I4T-MC-JVDF Statistical Analysis Plan Version 3

An Open-Label, Multicenter, Phase 1 Study of Ramucirumab plus Pembrolizumab in Patients with Locally Advanced and Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma, Non- Small Cell Lung Cancer, Transitional Cell Carcinoma of the Urothelium, or Biliary Tract Cancer

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1. Statistical Analysis Plan for LY3009806: I4T-MC-JVDF: An Open-Label, Multicenter, Phase 1 Study of Ramucirumab plus Pembrolizumab in Patients with Locally Advanced and Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma, Non-Small Cell Lung Cancer, Transitional Cell Carcinoma of the Urothelium, or Biliary Tract Cancer

Ramucirumab (LY3009806) and Pembrolizumab (MK3475)

This is an open-label, multicenter, Phase 1 study of ramucirumab plus pembrolizumab: Phase 1a (dose-limiting toxicity) and Phase 1b (safety and preliminary efficacy) will include patients with locally advanced and unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma, non-small cell lung cancer, or transitional cell carcinoma of the urothelium.

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Protocol I4T-MC-JVDF
Phase 1

Statistical Analysis Plan Version 1 approved by Lilly on 19 June 2015
Statistical Analysis Plan Version 2 approved by Lilly on 28 March 2016
Statistical Analysis Plan Version 3 electronically signed and approved by Lilly on date provided below.

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2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

3. Revision History

Version 1 of this Statistical Analysis Plan (SAP) was approved prior to unblinding (or the first visit when a subject receives study drug or any other protocol intervention if the clinical trial is open-label).

Version 2 of the SAP was approved prior to the first patient visit (FPV) of the 3 additional cohorts: 2L-3L biliary tract cancer (BTC), 1L gastric or gastroesophageal junction adenocarcinoma (gastric-GEJ), and 1L non-small cell lung cancer (NSCLC). The overall changes and rationale for the changes incorporated in Version 2 are as follows:

- Add 3 additional cohorts: 2L-3L BTC, 1L gastric-GEJ, and 1L NSCLC;
- Clarify the timing of the final analysis (safety and preliminary efficacy);
- Clarify the timing of interim analyses (safety and preliminary efficacy);
- Power and sample size determinations for the 3 additional cohorts.

This version of the SAP (Version 3) corrects the illustration for the duration of response by irRECIST (Scenario 2), and was approved prior to the public disclosure of this document.

4. Study Objectives

4.1. Primary Objective

The primary objective of this Phase 1a and 1b study is to assess the safety and tolerability of 2 dosing regimens of ramucirumab plus pembrolizumab.

4.2. Secondary Objectives

The secondary objectives of this study are as follows:

- to characterize the pharmacokinetics (PK) of ramucirumab when co-administered with pembrolizumab (Phase 1a, Phase 1b)
- to assess the preliminary efficacy of ramucirumab plus pembrolizumab (Phase 1b)

4.3. Exploratory Objectives

The exploratory objectives of this study are as follows:

- to explore the association between biomarkers and clinical outcomes (Phase 1b)
- to characterize biomarker measures of immune functioning and angiogenesis (Phase 1b)
- to assess immunogenicity of ramucirumab when co-administered with pembrolizumab (Phase 1b).

5. A Priori Statistical Methods

5.1. Sample Size Determination

The primary objective for this dose-limiting toxicity (DLT) Phase 1a and Expansion Phase 1b study is to evaluate safety and tolerability. The sample size of Expansion Phase 1b was selected to allow adequate assessment of safety at the recommended doses for ramucirumab and pembrolizumab for each tumor type and dose schedule, separately.

5.1.1. Phase 1a

Phase 1a DLT Observation: up to 12 DLT-evaluable patients.

5.1.2. Phase 1b

Phase 1b Expansion: 155 patients; 15 patients each for Cohorts A and B (2L-3L gastric-GEJ), 25 patients each for Cohorts A1, A2, C, D, and E (2L-3L BTC, 1L gastric-GEJ, 2L-4L NSCLC, 2L-4L urothelial cancer, and 1L NSCLC, respectively).

The primary objective of Study I4T-MC-JVDF (JVDF) is the safety and tolerability of ramucirumab in combination with pembrolizumab. During Expansion Phase 1b, 25 to 30 patients per tumor type will be treated, to provide a preliminary assessment of tumor response and an assessment of safety. For each of the tumor types, the objective response rate (ORR) values in the simulations are provided as a reference for estimation of statistical power rather than a basis of any decision criteria. All efficacy endpoints will be utilized to determine next steps of development of the combination.

