Statistical Analysis Plan Version 2 I7W-MC-JQBA

A Phase 1 Study of LY3127804 as Monotherapy and in Combination with Ramucirumab in Patients with Advanced Solid Tumors

NCT02597036

Approval Date: 15-Nov-2017

1. Statistical Analysis Plan: I7W-MC-JQBA: A Phase 1 Study of LY3127804 as Monotherapy and in Combination with Ramucirumab in Patients with Advanced Solid Tumors

LY3127804

This Phase 1 study is a multicenter, nonrandomized, open-label, dose-escalation study to determine a recommended schedule and dose range for LY3127804 that may be safely administered as monotherapy (Part A) and in combination with a fixed regimen of ramucirumab to patients with advanced and/or metastatic cancer (Parts B and C).

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Protocol I7W-MC-JQBA
Phase 1

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly on 05 November 2015
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below

Approval Date: 15-Nov-2017 GMT

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to first patient visit.

Statistical Analysis Plan (SAP) Version 2 was updated per protocol (d) and approved prior to study completion.

The overall changes and rationale for the changes incorporated in Version 2 are as follows:

- Part D was removed from the study since the primary and secondary endpoints were met and data collected from Parts A-C were adequate to fulfil primary objective of this study. Additional patient enrollment was not required.
- Part E was removed from the study since it was concluded based on Lilly's current oncology portfolio strategies that combining paclitaxel with LY3127804 for treating second-line gastric cancer was no longer desired to be investigated in this particular study.
- The necessary corrections were made in all sections and subsections of this protocol to align with the deletion of Parts D and E from the current study design.
- Clarified the testing of the higher dose 27 mg/kg through the addition of new cohorts of LY3127804 to Parts A and B to confirm MTD from expected DLTs at that particular dose.

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to determine a recommended Phase 2 dose (RP2D) range and schedule of LY3127804, as monotherapy and in combination with ramucirumab that may be safely administered to patients with advanced solid tumors.

4.2. Secondary Objectives

The secondary objectives of this study are:

- to characterize the safety and toxicity profile of LY3127804 as monotherapy and in combination with ramucirumab.
- to assess the maximum tolerated dose (MTD) of LY3127804 monotherapy and in combination with ramucirumab based on the dose-limiting toxicity (DLT), if applicable.
- to assess the PK parameters of LY3127804 monotherapy and when administered in combination with ramucirumab.
- to assess limited PK (peak and trough concentration) of ramucirumab when given in combination with LY3127804.
- to evaluate the incidence and level of antibodies against LY3127804 (anti-drug antibodies [ADAs]) and ramucirumab.
- to document any antitumor activity of LY3127804 as monotherapy and in combination with ramucirumab.
- to estimate PFS of LY3127804 monotherapy and when given in combination with ramucirumab.

4.3. Exploratory Objectives

The exploratory objectives of this study are:

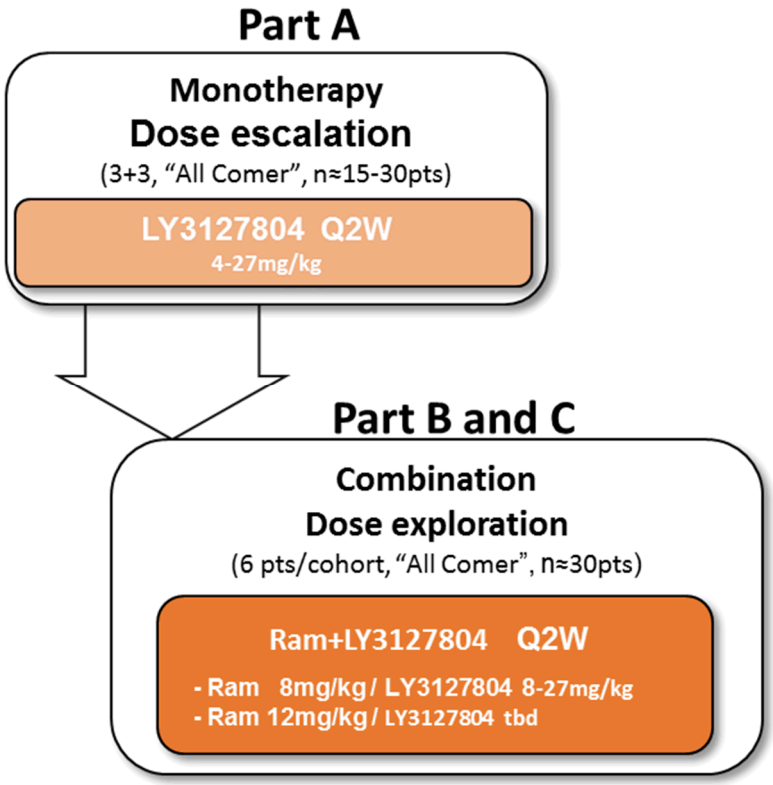
- to evaluate tumor tissue, blood, and DNA for biomarkers related to the gene and gene products associated with mechanism of action of LY3127804, Tie2-Ang2-Ang1, and VEGF-signaling pathway and the tumor biology of the respective tumor types enrolled in the study, which may include but are not necessarily limited to tumor expression (eg, Ang-2, Tie-2, Tie-1,VEGFR-2) and circulating biomarker (eg, Ang-2, Ang-1, s-Tie-2, VEGF-A) and their potential association with the objectives of the study (including PK/PD biomarker relationship)
- to explore biological activity of LY3127804 as monotherapy and when given in combination with ramucirumab based on dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)

