I4T-JE-JVCW Statistical Analysis Plan Version 2

A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of S-1 and Oxaliplatin With or Without Ramucirumab as First-line Therapy Followed by Paclitaxel With Ramucirumab as Second-line Therapy in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

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1. Statistical Analysis Plan for Clinical Study: I4T-JE-JVCW: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of S-1 and Oxaliplatin With or Without Ramucirumab as First-line Therapy Followed by Paclitaxel With Ramucirumab as Second-line Therapy in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

Ramucirumab (LY3009806) Gastric or Gastroesophageal Junction Adenocarcinoma

This is a randomized, placebo-controlled, double-blind, Phase 2 study of patients with metastatic gastric or gastroesophageal junction adenocarcinoma. Patients will be randomized to receive ramucirumab drug product (8 mg/kg) in combination with S-1 and oxaliplatin versus placebo in combination with S-1 and oxaliplatin administered every 3 weeks followed by treatment with ramucirumab plus paclitaxel every 4 weeks.

Eli Lilly Japan K.K.
Protocol I4T-JE-JVCW
Phase 2

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to the first unblinding.

Version 2 was approved prior to the first unblinding. Here is the summary of updates:

Section 4.3: TTP, DOR, and ECOG PS were added.

Section 6.1: Handling of stratification factors were clarified.

Section 6.1.1: Baseline definitions and Study Day definitions were clarified.

Section 6.1.1.1 : The PFS, PFS2, and PFS2-1 definitions were clarified. DCR, DOR, ECOG PS, TTP, DCR2, DOR2, ECOG PS2, TTP2 were added.

Section 6.1.1.2: Exposure related variables were modified for Part A and were newly defined for Part B.

Section 6.2: The definition of covariates were updated.

Section 6.6.1: PPS1 (originally called PPS), PPS2, FAS3, SPA were defined.

Section 6.6.2: The definition of important protocol deviation was added. The actual list of the important protocol deviation was moved from the SAP to a sparate sheet.

Section 6.7: The definition of the patient demographics was updated. The time point of the baseline disease characteristics was specified as initial diagnosis only, not study entry.

Section 6.8: This section included transfusions.

Section 6.10.1: Detail of restricted mean difference analysis was added.

Section 6.10.2: New populations (PPS2, FAS3) were introduced for some analyses.

Section 6.10.2.5: New exploratory analyses were added, including TTP, TTP2, DOR, DOR2, ECOG PS, ECOG PS2, and a gap analysis.

Section 6.11: The definition of 12 systemic therapy was specified.

Section 6.12: Time point of safety analysis (Part A, Part B) were clarified.

Section 6.12.1: Exposure related definitions were clarified.

Section 6.12.2: AE related analyses were clarified.

Section 6.12.3: Death, SAEs, and other significant AEs related analyses were clarified.

Section 6.12.4: Clinical laboratory related analyses were clarified.

Section 6.12.5: Transfusions related analyses were moved to Section 6.8. Hospitalizations related analyses were clarified.

Section 6.12.6: Vital related low/high limits (normal range) were specified.

Section 6.12.7: Safety related subgroup analysese were specified.

Section 6.13: Subgroup analysis including efficacy and safety were summarized.

Section 6.14: Definitions of immunogeneicity analyses were clarified.

Section 9 (Appendix): Censoring rule diagrams were added.

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to compare progression-free survival (PFS) of ramucirumab in combination with S-1 and oxaliplatin versus placebo in combination with S-1 and oxaliplatin as first-line treatment in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma.

4.2. Secondary Objectives

Secondary objectives of this study are to assess and compare ramucirumab in combination with S-1 and oxaliplatin versus placebo in combination with S-1 and oxaliplatin for the following:

- progression-free survival 2 (PFS2)
- overall survival (OS)
- objective response rate (ORR)
- disease control rate (DCR)
- pharmacokinetics (PK) of ramucirumab and anti-ramucirumab antibodies (immunogenicity)
- safety and toxicity profile

4.3. Exploratory Objectives

The exploratory objectives of the study include following analysis:

- ORR of second-line therapy (ORR2)
- DCR of second-line therapy (DCR2)
- PFS of second-line therapy (PFS2-1)
- OS of second-line therapy (OS2)
- the relationship between biomarkers and clinical outcomes.
- the time to progression (TTP)
- duration of response (DOR)
- time to deterioration in ECOG performance status

Complete list of the exploratory analysis are specified later.

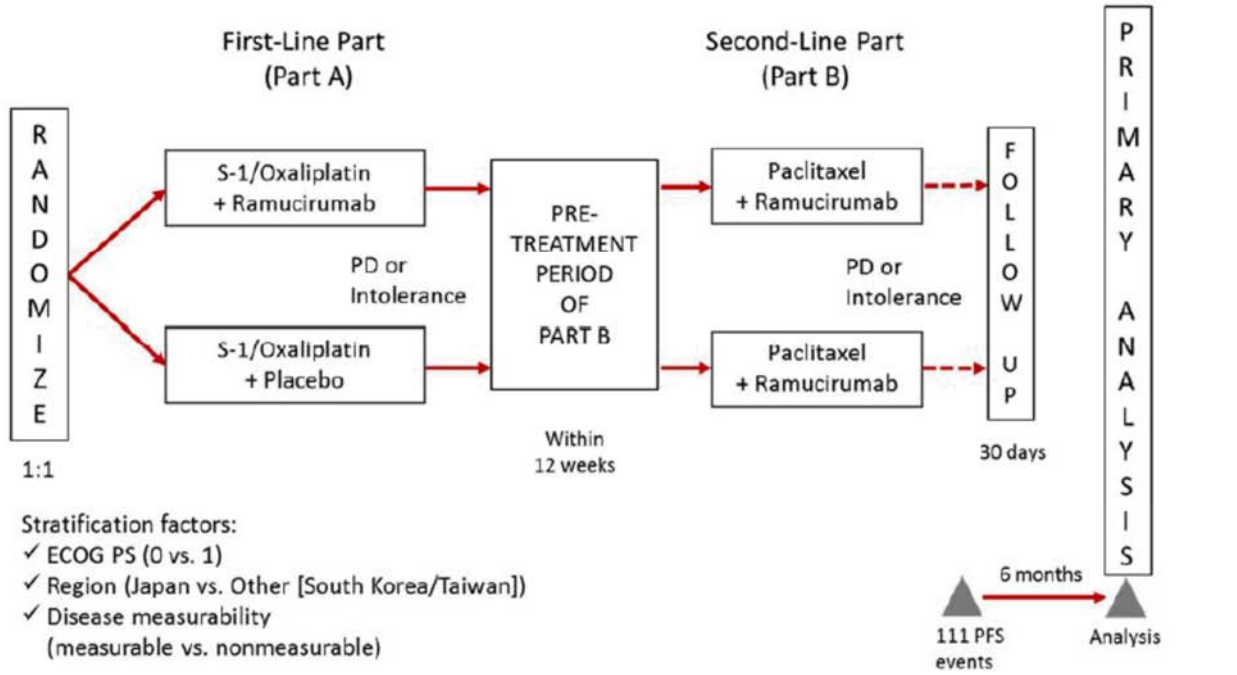
5. Study Design

5.1. Summary of Study Design

Study JVCW is a multicenter, randomized, placebo-controlled, double-blind, Phase 2 study of patients with metastatic gastric or GEJ adenocarcinoma. Patients will be randomized to receive ramucirumab (8 mg/kg) in combination with S-1 and oxaliplatin versus placebo in combination with S-1 and oxaliplatin (Part A) followed by open-label treatment with ramucirumab plus paclitaxel (Part B).

Figure JVCW.5.1 illustrates the study design.

The study will enroll approximately 190 patients evenly divided between the 2 treatment arms. Primary efficacy analysis will take place 6 months after 111 PFS events have occurred. Randomization will be stratified by ECOG performance status (PS; 0 vs. 1), region (Japan vs. Other [South Korea/Taiwan]), and disease measurability (measurable vs. nonmeasurable).



Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; PD = progressive disease; PFS = progression-free survival.

Figure JVCW.5.1. Illustration of study design for Protocol I4T-JE-JVCW

Terms used to describe the periods during the study are defined below:

- **Baseline:** begins when the informed consent form (ICF) is signed and ends on the day before the day of first dose of study treatment (or discontinuation, if no treatment is given) in Part A. Patients must be randomized to treatment within 21 days of signing the ICF, and first treatment will be administered within 7 days following randomization.
- **Treatment Period:** begins at the first study treatment and ends when the patient and the investigator agree that the patient will no longer continue study treatment.