For gastric-GEJ and BTC (2L-3L), and NSCLC and urothelial cancer (2L-4L), the null hypothesis is based on the assumption that the ORR is no greater than 10% to 15% and the target treatment effect (alternative response rate) of the combination treatment on ORR is greater than 20% to 30%. Based on these assumptions, a sample size of n=25 to 30 (n=30 for combined Gastric Cohorts A and B) provides statistical power of approximately 60% to 90%, with a 1-sided nominal 0.20 significance level (Table JVDF.1).

For first-line NSCLC and gastric-GEJ, the null hypothesis is based on the assumption that the ORR is no greater than 30% to 35% and the target treatment effect (alternative response rate) of the combination treatment on ORR is greater than 45% to 55%. Based on these assumptions, a sample size of n=25 provides statistical power of approximately 65% to 90%, with a 1-sided 0.20 significance level (Table JVDF.2).

Table JVDF.1. Summary of Statistical Power for Overall Response Rates for NSCLC 2-4L, Bladder 2-4L, BTC 2-3L, and Gastric 2-3L

	NSCLC, Bladder, and BTC				Gastric (combined preliminary efficacy)			
	Low Case	High Case	Low Case	High Case	Low Case	High Case	Low Case	High Case
	N=25	N=25	N=25	N=25	N=30	N=30	N=30	N=30
Null response rate	0.10	0.10	0.15	0.15	0.10	0.10	0.15	0.15
Target response rate	0.20	0.25	0.25	0.30	0.20	0.25	0.25	0.30
Power	57.9%	78.6%	62.2%	80.7%	74.5%	90.2%	65.2%	84%

Abbreviations: BTC = biliary tract cancer; L=line; N = number of patients; NSCLC = non-small cell lung cancer.
Note: low case = 10% difference between alternative response rate and null response rate for overall response rate; high case = 15% difference between alternative response rate and null response rate for overall response rate.

Table JVDF.2. Summary of Statistical Power for Overall Response Rates for NSCLC 1L and Gastric 1L

	NSCLC (1L) and Gastric (1L; combined preliminary efficacy)			
	Low Case	High Case	Low Case	High Case
	N=25	N=25	N=25	N=25
Null response rate	0.30	0.30	0.35	0.35
Target response rate	0.45	0.50	0.50	0.55
Power	75.8%	88.5%	65.5%	81.7%

Abbreviations: 1L = First-Line; N = number of patients; NSCLC = non-small cell lung cancer.
Note: low case = 15% difference between alternative response rate and null response rate for overall response rate; high case = 20% difference between alternative response rate and null response rate for overall response rate.

5.2. Derived Endpoint Definition

5.2.1. Safety Endpoint

Safety measures that will be used in the study include adverse events (AEs), DLTs (in the Phase 1a part of the study), clinical laboratory test results, vital signs, and electrocardiogram (ECG) parameters. All AEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Adverse event terms will also be derived from verbatim text using the Medical Dictionary for Regulatory Activities (MedDRA™) dictionary.

5.2.1.1. Dose-Limiting Toxicity

A DLT is defined as considered to be related to study regimen by the investigator, and fulfills any 1 of the following criteria using NCI CTCAE Version 4.0:

1. Nonhematologic toxicity as follows:
    a) Grade 4 nonlaboratory toxicity

b) Grade 3 nonlaboratory toxicity (for example, nausea, vomiting, and diarrhea) lasting >3 days despite optimal supportive care

c) Any Grade 3 or Grade 4 laboratory value if:

i. Medical intervention is required to treat the patient, or

ii. The abnormality persists for >1 week.

Note: Liver function abnormality: For patients with liver metastasis who begin treatment with Grade 2 aspartate aminotransferase (AST) or alanine aminotransferase (ALT), if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 7 days.

2. Hematologic toxicity, as follows:

a) Grade 4 toxicity lasting ≥7 days, or

b) Grade 3 thrombocytopenia if associated with bleeding and requires platelet transfusion, or

c) Febrile neutropenia Grade 3 or Grade 4

3. Grade 5 toxicity (that is, death)

4. Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose-limiting, for example:

a) Any toxicity that is possibly related to study treatment that requires the withdrawal of the patient from the study during Cycle 1, or

b) A delay of >14 days due to persistent Grade ≥2 toxicities in initiating Cycle 2, with the exception of Grade 2 fatigue.