5. Study Design

5.1. Summary of Study Design

Study JQBA is a multicenter, nonrandomized, open-label, dose-escalation followed by dose-expansion, Phase 1 study that consists of 3 parts:

- Part A: dose escalation of LY3127804 to determine a RP2D range and schedule for LY3127804 monotherapy that may be safely administered to patients with advanced and/or metastatic cancer
- Part B: dose exploration of LY3127804 in combination with a fixed dose of ramucirumab 8 mg/kg to determine a RP2D range and schedule for LY3127804 that may be safely administered in combination with ramucirumab 8 mg/kg Q2W
- Part C: LY3127804 in combination with ramucirumab 12 mg/kg Q2W to determine a RP2D and schedule for LY3127804 that may be safely administered in combination with ramucirumab 12 mg/kg Q2W (Figure JQBA.5.1)



Abbreviations: pts = patients; Q2W = every 2 weeks; Ram = ramucirumab.
Note: A treatment cycle is defined as an interval of 28 days.

Figure JQBA.5.1. Study design for I7W-MC-JQBA.

In **Part A,** the **LY3127804 single-agent, dose-escalation** part of the study, LY3127804 will be investigated as a monotherapy at a dose ranging from 4 mg/kg up to 27 mg/kg, given Q2W. Cohorts of 3 patients will be enrolled at each of the planned monotherapy dose levels. PK

samplings and ECGs are being performed at expected time of maximal plasma concentration of LY3127804 to rule out the potential for LY3127804 to affect the QTc interval. The sponsor and the investigators will review and discuss all available patient safety data prior to dose escalation. In addition, available PK results from the previous cohort will be reviewed prior to dose escalation. The decision will be documented in writing.

Part B (LY3127804 dose exploration with ramucirumab 8mg/kg) will be opened after patients in Cohort A2 (ie, LY3127804 monotherapy at 8 mg/kg, Q2W) have completed the DLT period and the dose was assessed to be safe. An analysis of the data will be conducted, and feasibility to combine LY3127804 with ramucirumab dose of 8 mg/kg will be evaluated. Based on the results from this analysis, the dose exploration of B cohorts will be initiated (LY3127804 dose [ranging from 8 mg/kg up to 27 mg/kg] + ramucirumab at a fixed dose of 8 mg/kg) at the same time as LY3127804 monotherapy will be dose escalated at higher doses. Dose escalation for LY3127804 will occur up to 27 mg/kg Q2W or until the MTD has been reached; while for all dose levels starting from 8 mg/kg onwards, the feasibility of combining LY3127804 with ramucirumab will be explored. Cohorts of 6 patients will be scheduled at each of the planned combination dose levels. Safety data over the first 28 days of treatment with any LY3127804 dose and the available PK/PD data at that time will be reviewed prior to dose-escalation decision to the next dose level. More detailed information about the dose-escalation method and dosing decision in the course of Parts A to C of the study are available in Section **Error! Reference source not found.** and Section **Error! Reference source not found.**.