  - ***Part A:*** begins at the first study treatment of Part A and ends when the patient and the investigator agree that the patient will no longer continue study treatment of Part A, and a treatment cycle will be defined as a period of 21 (± 3) days.
  - ***Pre-treatment period of Part B*** begins the day after the decision is made that the patient will no longer continue study treatment of Part A. The period ends prior to the first study treatment of Part B or prior to the start date of the post-discontinuation follow-up period defined below.
    Note that if a patient decides not to go to Part B at the timing of Part A discontinuation, then the patient goes to post-discontinuation follow-up period directly from Part A.
  - ***Part B:*** begins at the first study treatment of Part B and ends when the patient and the investigator agree that the patient will no longer continue study treatment of Part B, and a treatment cycle will be defined as a period of 28 (± 3) days.
- **Post-discontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.
  - ***Short-term safety follow-up*** begins the day after the decision is made that the patient will not move to Part B or no longer continue study treatment of Part B and lasts approximately 30 (±7) days.
  - ***Long-term follow-up*** begins 1 day after short-term safety follow-up is completed and continues until the patient's death or overall study completion to collect additional data (survival data and subsequent anticancer treatments).
- **Continued Access Period:** begins after primary endpoint analysis has been performed and evaluated, and sufficient OS-related information is collected for analysis, as determined by the Sponsor. During the continued access period, patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met. The continued access period includes continued access follow-up.
  - ***Continued access follow-up*** begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 (±7) days.

5.2. Determination of Sample Size

The primary objective of this study is to compare PFS of ramucirumab in combination with S-1 and oxaliplatin versus placebo in combination with S-1 and oxaliplatin as first-line treatment in patients with metastatic gastric or GEJ adenocarcinoma.

The study will enroll approximately 190 patients in 1:1 randomization and the primary endpoint analysis will be performed 6 months after observing 111 PFS events. The expected number of PFS events at this time point is 136 and the probability of having a 2-sided p-value of less than 0.2 (correspond to 1-sided 0.1) using a log-rank test in terms of PFS would be approximately 85%, assuming the recruitment rate of 8 patients per month, the HR of 0.67 (median 6 months vs. 9 months) and approximately 10% of enrolled patients would be censored before the data cut-off. The probability of having a 2-sided p-value of less than 0.2 with 111 events under the same assumption would be 80%.

5.3. Method of Assignment to Treatment

Upon completion of all screening evaluations to confirm a patient's eligibility, the site will register the patient via the interactive web response system (IWRS), which is accessible 24 hours a day. The IWRS registration consists of assigning the patient a unique study identification number and randomizing the patient to 1 of the 2 treatment arms on a 1:1 basis.

The IWRS will assign patients to treatment arms according to a stratified method of randomization (i.e., independent randomization within each of the following prognostic factors):

- ECOG PS (0 vs. 1)
- region (Japan vs. Other [South Korea/Taiwan])
- disease measurability (measurable vs. nonmeasurable)

Once the patient is registered through the IWRS, he/she is considered to be enrolled in the study.

6. A Priori Statistical Methods

6.1. 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 clinical study report (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 0.2, and all confidence intervals (CIs) will be given at a two-sided 80% level, unless otherwise stated. Statistical analysis will be performed using SAS software (SAS, Version 9.2 or higher).

If stratification factors (geographic region, measurability, ECOG PS) are used for an analysis, it is based on eCRF data unless otherwise specified. If stratification factors are not recorded in eCRF before the randomization, then the last available values (e.g. ECOG PS) on or before first dose date will be used as Randomization stratification factors (per eCRF).

6.1.1. Definitions of Analysis Variables

Definitions of efficacy, safety variables are listed in Section 6.1.1.1, and Section 6.1.1.2, 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 for Part A** :
  - Efficacy: The last measurement on or prior to the date of randomization will serve as the baseline measurement. In the event such a value is missing, the first assessment completed prior to the first study drug administration will be used as the baseline assessment, so long as this assessment was taken within 7 days of randomization.
  - Safety: The last non-missing measurement prior to the first study drug administration will be used as the baseline assessment.
  - Demographic and other baseline characteristics: The last measurement on or prior to the date of randomization will serve as the baseline measurement. In the event such a value is missing, the first assessment completed on or prior to the date of first study drug administration will be used as the baseline assessment.
- **Baseline measurement for Part B:**
  - Efficacy and safety: the last non-missing measurement prior to first dose of study treatment in Part B for safety analyses and efficacy analyses.
  - Demographic and other baseline characteristics: It is the same as Part A.

- **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 (initial diagnostic) 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:**
    - For safety analysis: Study day is calculated as:
        - Assessment date – first dose date + 1; if the assessment was performed on or after the first dose day.
        - Assessment date – first dose date; if the assessment was performed prior to the first dose date.
    - For efficacy analysis: Study day is calculated as:
        - Assessment date – randomization date + 1; if the assessment was performed on or after the randomization date.
        - Assessment date – randomization date; if the assessment was performed prior to the randomization date.

6.1.1.1. 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 first radiographic documentation of progression (as defined by RECIST v.1.1) or the date of death due to any cause, whichever is earlier on or before starting any anti-cancer treatment including the treatment of Part B. More specifically,

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

The detailed censoring rule is provided in Table JVCW. 6.1.. Refer to the flow chart in Section 9 (Appendix) to identify censoring reasons.

Table JVCW. 6.1 Censoring Rule of Progression-Free Survival Primary 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 death reported after 2 scan intervals following randomization	Censored	Date of randomization
New anticancer treatment (including curative surgery for cancer and the second-line therapy (RAM+PTX)) started	Censored	Date of adequate radiological assessment on or prior to the new anticancer 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 = clinical response; PD = progressive disease; PR = partial response; SD = stable disease; RAM+PTX = ramucirumab + paclitaxel.

Note:

Symptomatic deteriorations (i.e., symptomatic progressions, which are not radiologically confirmed) will not be considered as progressions.

Adequate radiological tumor assessment refers to an assessment with one of the following responses: CR, PR, SD, PD, Non-CR/Non-PD or NE (not evaluable).

The 2 scan intervals are counted from the date of last adequate tumor assessment to the date of next two scheduled tumor assessment plus 14 days (adjusted by tumor assessment window).

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 JVCW. 6.2**.** lists censoring rules for sensitivity analysis (SA) definitions.

Table JVCW. 6.2 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 radiographic domumented progression or death	A) date of radiographic documentation of progression or death, whichever is earlier B) last adequate radiological assessment if no radiographic documented progress or death occurred	A) Progressed B) Censored

Sensitivity Analysis (SA) Definition #	Situation	Date of Progression or Censor	Progressed / Censored
SA 3: Ignore missing tumor assessment	Death or radiographic documented progression after ≥2 consecutively missed tumor assessment visits	Date of radiographic documentation of progression or death, whichever is earlier	Progressed
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

Disease control rate (DCR) is defined as portion 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 7 of the protocol for definitions of CR, PR, and SD.

Duration of response (DOR) is defined as the duration from the date of first evidence of a CR or PR during Part A to the date of radiographically documented progression defined by RECIST v.1.1, or the date of death due to any cause, whichever is earlier. If a responder is not known to have died or have radiographically documented progression as of the data inclusion cutoff date, DOR will be censored at the date of the last adequate tumor assessment. This is defined for responders only.

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.

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.

Time to deterioration (TtD) in ECOG performance status (ECOG PS) is defined as the time from the date of randomization to the first date observing ECOG PS ≥2 (that is, deterioration from baseline status of 0 or 1). Patients without PS deterioration will be censored at their last documented assessments of 0 or 1.

Note: ECOG PS performed after initiation of new anticancer treatment (systemic therapy) including second line therapy, will be excluded from the analysis.

Time to progression (TTP) is defined as the time from the date of randomization to the date of radiographic progression (according to RECIST v.1.1). If the patient died due to any reason without radiographic progression, TTP is censored at the last adequate tumor assessment.

Progression-free survival 2 (PFS2) is defined as the time from the date of randomization to second disease progression (defined as the date of first tumor assessment observing PD defined by RECIST v.1.1, after the start of second-line therapy using the last tumor assessment before starting the second-line therapy (RAM+PTX) as the baseline assessment), or death of any cause, whichever occurs first. If the second-line therapy was not started, the OS will be substituted for PFS2. If a post-discontinuation therapy was started before observing PD after the start of second-line therapy, the PFS2 will be censored at the date of the last adequate tumor assessment on or before staring the post-discontinuation therapy.