Any infusion or hypersensitivity reactions occurring during the infusion of the drug are not considered dose-related and therefore will NOT be considered to be a DLT.

After each of the 3 patients in a dose schedule completes the observation period, a safety analysis will occur; the data will be reviewed by study investigators and the Lilly clinical research physician/clinical research scientist (CRP/CRS), and the findings will be documented, indicating whether each dose schedule is or is not well tolerated. The results of this meeting will inform the decision whether or not to move to the expansion phase.

5.2.1.2. Exposure-Related Variables

- **Cumulative dose**
  - For ramucirumab, cumulative dose (mg/kg) is calculated as sum of all calculated dose levels, where calculated dose level (mg/kg) = (actual total dose [mg]) / (closest body weight [kg] prior to the treatment).
  - For pembrolizumab, cumulative dose (mg) is calculated as sum of all dose levels.

- **Duration of treatment (week)**
  - Duration of treatment (week) of ramucirumab is calculated as (date of first dose in last cycle – date of first dose + 21)/7.
  - For pembrolizumab, duration of treatment (week) is calculated as (first date of the last cycle when pembrolizumab is distributed – date of first dose + 21)/7 for pembrolizumab.

  Note. Twenty-one days is added because the administration is every 21 days. In Schedule 1, ramucirumab is administered with 8 mg/kg on Day 1 and Day 8, while pembrolizumab is administered with 200 mg fixed on Day 1 every 3 weeks. In Schedule 2, ramucirumab with 10 mg/kg and pembrolizumab with 200 mg fixed are administered on Day 1 every 3 weeks. Last cycle stands for the last cycle with planned dose, regardless of whether the actual dose received is 0 or not.

- **Dose intensity** (mg/kg/week for ramucirumab or mg/week for pembrolizumab) is calculated as cumulative dose/component-specific duration of treatment in weeks.
- **Relative dose intensity** (%) is calculated as dose intensity/planned dose intensity * 100, where for Schedule 1, ramucirumab planned dose intensity = 5.3 mg/kg/week and it is 3.3 mg/kg/week for Schedule 2. The planned dose intensity = 66.7 mg/week for pembrolizumab (or according to the planned dose recorded in the electronic case report form [eCRF]).

5.2.1.3. Adverse Event-Related Variables

Adverse event-related variables are listed below:

- **Dose-limiting toxicity (DLT):** Please refer to Section 5.2.1.1 for the definition of DLT.
- **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.
- **Treatment-emergent adverse event (TEAE)** is defined as an event that first occurred or worsened in severity between first dose of study treatment and 90 days after the last dose of study treatment and related SAEs reported beyond 90 days after the last dose of study treatment, where last dose stands for actual dose, that is, 0 dose is not counted as last dose.
- **Adverse events of special interest (AESIs)** for ramucirumab include arterial thromboembolic events (ATEs)*, congestive heart failure (CHF)*, fistula (gastrointestinal [GI]* and non-GI), gastrointestinal perforation (non-fistula)*, hemorrhage (also GI hemorrhage as a subcategory and pulmonary hemorrhage [composite term])*, healing complication, hypertension*, infusion-related reaction (IRR) including anaphylactic reaction, liver injury/failure*, proteinuria*, reversible posterior leukoencephalopathy syndrome (RPLS), and venous thromboembolic events*.

Notes:

1. All AESIs are compound level.
2. Each AESI is defined by a set of MedDRA preferred terms (PTs).
   2.1. For RPLS, the PTs were directly selected from MedDRA.
   2.2. For AESIs marked with *, the PTs were selected from the applicable standardized MedDRA queries (SMQs) v.15.0 or higher.
   2.3. For non-GI fistula, all PTs containing the text string "fistula" need be used for analysis.
   2.4. For the rest of the AESIs, the PTs were identified through medical review of all unique PTs collected in all ramucirumab studies for compound-level AESIs.
3. Categories of AESIs may be modified as the understanding of the safety of the investigational drug increases. The final list of categories will be reported in the clinical study report (CSR).