Part C (LY3127804 with ramucirumab 12 mg/kg) will be opened once all the combination B cohorts (B2, B3, B4, B5 and B6) have been completed (unless prohibited by DLTs). After completion of Part B, an analysis will be triggered, and based on safety and tolerability data observed in Part B cohorts, it will be determined if and at which dose it is appropriate to combine LY3127804 with ramucirumab at a dose of 12 mg/kg. Based on the result from this analysis, a combination C cohort may be initiated (LY3127804 + ramucirumab dose of 12 mg/kg, 6 patients).

The planned duration of treatment is not fixed; patients will remain on study until study discontinuation. All patients will undergo disease assessment every 8 weeks (prior to the onset of the subsequent treatment cycle).

5.2. Determination of Sample Size

To determine the RP2D of LY3127804, an adequate sample size is required. A sufficient sample size will allow for an accurate evaluation of the relationship between exposure and toxicity, as well as an evaluation of the relationship between exposure and pharmacologic effects using descriptive statistics and appropriate modeling techniques, if data warrant. The overall sample size for this study is estimated to be a total of approximately up to 72 patients.

In Part A, approximately 15 to 30 patients (3 per cohort/dose level with 6 per cohort/dose level at which a DLT has been observed) are planned to be enrolled following a 3+3 dose-escalation scheme in this dose-escalation portion for LY3127804 monotherapy. The actual sample size will depend on the incidence of DLTs.

In Part B, approximately 24 patients (6 per cohort/dose level) are planned to be enrolled. The choice of having 6 patients per combination cohort is based on the assumption that this combination treatment can be beneficial for the patients (therapeutic dose of ramucirumab) and the intention to have a broad (safety) base before escalating to a higher dose of LY3127804 in the combination setting. In line, 6 patients will be enrolled in combination dose-exploration Cohort in Part C.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment in this trial will be assigned to receive LY3127804 as monotherapy or in combination with ramucirumab. Before each patient's enrollment into the study, an eligibility check must be conducted between the investigational site and the Lilly clinical research personnel to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor will confirm the dose cohort and identification number assignment for each patient.

6. A Priori Statistical Methods

6.1. General Considerations

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

The analyses for this study will be descriptive, except for possible exploratory analyses as deemed appropriate. Data analyses will be provided by dose levels and for all patients combined wherever appropriate. For continuous variables, summary statistics will include number of patients (N), mean, median, standard deviation (SD), standard error (SE), minimum, and maximum. Categorical endpoints will be summarized using N, frequency, and percentages.

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

In Parts A through C, all data will be summarized by cohort (and all patients combined when appropriate), unless stated otherwise.

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 changes to the data analysis methods described in the protocol and the justification for making the changes will be described in the clinical study report.

Table JQBA.6.1 explains the data-handling conventions and rules used in the analysis.

Table JQBA.6.1. Data Handling Conventions and Rules

Term	Definition or Rule
Study Day	If assessment is on or after date of first dose then (date of assessment) – (date of first study drug dose) +1
	If assessment precedes first dose of drug then (date of assessment) – (date of first study drug dose)
	There is no study Day 0. Study Day 1 is the date of first dose and study Day -1 is the day before the first dose.
Cycle Day	If assessment is on or after date of first dose in the cycle then (date of assessment) – (date of first study drug dose in cycle) +1
	If assessment precedes first dose of drug in a cycle then (date of assessment) – (date of first study drug dose in cycle)
	There is no cycle Day 0. Cycle Day 1 is the date of first dose in the cycle and cycle Day -1 is the day before the first dose.
Baseline	For change from baseline analyses, baseline value is defined as the last reported measure on or before the first dose (prior to the dose administration). For change from baseline within a cycle, the measure prior to the first dose of that cycle is baseline.
Entered	Patients who sign the informed consent document
Screen Failures	Patients who have signed informed consent, do not meet eligibility criteria and are not enrolled
Safety Population	Patients who have received at least 1 dose of study drug. This population will be used for the analysis of baseline characteristics and efficacy and safety data.
MTD Population	Patients who complete the initial 4 weeks of therapy or experience a DLT during the first cycle will be included in the MTD population. Patients who discontinued during the initial 4 weeks due to reasons other than DLT will be excluded from the MTD population. The MTD population will be used for the evaluation of DLTs in order to determine the RP2D.

