg plus Paclitaxel compared with ramucirumab 8 mg/kg plus paclitaxel from JVCZ. Both PFS analyses 1 and 2 will be analyzed at the same level of significance 0.05.

5.10.1. Primary and key Secondary Efficacy Analyses

The PFS analysis 1 and 2 are described in Section 5.1. The hazard ratio of PFS analysis 1 is equal to HR1*HR2, where HR1 is 0.635, the observed HR (ramucirumab 8 mg/kg compared with placebo) in RAINBOW; HR_2 (12 mg/kg compared to 8 mg/kg) will be estimated HR using Cox proportional hazards (PH) model with assigned treatment as the only covariate. The stratification will be the same as that used for randomization. This Cox PH model will be referred to as the primary Cox PH model henceforth. The test statistic for PFS analysis 1 is $Z = Z_1 + Z_2$ with variance $Var(Z) = Var(Z_1) + Var(Z_2)$, where $Var(Z_1)=0.007$ from RAINBOW; Z_2 and $Var(Z_2)$ will be estimated from the primary Cox PH model.

The following analyses of PFS will also be performed:

- Summary of PFS events (number and percentage), censoring rate, and reasons for censoring
- Restricted mean difference in PFS between the treatment groups and its 95% CI, with the area under the Kaplan-Meier survival curve calculated up to the minimum across treatment arms of the maximum observed (i.e., event or censored) time
- Kaplan-Meier survival curve (Kaplan and Meier 1958) by treatment group will be provided
- The Kaplan-Meier method will be used to estimate parameters (medians, quartiles, and percentages), as well as difference of percentage and associated 95% CI and p-values for landmark analyses on each treatment group at 3, 6, 9, 12, and 24 months. Patients who did not have the event at the corresponding time point will be considered right-censored observations.

5.10.2. Secondary Efficacy Analyses

5.10.2.1. Supportive Analyses of PFS Analysis 1 and 2

Since PFS analysis 1 is based on PFS analysis 2, the following supportive analyses will be performed for PFS analysis 2 only:

- Hazard ratio for treatment effect will be estimated using an unstratified Cox PH model.
- As a sensitivity analysis, the PFS analysis 2 will be repeated using stratification based on the CRF values.
- Hazard ratio for treatment effect will be estimated using a multivariate Cox PH model to be constructed by selecting covariates among all the variables in Section 5.3 using stepwise selection method. The stepwise selection will use an entry p-value 0.10 and exit p-value 0.15. The treatment factor will not be used for stepwise selection, but be added to the final model. HR for treatment effect and corresponding 95% CI will be estimated from the final model.

- As a sensitivity analysis, the PFS analysis 2 will be repeated for the per-protocol population.
- As sensitivity analyses, the PFS analysis 2 will be repeated using different PFS censoring rule as defined in Table JVCZ.5.2, to evaluate whether and to what extent the conclusion of the PFS analysis under the primary definition would be affected under the different censoring rules.
- As an exploratory analysis of primary endpoint, individual patient data from JVCZ and RAINBOW may be pooled together. The PFS analysis directly comparing ramucirumab 12 mg/kg plus paxlitaxel from JVCZ and placebo plus paxlitaxel from RAINBOW may be performed using pooled individual patient data. If statistical significant difference exists between the two 8 mg/kg arms, additional adjusted analysis may be explored.

5.10.2.2. Analyses of Other Secondary Efficacy Endpoints

Tumor response (CR+PR) rate and disease control (CR+PR+SD) rate will be reported along with exact confidence bounds (CI: 95%) and compared using the Cochran-Mantel-Haenszel test adjusting for the stratification variables.

5.10.2.3. Analyses of Exploratory Efficacy Endpoints

Overall survival will be analyzed similarly to PFS Analysis 1 and Analysis 2. Univariate and multivariate Cox regression model may be used to explore potential prognostic and/or predictive factors.

It is expected that Asian patients tend to have noticeably longer OS than non-Asian patients. Since JVCZ does not enroll patients from Asia while RAINBOW enrolled significant number of Asian patients, two additional exploratory analyses will be performed in attempt to account for such regional difference in the analyses of pooled individual patient data to compare 12mg/kg plus paclitaxel from JVCZ with placebo arm from Rainbow study. One is to adjust region (Asian and non-Asian) in the Cox regression model and the other is to use only the subgroup of non-Asian patients.

Patient listings of tumor assessments (target and non-target lesion assessments and tumor response), PFS, and OS will be provided.