- **Consolidated AEs** include abdominal pain, anemia, fatigue, hyperbilirubinaemia, hypercalcaemia, hyperkalaemia, hypermagnesaemia, hypernatraemia, hyperphosphataemia, hypoalbuminaemia, hypocalcaemia, hypokalaemia, hypomagnesaemia, hyponatraemia, hypophosphataemia, intestinal obstruction, leukopenia, myocardial infarction, neuropathy, neutropenia, rash, renal failure, thrombocytopenia, and urticarial.
  Note. Consolidated AEs are composite AE terms consisting of synonymous PTs to allow meaningful interpretation of the AE data. Additional consolidated AE categories may be added as needed. The final list of consolidated AE categories will be reported in the CSR.

- **Events of clinical interest (ECIs)** for pembrolizumab include 2 categories:

  1. An overdose of pembrolizumab (≥1000 mg [5 times the dose]) not associated with clinical symptoms or abnormal laboratory results

  2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal (ULN) and an elevated total bilirubin lab value that is greater than or equal to 2X ULN and, at the same time, an alkaline phosphatase lab value that is less than 2X ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

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

  - death
  - initial or prolonged inpatient hospitalization
  - a life-threatening experience (that is, immediate risk of dying)
  - persistent or significant disability/incapacity
  - congenital anomaly/birth defect

- considered significant by the investigator for any other reason

5.2.1.4. Efficacy Analysis Variables (RECIST v.1.1)

Definition of efficacy analysis variables are listed alphabetically.

Disease Control Rate (DCR) is defined as the proportion of treated patients achieving a best overall response of complete response (CR), partial response (PR), or stable disease (SD) per Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST v.1.1). Patients who do not have any postbaseline 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 the start of treatment until disease progression, in the order of CR, PR, and SD.

Duration of Response (DoR) is defined only for responders (patients with a confirmed CR or PR). It is measured from the date of first evidence of a confirmed CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier. If a responder is not known to have died or have objective progression as of the data inclusion cutoff date, DoR will be censored at the date of the last complete objective progression-free disease assessment.

Objective response rate (ORR) is defined as the proportion of enrolled patients who have received any amount of either study drug, have at least 1 postbaseline tumor image, and achieve a best overall response of CR or PR. The ORR will be assessed based on RECIST v.1.1 (Eisenhauer et al. 2009) and immune-related RECIST (irRECIST).

Time-to-response (TTR) is defined as the time from the date of first study treatment until the first evidence of a confirmed CR or PR.

Progression-free survival (PFS) is defined as the time from the date of first study treatment until the date of the first observed radiographically documented progressive disease (PD) or death due to any cause, whichever is earlier.

Table JVDF.3 lists rules for determining date of progression or censor for PFS. The censoring is taken in the following order:

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

Note. If there are multiple dates associated with 1 radiological tumor assessment, the assessment date will be set to the first date when the overall response is PD and the last date otherwise. A radiological tumor assessment is considered adequate if its response is CR, PR, SD, or PD.

PFS (day) = Date of progression / censor – date of first treatment + 1

Table JVDF.3. Rules for Determining Date of Progression or Censor for Progression-Free Survival

Rule	Situation	Date of Progression or Censor	Outcome
1	No baseline tumor assessments	Date of first treatment	Censored
2	No postbaseline assessments and no death	Date of first treatment	Censored
3	No documented progression and no death (with a postbaseline tumor assessment)	Date of last adequate tumor assessment	Censored
4	Patient lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last adequate tumor assessment	Censored
5	Documented progression	Date of documented progression If a tumor assessment was done on multiple days, use the earliest date for that visit.	Progressed
6	Death without documented progression	Date of death	Progressed
7	Documented progression or death after missing ≥2 consecutive postbaseline tumor assessments	Date of last adequate tumor assessment before missed assessments or date of first treatment, whichever is later	Censored

Note: Progression-free survival and associated outcome is determined by the earliest of the dates above, if more than 1 situation applies.

Time-to-response, DoR, DCR, and PFS will be assessed based on RECIST v.1.1. Exploratory analysis of TTR, DoR, and PFS may be conducted using irRECIST.

Overall survival (OS) is defined as time from the date of first treatment to the date of death from any cause. For each patient who is not known to have died as of the data inclusion cut-off date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the data-inclusion cut-off date (contacts considered in the determination of last contact date include AE date, lesion assessment date, visit date, and last known alive date).

5.2.1.5. Efficacy Analysis Variables (irRECIST)

For Study JVDF, RECIST v.1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab (irRECIST). Immune-related RECIST will be applied as detailed in the study protocol, and the resulting data will be included in the clinical database.