Abbreviations: DLT = dose-limiting toxicity; MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose.

6.2. Adjustments for Covariates

Adjustment for covariates is not applicable. However, the following variables are of interest, and analysis with respect to these variables will be discussed in subgroup analyses if appropriate:

- Age (≤65 years vs. > 65 years)
- Sex (male vs. female)
- Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs. 2 in Parts A-C)

6.3. Handling of Dropouts or Missing Data

Missing data will not be imputed.

6.4. Multicenter Studies

This is a multicenter, nonrandomized, open-label study. Enrollment by center will be summarized. Because of the limited sample size, endpoint analyses will not be conducted by enrollment center.

6.5. Multiple Comparisons/Multiplicity

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

6.6. Population for Analysis

Safety and efficacy analyses will be conducted on safety population (all patients who have received at least 1 dose of ramucirumab and/or LY3127804).

Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of ramucirumab and/or LY3127804 and have sufficient samples collected to allow the estimation of ramucirumab and/or LY3127804 PK parameters.

Pharmacodynamic analyses will be conducted on patients who have received at least 1 dose of ramucirumab and/or LY3127804 and have undergone PD assessments.

6.7. Patient Disposition

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

- The number and percentage of patients entered into the study, treated, as well as the number and percentage of patients completing study.
- All patient discontinuations will be documented, and the extent of each patient's participation in the study will be reported. Data on patient discontinuation from study drug and study (overall and by reason for discontinuation) will be listed.

Screening failures will be listed and summarized if appropriate.

6.8. Patient Characteristics

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

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

6.9. Treatment Compliance

Ramucirumab and LY3127804 will be administered intravenously (IV) at the investigational site, under the direction of the investigator. As a result, patient's compliance with study drug administration is ensured.

Potential discontinuation of a patient due to study noncompliance (not attending the scheduled visits) will be presented overall as well as for each cycle if appropriate.

6.10. Concomitant Therapy

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

Prior therapies, including systemic, radiotherapy, and cancer surgeries, will be listed and summarized by cohort and overall. The Lilly WHO Drug Version at study completion will be used to code therapy.

6.11. Safety Analyses

All patients who receive at least 1 dose of ramucirumab and/or LY3127804 will be evaluated for safety and toxicity. The National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0) will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all adverse events (AEs) and other symptoms.

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drugs
- dose delays and dose adjustments
- laboratory values
- vital signs
- DLTs at each dose level for Parts A through C
- electrocardiogram (ECG) readings
- deaths on treatment and within 30 days of treatment discontinuation

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

Dose-Limiting Toxicity

A DLT is defined as an AE during Cycle 1 (first 28 days of exposure) in Parts A through C, that is possibly related to the study drug(s) and fulfills any 1 of the following criteria using NCI-CTCAE v4.0 (NCI 2009):

- ≥ Grade 3 nonhematologic toxicity despite maximal medical management. Some exceptions will be made as presented in the protocol.
- Grade 4 hematologic toxicity of ≥5 days duration
- any febrile neutropenia (absolute neutrophil count <1.0x109/L, fever ≥38.5°C)

- CTCAE Grade 4 thrombocytopenia (unless recovered in 24 hours and in the absence of bleeding) or Grade 3 thrombocytopenia complicated with ≥ Grade 2 bleeding evidence of newly developed edema characterized by a body weight increase >10% as compared to the onset of therapy
- nephrotic syndrome or proteinuria exceeding 3.5 g/24 hours
- any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (for example, any toxicity that is possibly related to the study medication that requires the withdrawal of the patient from the study during Cycle 1)

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

Maximum Tolerated Dose

For the purpose of this study, the MTD is defined as the highest tested dose in a single-agent setting that has <33% probability of causing a DLT. MTD in the combination setting will be determined based on the nature and timing of the DLTs in the combination setting.

6.11.1. Extent of Exposure

LY3127804

LY3127804 will be administered as an IV infusion by injection Q2W on Days 1 and 15 of a 28-day cycle.

Ramucirumab

Ramucirumab will be dosed after administration of LY3127804 on Days 1 and 15 of a 28-day cycle in Parts B, C, and D of this study.

LY3127804 in combination with Ramucirumab

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

The number of cycles of treatment received, cumulative dose (mg/kg or mg/m2), dose intensity (mg/kg/week or mg/m2/week), relative dose intensity, and duration of treatment will be summarized. Dose adjustments (dose reductions, dose delays) including the reasons for dose adjustment will also be listed and summarized.

