Statistical Analysis Plan: I4T-MC-JVDA

A Phase 1 Study of Ramucirumab, a Humanized, Monoclonal Antibody Against the Vascular Endothelial Growth Factor-2 (VEGFR-2) Receptor in Children with Recurrent or Refractory Solid Tumors, including CNS Tumors

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1. Statistical Analysis Plan: I4T-MC-JVDA: A Phase 1 Study of Ramucirumab, a Humanized, Monoclonal Antibody Against the Vascular Endothelial Growth Factor-2 (VEGFR-2) Receptor in Children with Recurrent or Refractory Solid Tumors, including CNS Tumors

Ramucirumab (LY3009806)

Phase 1 Study of Ramucirumab in Children with Recurrent or Refractory Solid Tumors, including CNS Tumors.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol I4T-MC-JVDA
Phase 1

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

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to final analysis of the study.

4. Study Objectives

4.1. Primary Objective

The primary objectives of the study are as follows:

- to estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of ramucirumab administered as an intravenous (IV) infusion over 60 minutes, every 2 weeks, to children with recurrent or refractory solid tumors
- to determine the tolerability of the MTD and/or RP2D of ramucirumab in children with recurrent or refractory central nervous system (CNS) tumors
- to define and describe the toxicities of ramucirumab administered on this schedule
- to characterize the pharmacokinetics (PK) and immunogenicity of ramucirumab in children with recurrent or refractory solid tumors including CNS tumors

4.2. Secondary Objectives

The secondary objective of the study is as follows:

- to preliminarily define the antitumor activity of ramucirumab within the confines of a Phase 1 study

4.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

- to explore the pharmacodynamics (PD) effects of ramucirumab in this pediatric population
- to explore potential predictive biomarkers relevant to pediatric cancers, cancer-related conditions, ramucirumab and angiogenesis

5. Study Design

5.1. Summary of Study Design

The study will be completed in 2 parts. Part A will be a safety and dose-finding phase of the study for patients with non-CNS solid tumors, and will include dose-escalation and dose-expansion components. Part B will include a safety evaluation specifically for patients with CNS tumors.

For the dose-escalation phase, a rolling 6 design will be used. Starting dose will be 8 mg/kg IV every 2 weeks (Q2W) with 3 doses per 42 day cycle (Dose Level 1). The decision rules of dose level assignment based on dose-limiting toxicity (DLT) are introduced in the section below. If the MTD is not exceeded (0 or 1 DLT/6 fully evaluable patients) at 8 mg/kg dose level, a second dose level will be explored at the escalated dose of 12 mg/kg IV Q2W with 3 doses per cycle (Dose Level 2). After accrual to Dose Level 2 is completed, PK comparisons from dose levels 1 and 2 will be performed. The goal is to expand at the dose level at which at least 5 out of 6 patients achieve a day 42 C_{min} >= 50 $\mu g/mL$. If PK analysis indicates that more than 1 patient treated at 12 mg/kg dose level has a day 42 C_{min} significantly less than 50 $\mu g/mL$, and the MTD has not been exceeded, additional dose levels will be considered. If the MTD in children and adolescents is exceeded at 8 mg/kg IV Q2W, de-escalation to 6 mg/kg will be considered, and the recommended dose will be based on the MTD.

An expansion cohort will accrue at the lowest tolerable dose at which C_{min} of $\geq$ 50 $\mu g/mL$ has been achieved in at least 5 out of 6 evaluable patients, to acquire PK data in a representative number of young patients (ie, patients <12 years old). If at least 10 out of the total of 12 evaluable patients have a steady state concentration of ramucirumab greater than 50 $\mu g/mL$, then the RP2D has been defined.

5.2. Determination of Sample Size

The primary objective for the dose-escalation phase and the dose-expansion cohort in Part A is to evaluate safety and tolerability in patients with non-CNS solid tumors for the purpose of determining a RP2D; the primary objective in Part B is to evaluate safety in patients with CNS tumors at dose selected as the RP2D in Part A. The sample size of each part of the study is selected to allow adequate assessment of safety at the recommended dose for ramucirumab.

Part A:

A minimum of 2 evaluable patients will be entered at each dose level for determination of MTD. Once the MTD or RP2D has been defined, up to 6 additional patients with recurrent or refractory solid tumors without restrictions on hematologic evaluability may be enrolled to acquire PK data in a representative number of young patients. The anticipated maximum number of evaluable subjects required to complete Part A is 24 patients. Assuming a 20% inevaluable rate, 29 patients may be enrolled.

Part B:

Once the RP2D has been determined in Part A, Part B will open to enroll children with relapsed or refractory CNS tumors who will receive ramucirumab at the MTD or RP2D. Part B of the study will require up to 6 evaluable patients enrolled at the MTD/RP2D as determined in Part A. Allowing for 20% inevaluability, 8 patients may be enrolled.

5.3. Method of Assignment to Dose Level

In the rolling 6 study design, 2 to 6 patients can be concurrently enrolled onto a dose level, based on the number of patients currently enrolled in the cohort, the number of DLTs observed, and the number of patients at risk for developing a DLT. Accrual is suspended when a cohort of 6 has enrolled or when the study endpoints have been met.