Immune-related objective response rate (irORR) is defined as the proportion of treated patients achieving a best overall response of PR or CR per irRECIST, particularly, the best

overall response by irRECIST closely related to confirmed response by RECIST. Immune-related ORR further captures responses after unconfirmed PD and does not require confirmation. For example:

- If the best response by RECIST v.1.1 is CR, then the best response by irRECIST is CR.
- If the best response by RECIST v.1.1 is PR, SD, or PD, the best response by irRECIST is the best response over the initial assessment (prior to PD by RECIST v.1.1) and the confirmation stage.

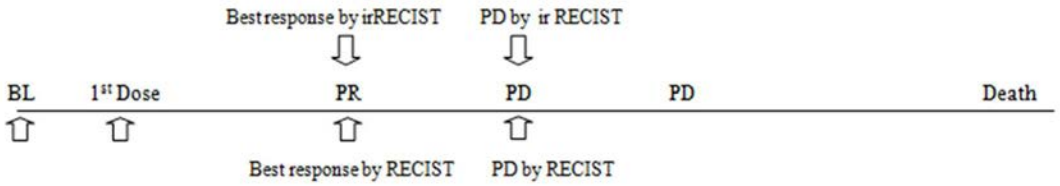
Overall, the best response by irRECIST should be the same or better than the best response by RECIST v.1.1 criteria. In addition, patients who do not have any postbaseline tumor response assessments for any reason are considered non-evaluable and will be included in the denominator when calculating the response rate.

Immune-related progression0free survival (irPFS) is defined as the date from the treatment started date to the time of PD assessed by irRECIST.

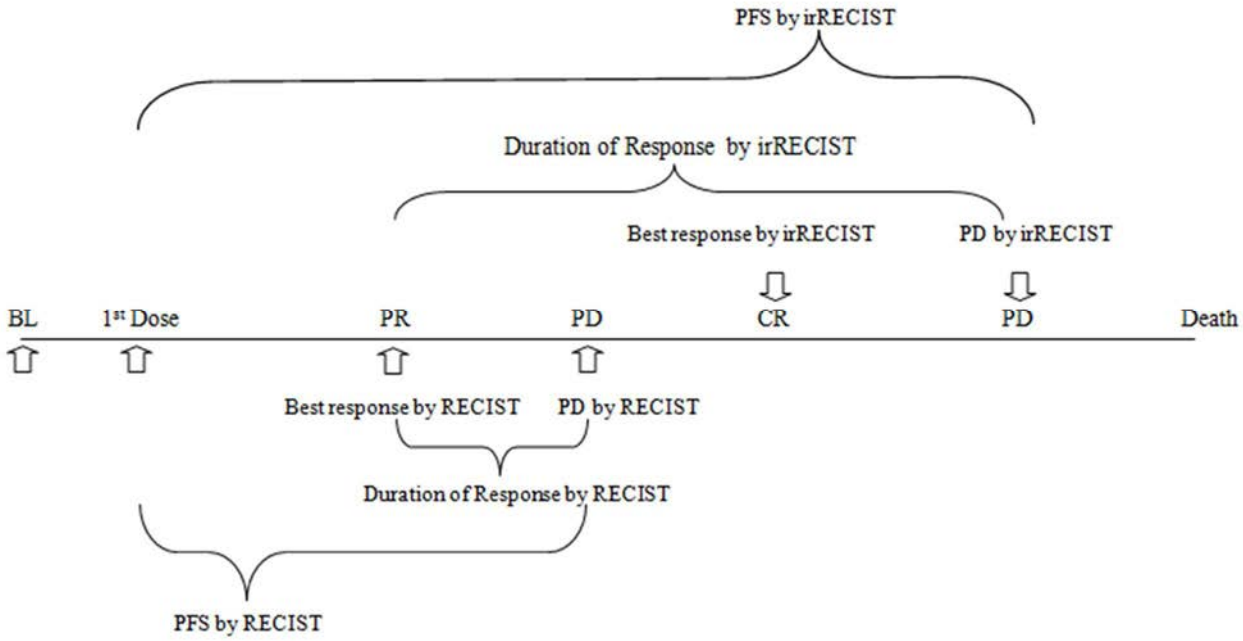
- If the initial PD is confirmed, then the date of immune-related (ir)PD is the initial PD date by RECIST v.1.1.
- If the initial PD is unconfirmed, then the date of irPD is the date of second PD.