6.11.2. Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will serve as the reference document, and thus will be used to report AEs. Any minor version of CTCAE Version 4.0 (for

example, CTCAE Version 4.03) may be used for this study. For AEs without matching terminology within the NCI-CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. The verbatim text for these AEs will be coded according to the available version of the Medical Dictionary for Regulatory Activities (MedDRA™). For analysis and reporting of AEs, the MedDRA coded terms corresponding to these CTCAE "other-specify" AEs will be used.

A treatment-emergent adverse event (TEAE) is defined as (i) adverse event that occurred after the administration of at least 1 dose of study therapy, regardless of causality; or (ii) adverse events already present during screening that worsen following exposure to the treatment, regardless of causality.

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

The number of patients who experienced a TEAE, serious adverse event (SAE), TEAE related to study drug, died, or discontinued from the study due to an AE will be summarized by cohort, by part. TEAEs will be summarized by System Organ Class (SOC), Preferred Term (PT), by decreasing frequency within SOC, and by maximum CTCAE severity grade, including the total of patients with maximum severity Grade ≥3.

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

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

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

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

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

6.11.4. Clinical Laboratory Evaluation

Laboratory data (including chemistry, hematology, and urinalysis) will be listed for all patients on therapy. Relevant hematology and chemistry laboratory values will be graded according to

CTCAE v4.0. The grades will be included on the listing and summarized by the maximum grade at each cycle over the entire study for all patients on therapy.

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

6.11.5. Vital Signs and Other Physical Findings

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

6.11.6. Electrocardiograms

All ECG data will be analyzed for safety and categorical analysis will be provided if appropriate. These ECG analyses may include number and percentage of individuals with abnormal ECG findings or ECG parameters at scheduled time points as well as changes from baseline for ECG parameters.

6.12. Efficacy (Antitumor Activity) Analyses

Overall Response Rate (ORR): ORR is defined as the proportion of all treated patients who exhibit a CR or PR relative to baseline as defined by Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST 1.1) (Eisenhauer et al. 2009).

Patients with response that is deemed not evaluable will be considered non-responders. ORR will be assessed within each cohort; ORR with 95% confidence intervals (CIs) will be estimated if appropriate.

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

- If a patient does not have a complete baseline disease assessment, then the PFS time will be censored at the first dose date, regardless of whether or not objectively determined disease progression or death has been observed for the patient; otherwise,
- If a patient is not known to have died or have objective progression as of the data inclusion cutoff date for the analysis, the PFS time will be censored at the last evaluable objective progression-free disease assessment date.
- If a patient has more than one missed visit prior to an event (progression or death), then the PFS time will be censored at the last evaluable assessment prior to the event.

Table JQBA.6.2. Definition of PFS

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

Abbreviations: PD = progressive disease; PFS = progression-free survival.

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

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

6.13. Bioanalytical and Pharmacokinetic/Pharmacodynamic Analyses

A separate SAP will be prepared for analyses of bioanalytical data, PK/PD, and immunogenicity data.

6.13.1. Pharmacokinetic Analyses

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

PK parameter estimates for LY3127804 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be maximum observed drug concentration (C_{max}) and area under the concentration-time curve (from time zero to time t, for which t is the last time point with a measurable concentration [$AUC_{0\text{-}tlast}$], from time zero to infinity [$AUC_{0\text{-}\infty}$]) of LY3127804. Other noncompartmental parameters, such as terminal elimination half-life, systemic clearance, and volume of distribution, may be reported.

PK parameter estimates $AUC_{0\text{-}\infty}$, area under the concentration versus time curve during a dosing interval at steady state ($AUC_{\tau\text{-}ss}$), and C_{max} will be evaluated to delineate effects of dose proportionality and temporal linearity. Log-transformed C_{max} and AUC estimates will be assessed to estimate ratios of geometric means and the corresponding 90% CIs. Summary

descriptive statistics of the PK parameters will be carried out by dose group and also per monotherapy/combination therapy.

The limited ramucirumab PK information collected following administration of ramucirumab in combination with LY3127804 will be summarized by time point (minimum observed drug concentration [C_{min}] and C_{max}) and compared with historical data following ramucirumab monotherapy.