Progression-free survival 2-1 (PFS2-1) is defined as the time from the date of starting the second-line therapy (RAM+PTX) to first disease progression (defined as the date of first tumor assessment observing PD defined by RECIST v.1.1, after the start of second-line therapy using the last tumor assessment before starting the second-line therapy (RAM+PTX) as the baseline assessment), or death of any cause, whichever occurs first. If a post-discontinuation therapy was started before observing PD after the start of second-line therapy, the PFS2-1 will be censored at the date of the last adequate tumor assessment on or before staring the post-discontinuation therapy.

Disease control rate 2 (DCR2) is defined as portion of patients receiving any quantity of study treatment for Part B achieving a best overall response of CR, PR, or SD per RECIST v.1.1 (using the last tumor assessment before starting the second-line therapy (RAM+PTX) as the baseline assessment). 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 baseline in Part B until disease progression, in the order of CR, PR, and SD. Refer to Attachment 7 of the protocol for definitions of CR, PR, and SD.

Duration of response 2 (DOR2) is defined as the duration from the date of first evidence of a CR or PR during Part B (with the baseline of the last tumor assessment before starting second-line therapy (RAM+PTX)) to the date of radiographically documented progression defined by RECIST v.1.1, or the date of death due to any cause whichever is earlier. If a responder is not known to have died or have radiographically documented progression as of the data inclusion cutoff date, DOR2 will be censored at the date of the last adequate tumor assessment. This is defined for responders only.

Objective response rate 2 (ORR2) is defined as the proportion of patients receiving any quantity of study treatment for Part B achieving a best overall response of PR or CR per RECIST v.1.1 (using the last tumor assessment before starting the second-line therapy (RAM+PTX) as the baseline assessment). 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) in Part B will be excluded from evaluating the best overall response.

Overall survival 2 (OS2) is defined as the time from the date of starting second-line therapy (RAM+PTX) to the date of death from any cause. If the patient was alive at the cutoff for analysis (or was lost to follow-up), OS2 data will be censored for analysis on the last date the patient was known to be alive.

Time to deterioration (TtD) in ECOG performance status 2 (ECOG PS2) is defined as the time from the start date of second-line therapy (RAM+PTX) to the first date observing ECOG PS ≥2 (that is, deterioration from baseline status of 0 or 1). If patients have ECOG PS ≥2 or missing at the baseline of the second-line therapy (Visit 200), then these patients will not be used for the analysis. Patients without PS deterioration will be censored at their last documented assessments of 0 or 1.

Note: ECOG PS 2 performed after initiation of new anticancer treatment (systemic therapy) will be excluded from the analysis.

Time to progression 2 (TTP2) is defined as the time from the date of starting the second-line therapy (RAM+PTX) to the date of radiographic progression (according to RECIST v.1.1). If the patient died due to any reason without radiographic progression, TTP2 is censored at the last adequate tumor assessment.

Note: CR and PR do not require confirmation.

Note: Censoring rules for PFS, DCR, DOR, ORR, TTP, see the efficacy censoring rule for first-line study treatment in Section 9 Appendix A.

Note: Censoring rules for PFS2, PFS2-1, DCR2, DOR2, ORR2, TTP2, see the efficacy censoring rule for second-line study treatment in Section 9 Appendix A.

6.1.1.2. 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 in Part A:

- Duration of treatment (weeks) = [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 before each cycle [kg])
  - Weekly dose intensity (mg/kg/week) = (Cumulative dose) / (Duration of Treatment)
  - 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

Oxaliplatin treatment in Part A:

- Duration of treatment (weeks) = [Date of last dose − Date of first dose+21] / 7

- Cumulative dose, dose intensity, relative dose intensity:
  - Cumulative dose (mg/m^2) = Sum of (dose administered at each infusion [mg] / Last available baseline BSA [m^2])
  - Weekly dose intensity (mg/ m^2/week) = (Cumulative dose) / (Duration of treatment)
  - Planned weekly dose intensity (mg/m^2/week) = 100mg/m^2/ 3 weeks = 33.3 mg/m^2/week
  - Relative dose intensity (%) = (Weekly dose intensity) / (Planned weekly dose intensity) x 100

S-1 treatment in Part A:

- Duration of treatment (weeks) = [(Date of last dose − Date of first dose) + 8] ÷ 7

- Cumulative dose, dose intensity, relative dose intensity:
  - Cumulative dose (mg) = Sum of (Dose administered each day [mg])
  - Weekly dose intensity (mg/week) = (Cumulative dose) ÷ (Duration of treatment)
  - Planned weekly dose intensity (mg/week)

    = 80 mg/day ×14 days / 3 weeks = 373.3333 mg/week for subjects with baseline BSA <1.25 m^2

    = 100 mg/day ×14 days / 3 weeks = 466.6667 mg/week for subjects with 1.25 m^2 =< baseline BSA <1.5 m^2

    = 120 mg/day ×14 days / 3 weeks = 560.0000 mg/week for subjects with baseline BSA >=1.5 m^2
  - Relative dose intensity (%) = (Weekly dose intensity) ÷ (Planned weekly dose intensity) x 100

Any treatment in Part A:

- Duration of treatment (weeks) = [Date of last dose− date of first dose+21] ÷ 7 , where date of last dose is based on the latest date of taking any of ramucirumab/placebo/S-1/Oxaliplatin in Part A and date of first dose is based on the earliest date of taking any of ramucirumab/placebo/S-1/Oxaliplatin in Part A. If date of last dose or date of first dose is missing, then duration of treatment (weeks)=0.

Ramucirumab in Part B:

- Duration of treatment (weeks) = [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 before each cycle [kg])
  - Weekly dose intensity (mg/kg/week) = (Cumulative dose) / (Duration of Treatment)
  - Planned weekly dose intensity (mg/kg/week) = 2 x 8mg/kg / 4 weeks = 4 mg/kg/week
  - Relative dose intensity (%) = (Weekly dose intensity) / (Planned weekly dose intensity) x 100

Paclitaxel in Part B:

- Duration of treatment (weeks) = [Date of last dose− date of first dose+14] ÷ 7
- Cumulative dose, dose intensity, relative dose intensity:
  - Cumulative dose (mg/m^2) = Sum of (dose administered at each infusion [mg] / Last available Part B baseline BSA [m^2])
  - Weekly dose intensity (mg/ m^2/week) = (Cumulative dose) / (Duration of treatment)
  - Planned weekly dose intensity (mg/m^2/week) = 3 x 80 mg/m^2/ 4 weeks = 60 mg/m^2/week
  - Relative dose intensity (%) = (Weekly dose intensity) / (Planned weekly dose intensity) x 100

Any treatment in Part B:

- Duration of treatment (weeks) = [Date of last dose− date of first dose+28] ÷ 7 , where date of last dose is based on the latest date of taking any of ramucirumab/paclitaxel in Part B and date of first dose is based on the earliest date of taking any of ramucirumab/paclitaxel in Part B. If date of last dose or date of first dose is missing, then duration of treatment (weeks)=0.

6.2. 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. For multivariable Cox model, all of the followings will be used as covariates

- Randomization stratification factors (per eCRF):
  - ECOG performance status (0 versus 1)

- Region (Japan vs. Other [South Korea/Taiwan])
- Disease measurability (measurable versus nonmeasurable)

- Other factors of interest:
  - Sex (males versus females)
  - Age (<65 versus ≥65 years)
  - Primary tumor location (gastric versus GEJ)
  - Peritoneal metastases (Yes versus No). If a patient have one of followings, then Peritoneal metastases=Yes:
    - Peritoneal Cavity
    - Peritoneal Lymph node
    - Peritoneum
    - Pelvic ascites
    - Peritoneal Dissemination
    - Abdominal cavity
    - Ascites
    - Retroperitoneal
    - Retroperitoneum
  - Histologic subtype (3 categories: diffuse, intestinal, mixed/unknown). Note that if the information is missing, then it is categorized as "unknown".
  - Number of metastatic sites (≤2 versus ≥3).
  - Liver metastasis (Yes versus No)
  - Prior neo-adjuvant or adjuvant therapy (Yes versus No)
  - Prior Gastrectomy (Yes versus No). If a patient have surgery with surgery intent =curative intent, then Prior Gastrectomy=Yes. Otherwise, =No.

6.3. 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, concomitant therapy, or post-discontinuation therapy:

- Onset date of an AE or start date of a concomitant therapy or post-discontinuation 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 before/after the yyyy-mm of first study treatment.
    - The day of the first study treatment, if the onset yyyy-mm is the same as yyyymm of the first study treatment.
  - If both the day and month are missing, the complete date will be set to:
    - January 01 of the year of onset, if the onset year is before/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 December 31 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, 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
- If the date has no missing year, but has missing month, then assign January to the month.