Duration of response by irRECIST is defined from the date of first documented irCR or irPR (responder) to the date of irPD or the date of death due to any cause, whichever is earlier.

Graphic Example:
Scenario 1: The initial PD is confirmed at the next scan (consecutive PD). The efficacy variables by irRECIST and RECIST are the same.



Scenario 2: The initial PD is not confirmed at the next scan (non-consecutive PD). The efficacy variables by irRECIST and RECIST v.1.1 are different.



In addition, the best response after initial PD may be listed. Other efficacy analysis based on irRECIST may be performed for exploratory analysis.

5.2.1.6. 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 AEs 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:
    - January 1 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.

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 a 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 10 May 2015 and a tumor assessment date was xx May 2015 (missing day), but it was known that it occurred after that visit, then after imputation, the tumor assessment date became 01 May 2015. 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 2015.

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 5.2.1.3 for details.

5.2.1.7. Analysis Population

Patients **entered** into the trial are those who sign the informed consent document.

Patients **enrolled** in the trial are those who have been assigned to a treatment and have received at least 1 dose of study treatment.

The **safety analysis and efficacy analysis set** will be based on all enrolled patients.

5.3. Description of Analysis

5.3.1. General Consideration

All data, including derived data, will be listed for all enrolled subjects by study phase, assigned LY3009806 dose, cohort, patient number, cycle, and time point where appropriate, unless stated otherwise in the following text or in the table shells.

In the Phase 1a part of the study, data will be summarized by assigned ramucirumab + pembrolizumab dose levels and schedules for preliminary analysis unless stated otherwise. Note: 2 dose schedules of ramucirumab were considered for the Phase 1a part of the study. In addition, data may be summarized by the same indication and dose schedule in combination with the Phase 1b part of the study. They are:

- 2L-3L Gastric (Schedule1): Cohort A + Phase 1a patients with same indication/dose schedule/level as Cohort A
- 2L-3L Gastric (Schedule2): Cohort B + Phase 1a patients with same indication/dose schedule/level as Cohort B
- 2L-4L NSCLC: Cohort C + Phase 1a patients with same indication/dose schedule/level as Cohort C
- 2L-4L Urothelial: Cohort D + Phase 1a patients with same indication/dose schedule/level as Cohort D
- 2L-3L Gastric (total): 2L-3L Gastric Schedule 1 + 2L-3L Gastric Schedule 2

In general, continuous variables will be presented using the mean, standard deviation, median, minimum, maximum, and number of patients with an observation (n).

For categorical variables, the population size (N), the number of events, the number of subjects with events (n), and the proportion of subjects with events (p=n/N) are usually reported.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

5.3.2. Patient Disposition

All patient discontinuation data collected on the eCRF will be listed, including the extent of the patient participation in the study. If known, a reason for their discontinuation from treatment and from study will be listed and summarized. All patients entered in the study will be included in the summary and listing.

All significant protocol violations will be listed by pre-determined categories (for example, inclusion/exclusion criteria, errors/missing data in the informed consent/assent process, non-compliance with protocol procedures, errors and missing data in drug dosage/intervention, errors in recording of DLTs, use of excluded treatments, patients continuing after meeting withdrawal criteria, or other violations as recorded on eCRFs or monitoring reports).

5.3.3. Demographics and Baseline Characteristics

5.3.3.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized and listed for all enrolled patients. At a minimum, sex, age, race, basis for initial diagnosis, initial pathological diagnosis, stage at initial diagnosis, baseline Eastern Cooperative Oncology Group performance status, height, weight, and alcohol and tobacco consumption habits will be summarized. For some subsets of patients, intermediate and study entry pathological diagnosis data will also be listed.

5.3.3.2. Historical Illnesses and Prior Therapies

Historical illnesses are events in the past that ended before the date informed consent is signed. Historical illnesses (coded according to MedDRA) will be listed for all enrolled patients.

Prior therapies, including systemic therapy, radiotherapy, and surgeries, will be listed for all enrolled patients. Prior radiotherapy and systemic therapy will be summarized by the number of patients with at least 1 of each type of treatment, as well as by reason for regimen (for example, palliative or curative). Additionally, the number of regimens of prior systemic therapy and (where available) the reason for prior regimens will be summarized.

5.3.4. Concomitant Therapy

Concomitant medications will be summarized and listed for the safety population.