5.10.3. Subgroup Analyses

Progression-Free Survival and OS HR for treatment effect and its 95% CI will be estimated using the unstratified Cox PH model for each of the subgroups listed in Section 5.3. A forest plot of the estimated HRs and their 95% CIs will be provided. If the number of events in a particular subgroup is less than 10 from any arm, this subgroup will excluded from subgroup analysis and will not be presented in forest plot.

5.11. Post-Discontinuation Therapy

The numbers and percent of patients reporting post-discontinuation therapies will be provided overall, and by type of therapy (surgery, radiotherapy, or systemic therapy). Surgery and

radiotherapy will be further characterized by intent. Systemic therapy will be further categorized by WHO drug terms.

Additional analysis may be explored for helping interpret OS results, for example time to PDT or censoring at the start of PDT in OS analysis.

5.12. Safety Evaluation

5.12.1. Exposure

The following exposure-related variables will be reported using summary statistics (number of patients, mean, and standard deviation) by treatment group:

- Exposure: duration of treatment; number of cycles received; number of patients completing ≥ one cycle, ≥ two cycles, …, ≥ six cycles, and mean, standard deviation; number of patients with dose adjustments: dose reduction, dose delay, and dose omission;
- Reasons for dose adjustments.

The following exposure-related variables will be reported using summary statistics (number of patients, mean, standard deviation, median, 1st and 3rd quartiles, minimum, and maximum) by treatment group:

- Dose intensity: cumulative dose; weekly dose intensity; relative dose intensity, overall weekly dose intensity, overall relative dose intensity.

Details of study drug administration will be included in patient listings.

5.12.2. Adverse Events

The most current version of MedDRA at time of analysis will be used when reporting AEs by MedDRA terms. Unless otherwise specified, when summarized by PT, AEs will be presented in decreasing frequency of PT across treatment arms; when summarized by SOC and PT, AEs will be presented in decreasing frequency of PT within system organ class (SOC) across treatment arms. If more than one AE is recorded for a patient within any SOC or PT term, the patient will only be counted once on the most severe grade and the closest relationship to treatment.

5.12.2.1. Overall Summary of Adverse Events

An overall summary of AEs will be provided to summarize the following categories using frequency counts and percentages:

- patients with at least one TEAE, SAE, Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 TEAE
- patients with AEs that led to death (all, on study therapy, up to 30 days after treatment discontinuation or)
- patients with SAEs that led to discontinuation.

The summary will be provided for regardless of study drug causality, and repeated for events deemed by the investigator to be related to study treatment. Comparison between the treatment groups will be performed using Fisher's exact test.

5.12.2.2. Treatment-Emergent Adverse Events (TEAEs)

The following summaries of TEAEs by treatment arm will be provided (*repeated for events deemed by the investigator to be possibly related to study medication):

- by PT*
- by SOC and PT*
- by maximum CTCAE grade and by SOC and PT*

Consolidated AE may be summarized for TEAE and study treatment-related TEAE. A patient listing of all AEs will be provided.

5.12.3. Deaths, SAEs, and Other Significant AEs

Reasons for deaths (study disease, AE [any AE, study treatment related AE, study procedural related AE]) will be summarized separately for 1) all deaths, 2) deaths up to 30 days after treatment discontinuation, and 3) deaths after 30-day post treatment discontinuation.

Serious adverse events will be summarized by SOC and PT, by PT and repeated for events deemed by the investigator to be possibly related to study medication, with consolidated summary performed if needed. A listing of SAEs will be produced.

In addition, the following analyses will be performed (*repeated for events deemed by the investigator to be possibly related to study medication, †include consolidated summary):

- Adverse events leading to death by PT†
- Adverse events leading to study treatment discontinuations by PT†
- Adverse events leading to study treatment dose modification by PT†
- Adverse events of Special Interests SIs by PT*
- Liver injury/failure*
  Note: Liver injury/failure is analyzed separately from other AESIs because its analysis requires a different format.
- Listing of AESIs.

5.12.4. Clinical Laboratory Evaluation

The severity of laboratory results will be classified according to CTCAE Version 4.0. The shifts in CTCAE toxicity grading from baseline to worst grade postbaseline (first dose up to 30 days after discontinuation of study treatment) will be produced.

A patient listing of all laboratory data will be provided with a flag for values outside of the laboratory normal range as well as investigator site, patient identifier, age, gender, race, weight and visit.