However, after imputation, check if the imputed date is logically consistent with other relevant date variable(s) and make appropriate correction if necessary. For example, if a visit start date was May 10, 2008 and a tumor assessment date was May xx, 2008 (missing day) but it was known that it occurred after that visit, then after imputation, the tumor assessment date became May 01, 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, May 10, 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 (both components).

- 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 6.1.1 and Section 6.10 for details.

6.4. Multicenter Studies

This is a multicenter, randomized, double-blind 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.

6.5. Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons will be made.

6.6. 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, randomized but not treated, treated, in Per-Protocol Set (PPS1 and PPS2).
- Reasons for discontinuation in Part A for the following patients groups:
  - Safety Population (SP)
  - screen fail patients (i.e., patients who entered but not randomized)
  - randomized patients who did not receive any study treatment
- Reasons for discontinuation in pre Part B for all patients who entered pretreatment period of Part B
- Reasons for not-entering Part B for Part A discontinued patients
- Reasons for discontinuation in Part B for SP2.
- Listings of
  - primary reason for discontinuation in Part A, primary reason for discontinuation in pre Part B, and primary reason for discontinuation in Part B.
  - date of randomization, first dose administration in Part A, last dose administration in Part A, treatment discontinuation in Part A, start date of pre Part B (Visit 200), first dose administration in Part B, last dose administration in Part B, and treatment discontinuation in Part B.

6.6.1. Analysis Populations

The following populations will be defined for this study:

Full Analysis Set (FAS): will include all randomized patients receiving any quantity of study treatment for Part A and grouped according to the treatment the patients were assigned. This population will be used for all baseline, protocol deviations, post-discontinuation therapy and efficacy analyses unless otherwise specified.

Per-Protocol Set 1 (PPS1): will include all patients who are randomized and received at least 1 cycle of study treatment in Part A, and do not have any of the selected important protocol deviations from screening to the end of Part A that could potentially affect the efficacy conclusions of the study. This population will be used for sensitivity analyses of PFS; other efficacy endpoints may also be analyzed. For the selected important protocol deviations, refer to Section 6.6.2.

Per-Protocol Set 2 (PPS2): will include all patients who are randomized and received at least 1 cycle of study treatment in Part A, and do not have any of the selected important protocol deviations from screening to the end of the short term follow up (up to Visit 801) that could potentially affect the efficacy conclusions of the study. This population will be used for sensitivity analyses of PFS, PFS2, and OS; other efficacy endpoints may also be analyzed. For the selected important protocol deviations, refer to Section 6.6.2.

Safety population (SP): will include all randomized patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the actual study treatment a patient has received, regardless of the treatment arm to which he or she was randomized. The safety population will be used for all safety analysis such as dosing/exposure, AEs, concomitant medication, laboratory tests, and vital sign analyses unless otherwise specified.

Full Analysis Set for Part B (FAS2): will include all patients receiving any quantity of study treatment for Part B and grouped according to the treatment the patients were assigned at randomization. This population will be used for analyses of PFS2, PFS2-1, ORR2, DCR2, OS2, and ECOG PS2.

Full Analysis Set for Part B both drug treatments (FAS3): will include all patients receiving any quantity of both ramucirumab and paclitaxel for Part B and grouped according to the treatment the patients were assigned at randomization. (If a patient takes only paclitaxel or only ramucirumab for Part B, then the patient will be excluded from this population.) This population will be used for exploratory analyses of PFS2 and PFS2-1.

Safety population for Part B study treatment (SP2): will include all patients who received any quantity of study treatment for Part B. The safety evaluation will be performed based on the actual study treatment a patient has received, regardless of the treatment arm to which he

or she was randomized. This population will be used for all dosing/exposure, AEs, concomitant medication, laboratory tests, and vital sign analyses for Part B unless otherwise specified.

Safety population for Part B ramucirumab (SP3): will include all patients who received any quantity of ramucirumab for Part B. The safety evaluation will be performed based on the actual ramucirumab treatment a patient received, regardless of the treatment arm to which he or she was randomized. This population will be used for some of dosing/exposure, AEs, concomitant medication, laboratory tests, and vital sign analyses for Part B.

Safety population for Part A only (SPA): will include all patients who satisfy following conditions:

Condition 1: Patients who are in SP (Safety population).

Condition 2: Patients who did not enter Part B or who entered Part B but did not take any study treatment (ramucirumab or paclitaxel) during Part B.

This population will be used for a post-discontinuation therapy summary.

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. All patients screened will appear on this listing.

6.6.2. Important Protocol Deviations

Important protocol deviations (IPD) are defined as a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of important study data or that might significantly affect a subject's rights, safety, or well-being (e.g., deviation from the key inclusion/exclusion criteria).The PPS1 and PPS2 (the definitions are in Section 6.6.1) are subsets of the FAS population and consists of the randomized and treated patients who do not have any of the selected IPD . All important protocol deviations, including whether they are affected to the per protocol sets, and whether they should be detected by programs are defined in a separate sheet.

Followgin listing will be created:

- Important Protocol Deviations
- Important Protocol Deviations Leading to Exclusion from PPS1 and PPS2

6.7. Demographic and Other Baseline Characteristics

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

- Patient demographics: age (years), gender, race, height (cm), weight (kg), BSA (m^2), Geographic region (2 categories: Japan, non-Japan), Country (3 categories: Japan, South Korea, Taiwan), Age subgroup A (2 categories: [Age<65] , [65<=Age], unit=year), Age subgroup B (3 categories: [Age<=45], [45<Age<70], [70<=Age], unit=year) , Prior Gastrectomy (2 categories:Yes, No)

- Potential prognostic factors as listed in Section 6.2
- Baseline disease characteristics at initial diagnosis:
  - disease stage
  - duration of disease (months) (from initial diagnosis of cancer to the randomization).
- 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 eCRF and interactive web response system (IWRS) values of the stratification factors, based on all randomized patients

Following patient listing will be created

- Demographics and Baseline characteristics
- Prior cancer therapies (surgery, radiotherapy, and systemic therapy)
- Randomization strata (IWRS and eCRF) based on all randomized patients
- Baseline Disease Characteristics

6.8. Concomitant Medications and Transfusions

The following concomitant medications used in study treatment period or the 30-day post-discontinuation follow-up period, except ones used after post-discontinuation therapy, 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
- Supportive care 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 frequency and percentage of patients with any blood transfusions experienced in study treatment period (Part A) or within 30 days after the decision is made to discontinue Part A, except ones used after post-discontinuation therapy, 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).

Following listing will be created:

- Prior and Concomitant medications
- Supportive Care

- Transfusions
- Prior Systemic Therapy for Gastric Cancer
- Prior Surgery for Gastric Cancer
- Prior Radiotherapy for Gastric Cancer

Note that each of following data will be grouped by pre-specified consolidated terms:

(1) Prior Systemic Therapy

(2) Concomitant therapy (Part A)

(3) Concomitant therapy (Part B)

(4) Prior Surgery and Prior Radiotherapy

(5) Radiotherapy (Part A) and Transfusion (Part A)

(6) Radiotherapy (Part B) and Transfusion (Part B)

6.9. Treatment Compliance

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

Since the low compliance of S-1 is one of the protocol deviations, the compliance will be monitored and ensured during the study.

The statistics of treatment compliance will not be summarized in this study. If non-compliance incident is considered as important protocol deviations, then it will be in the listing of important protocol deviations.

6.10. Efficacy Analyses

6.10.1. Primary Efficacy Analyses

The analysis of PFS will be based on stratified log-rank test and estimation of HR using stratified Cox regression model, stratified by randomization strata (eCRF). The point estimate of HR of approximately 0.8, which correspond to a p-value of less than 0.2 from 2-sided test with 136 events for the PFS, would be interpreted that ramucirumab + oxaliplatin + S-1 is a promising regimen as a first-line therapy for patients with advanced gastric or GEJ adenocarcinoma who have not received prior first-line chemotherapy.

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 Analysis

  The common method for describing benefit on the time scale is to calculate the difference in median event time between the 2 treatment arms. An alternative method for describing benefit on the time scale is to estimate the average difference between the Kaplan-Meier (KM) curves. This corresponds to calculating the difference in the average time to event for the 2 treatment arms (Irwin 1949; Karrison 1997; Meier et

al. 2004). Similar to the HR, this method uses all of the available information across the KM curves, but has the additional advantage of assessing benefit on the time scale.