5.3.5. Post-discontinuation Therapy

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

5.3.6. Exposure

The following exposure-related variables will be reported using summary by treatment arm:

- Exposure: duration of treatment; number of infusions received; number of patients completing ≥1 infusion, ≥2 infusions, …, x infusions, and mean, standard deviation; number of patients with dose modification (dose reduction, dose delay);
- Reasons for dose modification (delays and reductions) (scheduling conflict, AE summarized by PT).

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 phase and cohort:

- 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.

5.3.7. Safety Analyses

All patients who receive at least one dose of study therapy will be summarized for safety and toxicity.

Dose-limiting toxicities will be listed for the Phase 1a part of the study only by ramucirumab dose schedule.

The most current version of MedDRA at time of analysis will be used when reporting AEs by MedDRA terms. The NCI CTCAE Version 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. Unless otherwise specified, when summarized by PT, AEs will be presented in decreasing frequency of PT across treatment arms; when summarized by system organ class (SOC) and PT, AEs will be presented in decreasing frequency of PT within SOC across treatment arms. If more than 1 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. A patient listing of all AEs will be provided.

5.3.7.1. Treatment-Emergent Adverse Events

Treatment-emergent adverse events will be summarized by decreasing frequency of SOC by PT and by CTCAE grade regardless of causality and related to any study drug separately. Note, "by CTCAE grade" refers to the categories of all grade, Grade 3-4, and Grade 3-5. Consolidated TEAEs will also be summarized.

5.3.8. Deaths, Serious Adverse Events, and Other Significant Adverse Events

Reasons for deaths will be summarized separately for 1) all deaths, 2) deaths up to 30 days after the last infusion of study treatment, and 3) deaths after 30 days of last infusion of study drug. Reasons of deaths will also be listed.

Serious adverse events (SAEs) will be summarized by PT and repeated for events deemed by the investigator to be possibly related to study medication, with consolidated summary performed if needed. SAEs will be summarized both up to 30 and 90 days after end of therapy. A listing of SAEs will be produced.

In addition, the following analyses will be performed:

- AESIs for ramucirumab by PT
- AESIs for ramucirumab by PT related to study drug
- ECIs for pembrolizumab by PT
- ECIs for pembrolizumab by PT related to study drug
- Listing of AESIs, sorted in the order of phase, cohort, AESI category, PT, and patient identification
- Listing of AEs with outcome of death or discontinuation

5.3.9. Clinical Laboratory Evaluation

A patient listing of all abnormal laboratory data will be provided with a flag for values outside of the laboratory normal range as well as investigator site, patient identifier, age, sex, race, weight, and visit. Abnormal results will be listed separately for all enrolled patients.

In addition to the investigator-reported AEs, all relevant hematology and chemistry laboratory values will be graded according to NCI CTCAE Version 4.0. These derived values will be included on the listings of laboratory data.

5.3.10. Efficacy Analyses

For patients with PD, the initial determination of progression and the progression by irRECIST will be listed.

This Phase 1a trial was not designed to assess efficacy; however, antitumor activity is a secondary objective, and as such best overall response will be summarized for all patients evaluable for efficacy whose disease is assessable by RECIST v.1.1.

If appropriate, the following analyses will be performed for 2L-3L Gastric (Schedule1), 2L-3L Gastric (Schedule2), 1L Gastric, NSCLC (1L; 2L-4L), Urothelial (2L-4L), BTC (2L-3L), and 2L-3L Gastric (total).

- Objective response rate for each cohort will be estimated by dividing the total number of responders (RECIST v.1.1, irRECIST) by the number of patients whose disease at baseline is assessable by RECIST v.1.1. The estimates will be reported with exact 90% confidence intervals (CIs) for each treatment arm.
- Disease control rate for each treatment arm will be summarized and exact 90% CIs for each treatment arm will be provided.
- Progression-free survival will be estimated using a Kaplan-Meier (KM) method (Kaplan and Meier 1958) by median and exact 90% CI. Additional exploratory analyses using proportional hazards models to control for other factors may be performed. The PFS rate at 12, 18, and 24 weeks (including the 90% CI) may also be calculated. Efficacy analyses will be based on the enrolled patients.
- Overall survival, including 1- and 2- year survival rates, is determined from the date of first study treatment until death due to any cause. If the patient was alive at the data inclusion cut-off date for the analysis (or was lost to follow-up), OS will be censored on the last date the patient was known to be alive. The KM curves will also be presented.
- Individual changes in the tumor burden (sum of measurable lesions) over time will be presented graphically within a tumor type (waterfall plots and spider plots may be used) by tumor programmed death-1 T-cell co-receptor PD-1 expression at baseline.
- Duration of responses may be presented graphically using swimmer plots.
- Overall response rate will be summarized by tumor PD-1 expression at baseline.