Table JVDA.1 provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual. For example, when 3 patients are enrolled onto a dose cohort, if toxicity data is available for all 3 when the fourth patient entered and there are no DLTs, the dose is escalated and the fourth patient is enrolled to the subsequent dose level. If data is not yet available for 1 or more of the first 3 patients and no DLT has been observed, or if one DLT has been observed, the new patient is entered at the same dose level. Lastly, if 2 or more DLTs have been observed, the dose level is de-escalated. If the dose for the fourth patient is escalated, another patient will be enrolled in the subsequent dose level and restart the decision rules for the new dose level.

Table JVDA.1. Dose Level Decision Rules in Rolling 6 Design

# Pts Enrolled	# Pts with DLT	# Pts without DLT	# Pts with Data Pending	*Decision*
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate[a]
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate[b]
3	≥ 2	0 or 1	0 or 1	De-escalate[a]
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate[b]
4	≥ 2	0, 1 or 2	0, 1 or 2	De-escalate[a]
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate[b]
5	≥ 2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate[a]
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate[b]
6	≥ 2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate[a]

Abbreviations: DLT = dose-limiting toxicity; MTD = maximum tolerated soe; Pts = patients.

[a] If six patients already entered at next lower dose level, the MTD has been defined.

[b] If final dose level has been reached, the recommended dose has been reached.

6. A Priori Statistical Methods

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee. The study PK scientist will be responsible for designing, conducting, and interpreting the PK analysis and delivering PK parameters. The interpretation of final study results will be the responsibility of the clinical research physician (CRP) and the study statistician.

Exploratory statistical analysis procedures not specified in the present document will be executed as deemed appropriate by the statistician and study team.

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

- Unless otherwise specified, summary statistics stand for the number of patients with an observation (n), mean, standard deviation, median, minimum, and maximum for continuous variables; and population size (N), the number of events, the number of subjects with events (n) and the proportion of subjects with events (p=n/N) for categorical variables.
- **Safety population** will consist of subjects who receive any amount of study drug. The safety population will be used for all analyses of dosing, exposure and safety.
- **DLT-evaluable population** will consist of: 1) subjects who receive at lease 1 dose of the study drug and then experience DLT during Cycle 1; and 2) subjects who receive at least 85% of the prescribed dose in Cycle 1 and have an adverse event (AE) assessment in the first cycle. Dose-limitig toxicity-evaluation population will be used for evaluation of each dose level for dose-escalation.
- **Pharmacokinetic population** will include subjects who have sufficient PK data to derive at least one PK parameter.
- **Efficacy population** will include all patients who receive any quantity of study treatment at the dose recommended.

6.1. 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 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 of 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 of 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 day of a date is missing, but not the month or year, then assign Day 1 of the month to the day.
- If the the month of a date is missing, but not the day or the year, then assign January to the month.

After imputation, the imputed date should be logically consistent with other relevant date variable(s).

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

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

Time-to-event analysis: All censored data will be accounted for using appropriate statistical methods.

6.2. Patient Disposition

All patient discontinuation data 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 (eg, inclusion/exclusion criteria, errors/missing data in the informed consent/assent process, noncompliance with protocol procedures, errors and missing data in drug dosage/intervention, errors in recording DLTs, use of excluded treatments, patients continuing after meeting withdrawal criteria, or other violations as recorded on electronic case report form (eCRF) or monitoring reports).

6.3. Patient Characteristics

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

- patient demographics: age (years) and age group (<12 vs. ≥12), gender, race, ethnicity, weight (kg), height (cm), body surface area (BSA) (m^2) and Performance Level (Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50% for patients ≤ 16 years of age, see protocol for details)
- baseline disease characteristics: initial pathological diagnosis type and subtype, disease stage at initial diagnosis only, current disease stage and duration of disease (months) at study entry
- prior cancer therapies

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

6.4. Concomitant Therapy

The following concomitant medications will be summarized and listed for the safety population:

- Anticoagulation: Use of therapeutic anticoagulation with heparin, low-molecular weight heparin, or Coumadin should be avoided.
- Anti-platelet agents: Use of aspirin, ibuprofen or other non-steroidal anti-inflammatory drugs or anti-platelet agents for chronic use is not allowed while on study therapy.
- Anti-hypertensives: Patients who develop hypertension while on study therapy may be treated with anti-hypertensive agents and may remain on therapy as long as hypertension is well controlled on medication.

The use of belimumab (a monoclonal antibody for systemic lupus erythematosus) and bisphosphonate derivatives are prohibited while the patient is on study therapy.