5.12.5. Hospitalizations and Transfusions

The frequency and percentage of patients with any hospitalizations experienced during the study treatment period or 30-day post treatment discontinuation will be summarized by treatment group. Hospitalization incidence rates will be compared between the treatment groups using Fisher's exact test. In addition, total number of days in hospital and admissions will be summarized and compared using the Wilcoxon rank sum test. These will be further characterized by reason (study-drug-related, Lilly-study-drug-related, non-study-drug-related). **Note:** Discharge date will be imputed with last contact date for hospitalizations that are still ongoing at time of analysis.

The frequency and percentage of patients with any blood transfusions experienced during the study treatment period or 30-day post treatment discontinuation will be summarized by treatment group. Transfusions will be further characterized by transfused blood product (e.g., packed red blood cells, platelets, fresh frozen plasma, or whole blood). The proportions of patients having blood transfusions will be compared between the treatment groups using Fisher's exact test.

Details of hospitalizations and transfusions will be included in patient listings.

5.12.6. Vital Signs, Physical Findings, and Other Observations Related to Safety

A summary of ECOG PS at each scheduled time point will be provided. Actual value and change from baseline for vital sign measurements will be summarized at each assessment time point using summary statistics. electrocardiogram (ECG), echocardiogram, and multiple-gated acquisition (MUGA) measurements will be summarized at each assessment time point using summary statistics. Listings of ECOG PS, vital signs, ECG, echocardiogram, and MUGA data will be provided.

5.13. Pharmacokinetics and Immunogenicity

Serum concentrations of ramucirumab prior to infusion (minimum [C_{min}]) and at 1 hour post-end of ramucirumab infusion (approximately maximum [C_{max}]) will be summarized using descriptive statistics. Additional analysis utilizing the population PK approach based on an established population PK model may also be conducted if deemed appropriate. Relationships between ramucirumab exposure and measures of efficacy and safety will be explored if deemed appropriate.

For immunogenicity, the number and percent of patients with positive ramucirumab antibody response will be summarized. Additional efficacy or safety analyses may be performed in the subgroup of patients with positive ramucirumab antibody response. The antibody response and any alteration in ramucirumab PK may also be explored, as well as any relationship with

experiencing an infusion reaction. Further exploratory analyses may be performed as appropriate.

5.14. Translational Research

Translational research analyses will be performed according to a separate analysis plan.

5.15. Interim Analysis

An Assessment Committee (AC) internal to Lilly will be established prior to first patient visit. Interim analyses of safety and PK will be conducted after approximately a total of 80 and 160 patients complete 6 weeks of therapy or discontinue treatment due to any reason, whichever comes first. The AC will review interim analyses of safety and PK data. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients. There will be no prespecified rules for stopping the trial due to safety concerns. The AC will determine whether there are sufficient safety concerns to justify a change in the conduct of the study or the termination of study treatment and/or enrollment.

The AC comprises at least one physician (oncologist), one safety physician, one statistician, and one PK specialist responsible for the evaluation and interpretation of the results from the interim analysis. One of the AC members is designated as chairperson.

Since this is an open-label study, the study statistical team will be responsible for conducting the interim analysis and delivering the interim analysis reports. The study clinical trial manager will serve as AC secretary and be responsible for organizing meetings, ensuring that meeting logistics are established and recording minutes.

The following analyses will be performed for safety interim analysis:

Demographic and Other Baseline Characteristics

- Patient demographics

Patient Disposition

- Reasons for treatment discontinuation as well as patients continuing on the study

Exposure

- Summary statistics for exposure-related variables
- Dose intensity of study drugs
- Reasons for dose adjustments and dose delays

Adverse Events

- Overview of AEs
- TEAEs summarized by PT
- CTCAE Grade 3 and 4 TEAEs
- Treatment-related TEAEs summarized by PT
- Treatment-related CTCAE Grade 3 and 4 AEs
- SAEs summarized by PT
- AESIs
- Reasons for deaths

- AEs leading to study treatment discontinuations
- AEs leading to study treatment dose modification
- Listing of SAEs
- Listing of preexisting conditions and AEs

5.16. Clinical Trial Registry Analyses

For the purpose of fulfilling the Clinical Trial Registry (CTR) requirements, summary of SAEs (whether treatment emergent or not) and 'Other' AEs (i.e., non-serious TEAEs) by PT and treatment group will be performed. For each PT, the number of patients at risk, patients who experienced the event, and events will be presented. In addition, the summary will be provided as a dataset in XML format.

6. References

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53(282):457-481.

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