Additional exploratory analyses will be performed if warranted by data, and other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global Pharmacokinetic management. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation.

6.13.2. Pharmacodynamic Analyses

All patients treated in this trial will undergo blood sampling during the extent of their treatment.

PD data from all patients undergoing PD assessments will be analyzed.

6.13.3. Pharmacokinetic/ Pharmacodynamic Analyses

Relationship will be explored between LY3127804 concentration and biomarkers/PD response such as, but not limited to, Ang2/Ang1 ratio and other biomarkers (for example, markers of either Tie2-Ang2-Ang1 and VEGF pathways activity or tumor activity). Nonlinear mixed-effect modelling using software such as NONMEM may be used if appropriate to derive those relationships.

The PD endpoints versus time information will be analyzed (summary statistic performed by time point), and the change relative to pretreatment-baseline value will also be considered in the analysis.

In addition, if deemed appropriate based on the ECG read out, the central ECG database may be built using the stored digital central 12-lead ECGs. From those data, the relationship between LY3127804 concentration and ECG numerical results (Fridericia-corrected QT interval [QTcF] and change in QTcF relative to baseline) may be explored to identify whether LY3127804 may lead to QTcF prolongation and to support/supplement the analysis of the cardiac safety monitoring.

6.13.4. Biomarker Analyses

Biomarker analyses may include analysis for exploratory biomarkers related to the mechanism of action of LY3127804; angiogenesis; and the Ang1, Ang2, Tie2, and VEGF pathways to better understand relationships of cellular-signaling defects with clinical outcomes and mechanism of cancer and cancer-related conditions (paraneoplastic conditions and cancer pathobiology). These analyses may include, but are not limited to, candidate gene/genome-wide analysis for RNA, DNA, serum/plasma analytes (including any of these components derived from exosomes), or tissue biomarkers. The association of biomarkers with the objectives of the study may be assessed.

6.13.5. Immunogenicity

Immunogenicity data will be summarized, and any relationship of immunogenicity to study drug level, activity, and safety will be explored as appropriate.

6.14. Protocol Violations

All significant protocol deviations will be listed by parts and/or cohorts and by reasons (for example, inclusion/exclusion criteria, noncompliance with protocol procedures, use of excluded treatments, informed consent/assent process, continuing after meeting withdrawal criteria, etc.).

6.15. Interim Analyses and Data Monitoring

This is a dose-finding study; data will be reviewed on a cohort-by-cohort basis during the study until the RP2D range or MTDs are determined for monotherapy and combination dose level. The purpose of these cohort-by-cohort reviews (Safety Reviews) is to evaluate the safety data at each dose level/combination and determine if a DLT has been observed that would suggest MTD has been met or exceeded. The investigators and the Lilly study team will make the determination regarding dose escalation based on their review of the safety and tolerability data as described in this protocol for the dose escalation of LY3127804 as well as the feasibility of the different combination settings.

Safety and/or PK data (when available) will be reviewed during the study if needed for dose escalation, modifications to the dose-escalation strategy, or other design elements.

If it is deemed that enough data are obtained to assess the primary objective and the secondary objectives, a clinical study report might be created before the last patient visit. In this case, all data until the data-cutoff date will be used for the analysis of safety, efficacy, PK, and PD biomarkers. All data defined in the protocol will continue to be collected from patients on treatment after the data-cutoff date. These data may be reported separately, and the analyses on all patients including these data may not be performed.

6.16. Development Safety Update Report Analyses

The following reports will be produced for the Development Safety Update Report:

- Summary of patient demographics by age and gender
- Summary of patient demographics by racial groups
- Summary of cumulative patient exposure information
- Listing of patients who discontinued study treatment due to AEs
- Listing of patients who discontinued study treatment due to death, with the exception of those patients who discontinued due to study disease.

6.17. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized by treatment group and 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 group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- Adverse event reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

A participant flow will be created that will describe how many enrolled patients completed the study, and for those who did not, the frequency of each reason for not completing. The patients will be considered as completers if the patient completed DLT assessment for Parts A through C, the patient had a failure event, or was off treatment. This CTR analysis will be based on study discontinuation, not treatment discontinuation.

7. References

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, v4.0, DCTD, NCI, NIH, DHHS. 2009. Publish date: 29 May 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.

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