To estimate an improvement in PFS with ramucirumab, we will follow the method of Irwin (1949) detailed in Karrison (1997) and Meier et al. (2004) for estimating the "difference in average PFS," which we will refer to more formally as the restricted mean difference in PFS. The area under each KM curve will be calculated using numerical integration (trapezium rule) per Karrison and implemented in SAS using PROC LIFETEST. The difference between treatment arms and a 80% CI for the difference will be formed.

Since the KM curve may be ill-determined beyond a certain range, or even undefined (if the longest observation is censored), for evaluation and comparison of means, the area under each KM curve will be calculated between time 0 and restriction time T, which is why this is referred to as a "restricted mean." Following the suggestion of Karrison, the restriction time T will be chosen as largest time point t such that the standard error (SE) of the survival estimate at time t in each treatment group is no more than 0.075. For this purpose, we will use the simple, albeit conservative, formula proposed by Peto et al. (1977) for calculating the SE of S(t) as $\mathrm{SE}(\mathrm{S(t)}) = \mathrm{S(t)}\sqrt{(1-\mathrm{S(t)})/\mathrm{n(t)}}$, where n(t) is the number of patients still at risk at time t.

- 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), difference of percentage and associated 80% 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.
- Hazard ratio for treatment effect will be estimated using Cox proportional hazards (PH) model stratified identically to the primary log-rank test with assigned treatment as the only covariate, reported with 2-tailed 80% CIs and Wald's test p-value. This Cox PH model will be referred to as the primary Cox PH model henceforth.
- The summary of PFS event (including 25th percentile, median, 75% percentile, restricted mean, hazard ratio, PFS rate) will be created using 95% confidence interval.

In addition, listing of PFS was created.

6.10.2. Secondary Efficacy Analyses

6.10.2.1. Progression-free survival

The following sensitivity analyses will be performed for PFS:

- unstratified log-rank test and Cox models
- stratified log-rank test and Cox models, stratified by strata collected in IWRS
- analysis including both radiographic and symptomatic progressions as PFS events

- analysis for the per-protocol set 1 (PPS1) and PPS2
- sensitivity analysis for various PFS censoring rules.

As sensitivity analyses, the primary PFS analysis will be repeated using different PFS censoring rule as defined in Table JVCW. 6.2, 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.

Hazard ratio for treatment effect will be estimated using univariate (each vairable listed in Section 6.2) and multivariate Cox PH models (covariates only, no stratification) to be constructed by selecting covariates among all the variables listed in Section 6.2 using stepwise selection method. The stepwise selection will use an entry p-value <0.20 and exit p-value ≥0.25. The treatment factor will not be used for stepwise selection, but be added to the final model. HR for treatment effect and corresponding 80% CI will be estimated from the final model.

Note: A covariate may be removed from the analysis if the number of patients representing one level of that variable is insufficient or data collected on that variable are insufficiently complete.

6.10.2.2. Overall survival

The analysis of OS will be based on a stratified log-rank test, stratified by randomization strata (eCRF).

Estimation of HR using stratified Cox regression model, stratified by randomization strata (eCRF).

OS survival curves, medians with 80% CIs, and survival rates at various time points for each treatment group will be estimated using the Kaplan-Meier method.

OS will be analyzed for FAS.

The following sensitivity analyses may be performed for OS:

- unstratified log-rank test and Cox models
- stratified log-rank test and Cox models, stratified by strata collected in IWRS
- analysis for the per-protocol set 2 (PPS2)
- univariate and multivariate Cox regression model (same models used in PFS analysis) will be used to explore
  potential prognostic and/or predictive factors.

6.10.2.3. Progression-free survival 2

The analysis of PFS2 will be based on stratified log-rank test and estimation of HR using stratified Cox regression model, stratified by randomization strata (eCRF). The PFS2 median with 80% CI and survival curves for each treatment group will be estimated using Kaplan-Meier method.

An additional sensitivity analysis may be explored in which an event is defined as discontinuation of second-line treatment, second disease progression, or death from any cause, whichever occurs first.

An additional sensitivity analysis and Kaplan-Meier plots using FAS2, FAS3 and PPS2 will be performed.

6.10.2.4. Objective response rate and disease control rate

The best overall response will be determined using the RECIST v.1.1 guidelines.

The Objective Response Rate (ORR) will be calculated as the number of patients who achieve a best overall response of CR or PR, divided by the total number of patients randomized to the corresponding treatment group (FAS). Additionally, a subgroup analysis will be performed for patients with measureable disease. Patients who do not have a tumor response assessment for any reason are considered as nonresponders and are included in the denominator when calculating the response rate. The ORR with 80% CI observed in each treatment group will be summarized and compared using the Cochran-Mantel-Haenszel test adjusting for the randomization strata (eCRF).

The DCR was calculated as the proportion of randomized patients achieving best overall response of CR, PR, or SD per RECIST version 1.1

6.10.2.5. Exploratory efficacy analyses

For ORR2, DCR2, PFS2-1, and OS2 (time from the start date of second-line therapy to the date of death), analyses will be conducted on FAS2. For PFS2-1, an additional sensitivity analysis and Kaplan-Meier plots using FAS3 will be performed.

- ORR2 and DCR2 will be estimated together with 80% CIs for each treatment arm and in total.
- For PFS2-1 and OS2, the Kaplan-Meier method will be used to estimate the survival curves for each treatment arm and in total.
- ORR2 and DCR2 use the last tumor assessment before starting second-line therapy as the baseline assessment.
- PFS2-1 is defined as the time from the last tumor assessment date before starting second-line therapy to the first tumor assessment date observing PD, using the last tumor assessment before starting the second-line therapy as the baseline assessment, or date of death.

Time to progression (TTP) will be compared between both treatment groups using stratified log-rank test and Kaplan-Meier estimates. The listing will be created.

Time to progression 2 (TTP2) will be compared between both treatment groups using stratified log-rank test and Kaplan-Meier estimates using FAS2. The listing will be created.

Duration of response (DOR) will be compared between both treatment groups using unstratified log-rank test and Kaplan-Meier estimates. This analysis is for responders only. The listing will be created.

Duration of response 2 (DOR2) will be compared between both treatment groups using unstratified log-rank test and Kaplan-Meier estimates using FAS2. This analysis is for responders only. The listing will be created.

Time to deterioration in ECOG PS using FAS and ECOG PS2 using FAS2 will be analyzed using the Kaplan-Meier method and compared using a stratified log-rank test. Hazard ratio and its 80% CI will be estimated using stratified Cox PH model.

Gap analysis will be performed using OS where

Gap time = Data cut-off date (for OS analysis) - Censoring date.

Following scan time assessment plots will be created:

- Scan time during before Part A and Part A using FAS (2 arms)
- Scan time during pre-Part B, Part B, using FAS2 (2 arms)

Following listing will be created:

- Tumor Assessment
- Best overall Response

6.10.3. Subgroup Analyses

Progression-Free Survival and OS HR for treatment effect and its 80% CI will be estimated using the unstratified Cox PH model for each of the subgroups listed in Section 6.2 and for ascites (yes/no) subgroup (ascites or pelvic ascites). A forest plot of the estimated HRs and their 80% CIs will be provided. If the number of events in a particular subgroup is less than 15, this subgroup will not be presented in forest plot.

Additional subgroup analyses may be performed as deemed appropriate. The goal of subgroup analyses is to assess internal consistency of study results, and whether there is significant treatment heterogeneity across any of the subgroups. Appropriate interpretation is important since, even if all patient subgroups benefit to exactly the same extent in truth, smaller or larger estimated effects, even negative effects, may be seen for some subgroups simply by chance alone. Without appropriate interpretation, this can lead to erroneous conclusion in one or more subgroups, in particular where differential treatment effects are not expected across any of the factors assessed. In order to assist with interpretation of the subgroup results, the methodology of Fleming (Fleming 1995) will be followed to provide background information on the extent of variability that might be expected by chance alone.