In addition, exploratory analysis of TTR, DoR, and PFS may be conducted using irRECIST, and subgroup analysis of interest will be further explored.

5.3.11. Vital Signs, Physical Examinations, and Other Observations Related to Safety

All vital signs, including blood pressure and heart rate, will be listed for all enrolled patients.

5.3.12. Pharmacokinetic/Pharmacodynamic Analyses

The sampling schedule for drawing blood samples for ramucirumab PK is provided in Attachment 2 of the protocol. Serum concentrations of ramucirumab prior to infusion (minimum concentration [C_{min}]) and at 1 hour after the end of the ramucirumab infusion (approximately maximum concentrations) will be summarized using descriptive statistics. Population PK analyses for ramucirumab may be conducted using population PK approach. The relationship between ramucirumab exposure and selected safety outcomes may be explored. All PK/pharmacodynamics analysis and creation of tables, figures, and listings will be the responsibility of the Lilly Global PK/pharmacodynamic and Pharmacometrics group based on applicable Global PK/pharmacodynamic and Pharmacometrics Standard Operating Procedures and software approved by the Global PK/pharmacodynamic and Pharmacometrics group's management.

5.3.13. Immunogenicity Analysis

Immunogenicity (anti-ramucirumab antibody) incidence will be tabulated, and correlation to ramucirumab drug level, activity, and safety will be assessed, as appropriate. The measures that will be analyzed include baseline presence and level of anti-drug antibodies (ADA), treatment-emergent ADA, levels of neutralizing ADA, and incidence and levels of ADA related to IRR.

Tables, figures, and listings established for the study will contain the majority of information needed to fulfill Clinical Trial Registry (CTR) results reporting requirements related to outcomes specified in the CTR registration. Additional analyses will be performed for the purpose of fulfilling the CTR requirements.

5.3.14. Biomarker Analysis

Plans for the exploratory biomarker analyses will be described separately.

5.3.15. Interim Analysis

For the Phase 1a part of the study, the available safety and PK data will be reviewed on a cohort-by-cohort basis. The purpose of these data reviews is to evaluate the safety and tolerability for each dose schedule and determine if a DLT has been observed. The investigators and the Lilly study team will evaluate the totality of data to determine whether or not to move into the Expansion Phase 1b.

For the Phase 1b part of the study, in Cohorts A, B, C, or D, the final analysis of safety and preliminary efficacy will occur approximately 2 years after the first patient (from any of the above cohorts) received first study treatment. For Cohorts A1, A2, or E, the final analysis of

safety and preliminary efficacy will occur approximately 2 years after the first patient (from any of the above cohorts) received first study treatment. Interim analyses will occur at a cohort level when the patients have completed approximately 24 weeks of study treatment or discontinued for any reason. The interim analyses may be combined if they are expected to occur within approximately 1 month, and interim analyses may also be combined with the ongoing trial-level safety review or annual safety review for annual safety update reporting. The study is considered complete when analyses for all cohorts are conducted and no further analyses will be performed (including biomarker analyses).

An independent data monitoring committee may be initiated if 1 or more additional cohorts will be expanded to further explore safety and efficacy for the ramucirumab and pembrolizumab combination.

5.3.16. Additional Reports to Support Clinical Trial Registry (CTR) Reporting of Results

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an Extensible Markup Language (XML) file. Both SAEs and 'AEs are summarized by treatment arm and by MedDRA PT.
- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious.
- For each SAE and 'Other' AE, for each term and treatment arm, the following are provided:
    - the number of participants at risk of an event. If certain subjects cannot be at risk for some reason (for example, gender-specific AEs), then the study team must adjust the number to only include the patients at risk.
    - the number of participants who experienced each event term.
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, a threshold for frequency of 'Other' AEs can be implemented rather than presenting all 'Other' AEs. For example, 'Other' AEs that occur in fewer than 5% of patients in any treatment arm may not be included if a 5% threshold is chosen. The frequency threshold must be less than or equal to the allowed maximum of 5%.

6. References

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.02, DCTD, NCI, NIH, DHHS. 2009. Publish date: 15 Sep 2009.

Eisenhauer EA, Therasse P, Bogaert J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

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