6.11. Post-discontinuation Therapy

The numbers and percent of patients reporting post-discontinuation therapies (PDT) will be provided overall and by type of therapy (surgery, radiotherapy, or systemic therapy), on different time frames:

- therapies after discontinuation of Part A for population=SPA
- therapies after discontinuation of Part B for population=FAS2
- therapies after discontinuation of Part A (for those who do not enter Part B) and of Part B, for population=FAS
- therapies after discontinuation of Part A for population=FAS. This include Part B treatment (Ramucirumab+ Paclitaxel)

Surgery and radiotherapy will be further characterized by intent. Systemic therapy will be further categorized by WHO drug terms. More specifically, following 12 categories will be used:

Table JVCW. 6.3 Systemic Therapy category as post-discontinuation therapy

Index	Systemic Therapy
1	PTX/nab-PTX
2	CPT-11
3	DTX
4	PTX + RAM
5	RAM
6	S-1/Capecitabine
7	S-1 + DTX
8	SOX/CapeOX/FOLFOX
9	SP/FP/Cape +CDDP
10	FOLFIRI
11	ICI
12	Others

Abbreviation: CapeOX = Capecitabine + Oxaliplatin, CDDP = Cisplatin, CPT-11= Irinotecan, DTX = Docetaxel, FOLFOX = 5-FU + folinic acid + Oxaliplatin, FOLFIRI =5-FU + folinic acid + Irinotecan, FP = 5-FU + CDDP, ICI = Immune Checkpoint Inhibitor, PTX = Paclitaxel, RAM = Ramucirumab, SOX= S-1 + Oxaliplatin, SP = S-1 + CDDP.

Imbalances between treatment arms in PDT use can confound the evaluation of the treatment effect for OS. If a notable imbalance in PDT use is observed (either overall or with respect to important agents or classes of agent), a sensitivity analysis for OS will be conducted in which patients will be reweighted in such a way as put more weight on patients with PDT in the arm that had less PDT use, and less weight on patients with PDT in the arm that had more PDT use, and thereby the rate of PDT use will be balanced between arms on a weighted basis. The PDT-weighted analysis will help assess the impact of any observed difference in the rate of PDT use between arms.

Additional analysis may be explored for helping interpret OS results, for example time to PDT.

Following listings will be created:

- Post Discontinuation Systemic Therapy (use the subcategories in Table JVCW. 6.3)
- Post Discontinuation Surgery
- Post Discontinuation Radiotherapy

6.12. Safety Evaluation

Safety summaries will be provided separately for Part A and Part B. Unless otherwise specified (e.g. Section 6.12.5 Hospitalizations) , the following rule will be applied.

For patients who entered Part A and did not enter Part B: The safety summaries for Part A will include the events/measurements from the first dose date of study treatment in Part A to the end of the 30-day post-discontinuation follow-up visit (including Visit 801). Those patients will not be included in the safety summaries for Part B.

For patients who entered Part B: The safety summaries for Part A will include the events/measurements from the first dose date of study treatment in Part A to the day before the first dose date of study treatment in Part B. The safety summaries for Part B will include the events/measurements from the first dose date of study treatment in Part B to the end of the 30-day post-discontinuation follow-up visit (including Visit 801).

Safety listings will include the safety data through Part A and Part B. Safety summaries for Part A and safety listings will be based on the SP. Safety summaries for Part B will be based on the SP2 unless otherwise specified. Safety populations are defined in Section 6.6.1.

6.12.1. Exposure

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

- Exposure: number of infusions (except S-1); 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 omission, dose reduction, dose delay, dose withheld, and dose interruption;
- Reasons for dose adjustments.

Here is the general guideline for dose modification:

- **Part A: Ramucirumab/Placebo (Ram/Plb)**
  - If Ram/Plb is delayed within a Cycle, it is considered as dose Delay.
  - If Ram/Plb is skipped within a Cycle, it is considered as dose omission (Not administered) of Ram/Plb.
- **Part A: Oxaliplatin (Ox)**
  - If Day1 of next cycle is delayed due to delay of Ox, it's considered as delay of next cycle.
  - All other cases should be considered as omission (Not administered).
- **Part A: S-1**
  - In each cycle, a day when a patient actually started S-1 take is First dose date and a day when a patient actually completed S-1 take is Last dose date.
  - If all 28 administrations of a cycle are omitted, it's considered as omission (Not administered).
  - Other cases such as delay or omission during a cycle should be captured in Dose Withheld eCRF form.

- **Part B: Ramucirumab (Ram)**
  - In case Day1 administration is delayed to Day8 or Day15 administration is delayed to Day22, it's considered as Delay.
  - If Day1 administration is skipped or Day15 administration is skipped, it's considered omission (Not administered).
- **Part B: Paclitaxel (PTX)**
  - In case administration of PTX is delayed due to toxicity, start of next cycle will be delayed until recovery.
  - All other cases should be considered as omission (Not administered).

More specifically, dose reduction, dose delay, dose interruption, dose withheld in Table JVCW. 6.4 are directly from eCRF.

For the definition of dose omission of ramucirumab, placebo, oxaliplatin, and paclitaxel, it is based on a particular day, not a cycle.

Table JVCW. 6.4 Exposure data captured directly by eCRF

	RAM/PLA	S-1	Oxaliplatin	Paclitaxel.
Adjustments	Reduce only	Reduce only	Reduce only	Reduce only
Omission	X (derived)	X	X (derived)	X (derived)
Reduction	O	O	O	O
Delay	O	X	O	O
Interruption	O	X	O	O
Withheld	X	O (delay and omission is captured here)	X	X

Abbreviation: RAM/PLA = ramucirumab or placebo. O = Captured in eCRF. X = Not captured in eCRF.

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.

Following listing will be created:

- Ramucirumab/Placebo Administration
- S-1 Administration
- Oxaliplatin Administration
- Paclitaxel Administration
- Ramucirumab/Placebo Dose Exposure
- S-1 Dose Exposure
- Oxaliplatin Dose Exposure

6.12.2. Adverse Events

Adverse events will be summarized by MedDRA system organ class (SOC)/preferred term (PT), classified from verbatim terms. The incidence and percentage of patients with at least 1 occurrence of a preferred term will be included, according to the most severe NCICTCAE v. 4.03 grade. Causality (relationship to study drug), action taken, and outcome will be summarized separately. Duration of AE will be determined and included in the listings.

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 (Part A: sort by ramuricumab arm, Part B: sort by total); when summarized by SOC and PT, AEs will be presented in decreasing frequency of PT within system organ class across treatment arms (Part A: sort by ramuricumab arm, Part B: sort by total). 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.

6.12.2.1. 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 TEAE
- patients with AEs that led to death on study treatment (Part A)

  Note: It include events within 30 days after the decision is made to discontinue Part A.
- patients with AEs that led to study treatment discontinuation (Part A)
- patients with SAEs that led to study treatment discontinuation (Part A)

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.

Repeat the above summaries for Part B.

Following listings will be created:

- Adverse Events
- Adverse Events Leading to Dose Adjustment
- Adverse Events Leading to Discontinuation of any Study Treatment
- Adverse Events Leading to Death
- Adverse Events related to study treatment Leading to treatment discontinuation (Part A and Part B)

6.12.2.2. Treatment-Emergent Adverse Events (TEAEs)

The following summaries of TEAEs will be provided (*repeat for events deemed by the investigator to be possibly related to study medication, †include consolidated summary):

- by PT*†

- CTCAE Grade >= 3 TEAE by PT*†
- by SOC and PT*
- by maximum CTCAE grade and by PT*†

6.12.3. 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 followings:

[1] All deaths: population=SP

Definition: V1<= Death

[2-a] Deaths on therapy during Part A: population=SP

Definition: V1<= Death <= Last day of Part A

[2-b] Deaths on therapy during Part B: population=SP2

Definition: V201<= Death <= Last day of Part B

[3-a] Deaths after stopping Part A up to the short term follow-up: population=SPA

Definition: Last day of Part A < Death <= V801

[3-b] Deaths after stopping Part B up to the short term follow-up: population=SP2

Definition: Last day of Part B < Death <= V801

[4-a] Deaths after V801: population=SPA

Definition: V801< Death

[4-b] Deaths after V801: population=SP2

Definition: V801< Death

Note V1=Visit 1, V201=Visit 201, V801=Visit 801.

Serious adverse events (SAE) 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. In addition, SAE by maximum CTCAE grade will be summarized.

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 by max CTCAE grade by PT
- Adverse events of Special Interests leading to study treatment discontinuation (each treatment, any treatment)

- Liver injury/failure*
  Note: Liver injury/failure is analyzed separately from other AESIs because its analysis requires a different format.
- Association between Selected Adverse Events
  - Proteinuria vs. Renal Failure
  - Thrombocytopenia vs Bleeding Events

Following listing will be created:

- Deaths
- Treatment-Emergent Adverse Events of Special Interest (AESIs)
- Treatment-Emergent Liver Injury /Liver Failure Adverse Events
- Serious Adverse Events
- Interstitial lung disease (ILD)

6.12.4. Clinical Laboratory Evaluation

Day 1 (start of each cycle) should be assigned to the record of the actual day of Day 1. For Day 8 and Day 15, timepoint should be assigned based on the study drug administration date (e.g. ramuciumab/placebo for Part A Day 8, ramucirumab for Part B Day 15, paclitaxel for Part B Day 8). When the study drug administration is omitted or not performed, time point is assigned to the record of elapsed day from Day 1.

Laboratory results will be classified according to NCI-CTCAE v4.03. Incidence of laboratory abnormalities will be summarized. The shifts in CTCAE toxicity grading from baseline to worst grade postbaseline (first dose up to 30 days after the decision is made to discontinue Part A or Part B) 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.

Following listing will be created:

- Patietns with Grade >=3 Abnormal Laboratory Results
- Hemotology

- Coagulation Profile
- Serum Chemistry
- Urinaysis
- 24-hour Urine Collection and Urine Protein/Creatinine Ratio

6.12.5. Hospitalizations

The number of patients hospitalized in study treatment period (Part A) or within 30 days after the decision is made to discontinue Part A, will be presented by reason for hospitalization. The number of patients with 1, 2, 3, and > 3 hospitalizations due to AEs will be summarized. The total duration of hospitalizations will be summarized by treatment group for hospitalized patients only, along with the duration of hospitalization relative to duration on treatment. The analysis population is based on SP.

Similar analysis will be conducted for Part B. The number of patients hospitalized in during Part B or within 30 days after the decision is made to discontinue Part B, will be presented by reason for hospitalization.

Listing of hospitalization will be created

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

A summary of ECOG performance status 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.

Following vital low/high limits will be used

Table JVCW. 6.5 Vital low/high limits

Variables	Low	High
Systolic blood pressure (mm Hg)	<=90	>=140
Diastric blood pressure (mm Hg)	<=50	>=90
Pulse rate (bpm)	<50	>100
Weight (kg)	none	none

Abbreviations: mm HG = millimeters of mercury; bpm = beats per minutes; kg =kilograms.

Following listings will be created:

- ECOG performance status

- Vital signs
- ECG data

6.12.7. Subgroup Analyses

Following subgroup analyses for some of the safety analysis will be conducted:

- Geographic region (2 categories: Japan, non-Japan)
- Country (3 categories: Japan, South Korea, Taiwan)

Details are specified in the next section.

6.13. Subgroup Analysis

Subgroup analysis for efficacy and safety are specified in Section 9 and Section 6.12.7. Detailed subgroup analysis are specified in the list below

Table JVCW. 6.6 Subgroup Analysis

Category	Index	Analysis	Geographic region (JP/non-JP)	Country (JP/KR/TW)
Patient Disposition	PD1	Patients disposition	O	O
Patient Disposition	PD2	Reason for discontinuation as well as patients continuing on the study	O	O
Demographic/Baseline	DB1	Patient demographics	O	O
Demographic/Baseline	DB2	Disease characteristics	O	O
Demographic/Baseline	DB3	Prior cancer therapies	O	O
Efficacy	EF1	Summary of PFS	O	O
Efficacy	EF2	Summary of OS	O	O
Efficacy	EF3	Kaplan-Meier plot for PFS	O	O
Efficacy	EF4	Kaplan-Meier plot for OS	O	O

Efficacy	EF5	Forest plot of PFS HRs for treatment effect and its two-sided 80% CI estimated using the primary Cox PH model without the subgroup as a covariate, if any.	O	O
Efficacy	EF6	Forest plot of OS HRs for treatment effect and its two-sided 80% CI estimated using the primary Cox PH model without the subgroup as a covariate, if any.	O	O
Efficacy	EF7	Summary of PFS2	O	O
Efficacy	EF8	Summary of Best Overall Response (ORR and DCR)	O	O
Efficacy	EF9	Summary of ECOG PS deterioration	O	O
Exposure	EX1	Summary of exposure-related variables	O	O
Adverse Events	AE1	Overview of AEs	O	O
Adverse Events	AE2	TEAE by SOC and PT	O	O
Adverse Events	AE3	TEAE by SOC and PT*	O	O
Adverse Events	AE4	TEAE by CTCAE maximum grade	O	O
Adverse Events	AE5	TEAE by CTCAE maximum grade*	O	O
Adverse Events	AE6	TEAE by Age subgroup A and PT	O	O
Adverse Events	AE7	TEAE by gender and PT	O	O
Adverse Events	AE8	Summary of reason for deaths	O	O
Adverse Events	AE9	Listing of deaths and mortality status	O	O
Adverse Events	AE10	SAE by PT	O	O

Adverse Events	AE11	SAE by PT*	O	O
Adverse Events	AE12	Listing of SAE	O	O
Adverse Events	AE13	AE leading to study treatment discontinuation by PT	O	O
Adverse Events	AE14	AE leading to dose modification by PT	O	O
Adverse Events	AE15	AESI	O	O
Adverse Events	AE16	Listing of AESI	O	O
Vital Signs	VS1	Summary of vital signs	O	O
Laboratories Evaluations	LB1	Box plot of laboratory measurements by cycle	O	O
Post-discontinuation Therapy	PDT1	Summary tables	O	O

*Events deemed by the investigator to be possibly related to study treatment.

Abbreviations: JP=Japan; non-JP=non-Japan; KR=Korea; TW=Taiwan.

6.14. Pharmacokinetics and Immunogenicity

Serum concentrations of ramucirumab prior to infusion (C_{min}) will be summarized using descriptive statistics. Additional analysis utilizing a population pharmacokinetic approach based on an established population PK model may also be conducted if deemed appropriate.

A subject who is evaluable for treatment-emergent anti-drug antibodies (ADA) is treatment-emergent ADA-positive (TE ADA+) if either of the following holds:

- **Treatment-induced ADA+ subject:** The subject has baseline status of ADA Not Present and at least 1 postbaseline status of ADA Present with titer ≥ 2*MRD (see Assay Operating Characteristics).
- **Treatment-boosted ADA+ subject:** The subject has baseline and postbaseline status of ADA Present, with the postbaseline titer being 2 dilutions (4-fold) greater than the baseline titer. That is, the subject has baseline status of ADA Present, with titer 1:B, and at least 1 postbaseline status of ADA Present, with titer 1:P, with P/B ≥ 4.

For immunogenicity, the number and percent of patients with treatment-emergent ramucirumab ADA will be summarized.

Following listing will be created:

- Treatment-emergent adverse events for patients with either at least 1 sample of Ramucirumab ADA present or infusion-related reaction or both
- Antibody to ramucirumab and drug concentration data for patients who have at least 1 sample result of ADA present.

6.15. Translational Research

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

6.16. Interim Analysis

No interim analyses are planned for this study.

6.17. 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. 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).

7. Unblinding Plan

This unblinding plan refers to the process to be followed for the primary PFS analyses.

Randomization will occur using an IWRS system. Assignment to treatment groups will be determined by a computer-generated random sequence. Security measures will be taken so that treatment group code and other variables that can link patients to study arm will be blinded in the database. This blinding will be maintained until the primary data lock.

Data sets will be created for the purpose of aggregate data review in which treatment assignment and related data, such as study drug administration dates and amounts are scrambled so that personnel involved in the day-to-day conduct of the trial and development and validation of analysis programs will be blinded to patient treatment.

While every effort will be made to blind both the patient and the investigator to the identity of the treatment, the inadvertent unblinding of a patient may occur. This unblinding will not be sufficient cause (in and of itself) for that patient to be discontinued from study therapy or excluded from any safety or efficacy analysis.

In order to maintain the scientific integrity of this double-blind trial, access to study data will be strictly controlled. Treatment assignment will be scrambled in the reporting database until the database lock for the primary PFS analysis. No by-patient level treatment data will be accessible to anyone else (e.g., the rest of study team and investigators) until the database lock for the primary PFS analysis.

Following the primary PFS analysis (approximately 111 PFS events + 6 months), the aggregated study result may be disclosed if it is deemed necessary. Any such disclosure will be documented properly.

8. References

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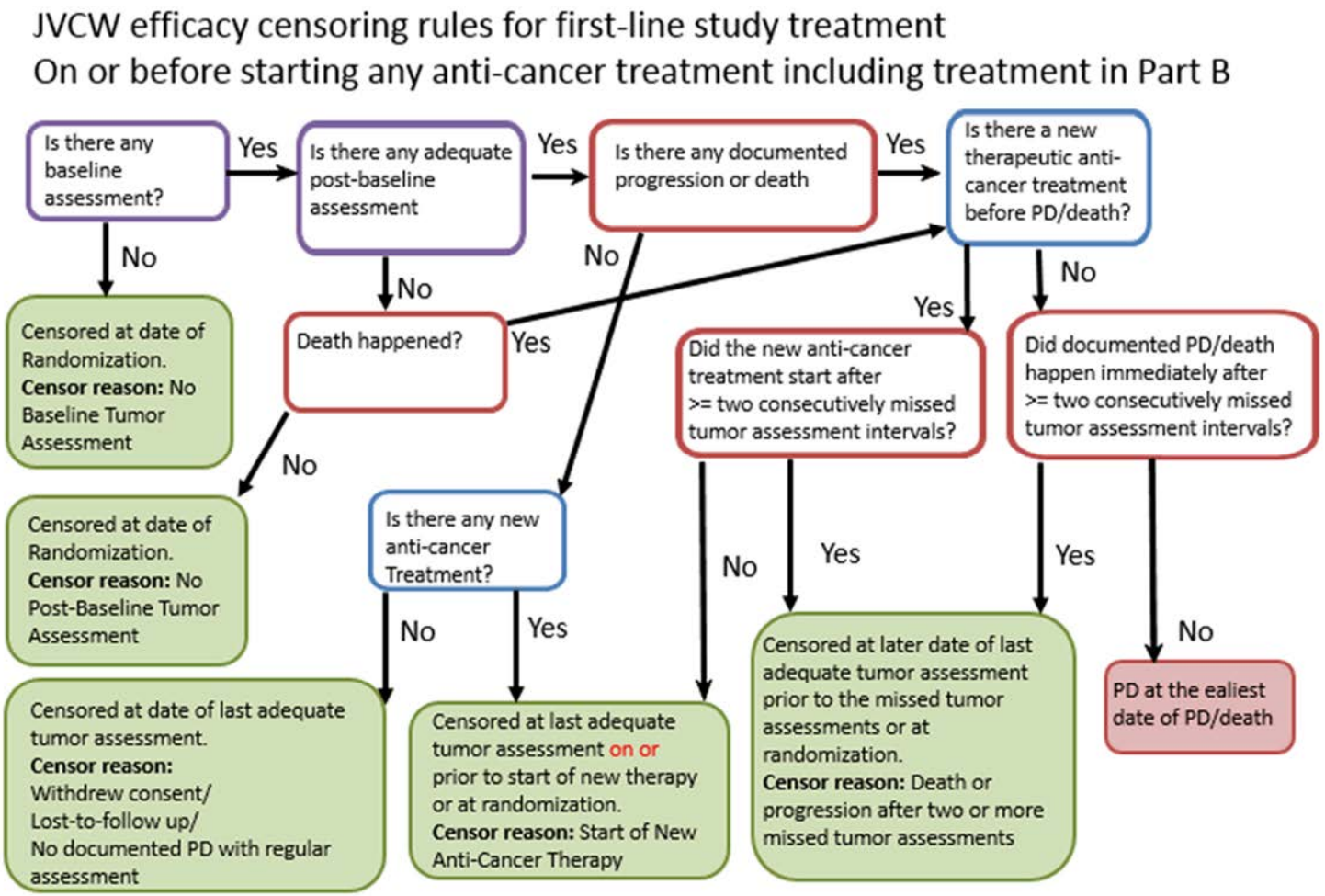
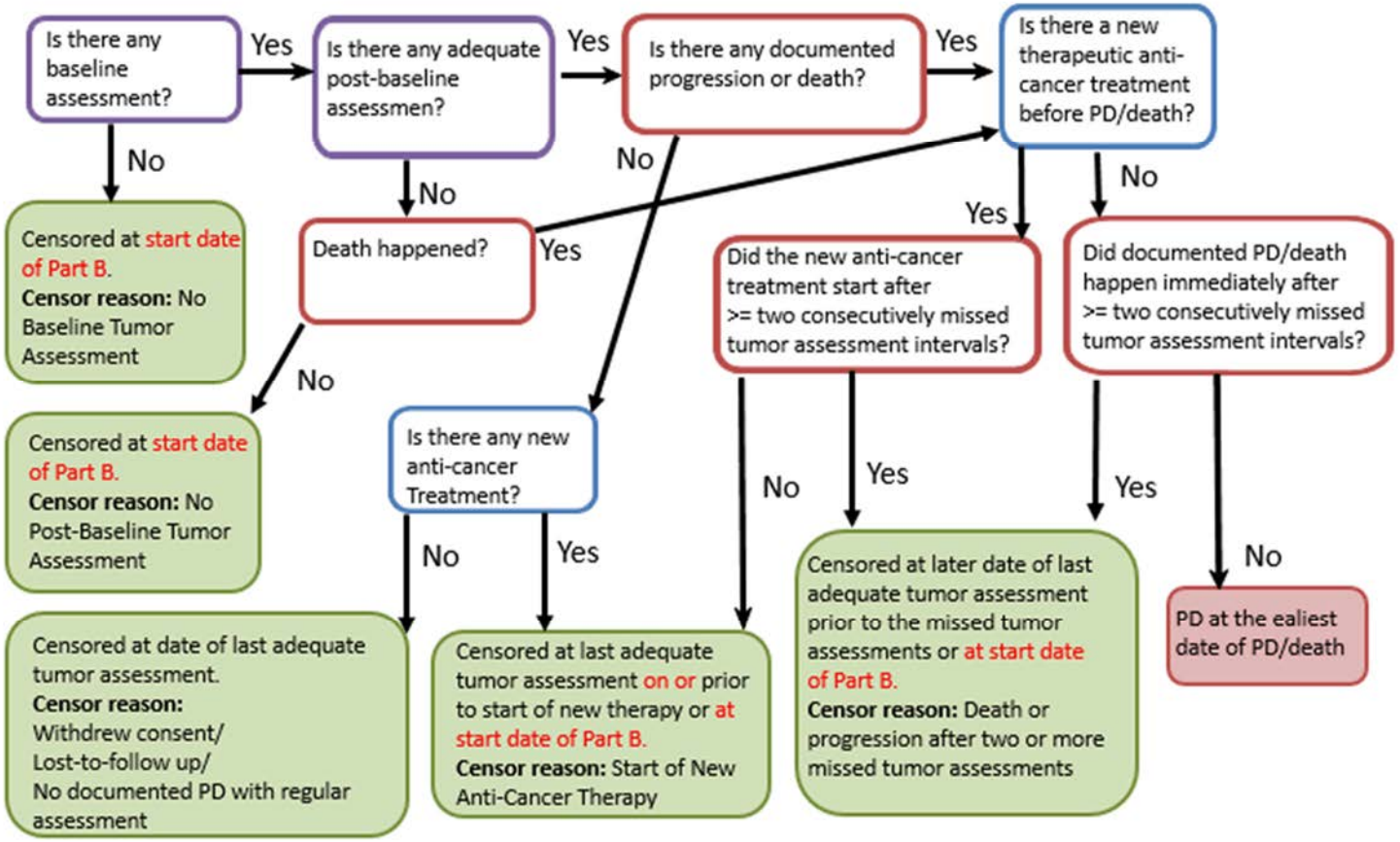
9. Appendix A

9.1. Censoring rules for Part A and Part B


JVCW efficacy censoring rules for first-line study treatment
On or before starting any anti-cancer treatment including treatment in Part B
Is there any baseline assessment?
Yes
Is there any adequate post-baseline assessment
Yes
Is there any documented progression or death
Yes
Is there a new therapeutic anti-cancer treatment before PD/death?
No
Censored at date of Randomization. Censor reason: No Baseline Tumor Assessment
No
Death happened?
Yes
No
Censored at date of Randomization. Censor reason: No Post-Baseline Tumor Assessment
No
Is there any new anti-cancer Treatment?
No
Censored at date of last adequate tumor assessment. Censor reason: Withdrew consent/ Lost-to-follow up/ No documented PD with regular assessment
Yes
Censored at last adequate tumor assessment on or prior to start of new therapy or at randomization. Censor reason: Start of New Anti-Cancer Therapy
Yes
Did the new anti-cancer treatment start after >= two consecutively missed tumor assessment intervals?
No
Yes
Censored at later date of last adequate tumor assessment prior to the missed tumor assessments or at randomization. Censor reason: Death or progression after two or more missed tumor assessments
No
Did documented PD/death happen immediately after >= two consecutively missed tumor assessment intervals?
Yes
Yes
No
PD at the ealiest date of PD/death

JVCW efficacy censoring rules for second-line study treatment



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