6.5. Efficacy Analyses

6.5.1. Efficacy Analysis Variables

Definition of efficacy analysis variables are listed below:

- **Objective response rate (ORR)** is defined as the proportion of treated patients achieving a best overall response of partial response (PR) or complete response (CR) 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 nonresponders and are included in the denominator when calculating the response rate.
- **Disease control rate (DCR)** is defined as the proportion of treated patients achieving a best overall response of CR, PR, or stable disease (SD) per 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.
- **Duration of response (DOR)** is defined from the date of first documented CR or PR (responder) 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, then the patient will be censored at the date of last evaluable tumor assessment.
- **Progression-free survival (PFS)** is defined as the time from the date of randomization until the date of radiographic documentation of progression (as defined by RECIST v. 1.1) based on investigator assessment or the date of death due to any cause, whichever is earlier. The censoring is taken in the following order:
    - If a patient does not have a baseline disease assessment, then the PFS time will be censored at the randomization date, regardless of whether or not objective progressive disease (PD) or death has been observed for the patient.
    - If a patient is not known to have died or have investigator-assessed PD as of the data-inclusion cut-off date for the analysis, the PFS time will be censored at the date of last postbaseline adequate radiological tumor assessment, or at the date of randomization if the patient does not have any postbaseline adequate radiological assessment.
- **Overall survival (OS)** is defined as time from the date of randomization 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).

6.5.2. Description of Efficacy Analyses

Best overall response is the best response recorded from the start of treatment until disease progression, in the order of CR, PR, and SD. Best overall response will be summarized for all patients evaluable for efficacy whose disease is assessable by RECIST 1.1.

If appropriate, the following analyses will be performed.

- Objective response rate will be estimated and reported for each dose level.
- Disease control rate will be summarized and provided for each dose level.

- Progression-free survival will be estimated using a Kaplan-Meier method (Kaplan and Meier 1958) by median and 95% confidence interval (CI). Additional exploratory analyses using proportional hazards models to control for other factors may be performed.
- Overall survival will be summarized using the Kaplan-Meier method.

6.6. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

All PK/PD analysis and creation of table, figures, and listings will be the responsibility of Lilly Global PK/PD and Pharmacometrics group based on applicable Global PK/PD and Pharmacometrics Standard Operating Procedures and software approved by Global PK/PD and Pharmacometrics group's management.

6.7. Safety Analyses

All patients who receive at least 1 dose of study therapy will be summarized for safety and toxicity. Dose-limiting toxicity will be listed for Phase 1a only by ramucirumab dose schedules. Please refer to the protocol for the definition of DLT.

The descriptions and grading scales found in the revised National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. Unless otherwise specified, when summarized by Preferred Term (PT), AEs will be presented in decreasing frequency of PT accross dose levels; when summarized by System Organ Class (SOC) and PT, AEs will be presented in decreasing frequency of PT within SOC across dose levels.

6.7.1. Extent of Exposure

The following exposure-related variables will be reported:

- **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).
- **Duration of treatment (week)** is calculated as (date of last dose in last cycle – date of first dose + 14)/7.
- **Dose intensity (mg/kg/week)** is calculated as cumulative dose / duration of treatment.
- **Relative dose intensity (%)** is calculated as dose intensity / planned dose intensity * 100.

The following analyses on the defined rexposure-related variables will be performed using summary statistics (number of patients, mean, and standard deviation) by dose group:

- Exposure: duration of treatment, number of cycles received, number of patients who received ≥1 cycle, ≥2 cycles, …, ≥8 cycles; and cumulative dose.
- Dose adjustment: number of patients with dose adjustments: dose reduction, dose omission and dose delay; reason for dose adjustments.

- Dose intensity: weekly dose intensity, relative dose intensity.

6.7.2. Adverse Events

Adverse events are 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 events (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.

Serious adverse events (SAE) are defined as any of the AEs 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
- considered significant by the investigator for any other reason based upon appropriate medical judgement

A summary overview of all AEs will be provided per study arm. The overview will tabulate number of subjects with:

- at least 1 TEAE
- at least 1 CTCAE grade ≥3 TEAE
- at least 1 serious AE
- discontinuation from study treatment due to AE
- discontinuation from study treatment due to SAE
- death due to AE on study treatment
- death due to AE within 30 days of last infusion or discontinuation from study treatment

The summary will be provided regardless of study drug causality, and repeated for events deemed by investigator to be possibly related to study medication.

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

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

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

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

Reasons for deaths will be summarized separately for 1) all deaths, 2) deaths on therapy, 3) deaths within 30 days of treatment discontinuation, and 4) deaths after 30 days of treatment discontinuation.

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

In addition, the following analyses will be performed:

- adverse events leading to death by PT
- adverse events leading to study treatment discontinuation by PT
- adverse events leading to study treatment dose modification by PT
- adverse events of special interest (AESI) by PT, and repeated for AESIs deemed by the investigator to be possibly related to study medication
- listings of AESI, AEs leading to death, AEs leading to discontinuation, and AEs leading to dose modifications

6.7.4. Clinical Laboratory Evaluation

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

A patient listing of all laboratory 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.

6.7.5. Vital Signs and Other Physical Findings

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

6.8. Annual Report Analyses

The following reports are needed for a Development Update Safety Report (DSUR):

- estimated cumulative subject exposure
- cumulative exposure to investigational drug, by demographic characteristics for ongoing unblinded clinical trials and completed clinical trials
- exposure information for ongoing clinical trials and clinical trials that completed during the reporting period
- listing of subjects who died during the DSUR reporting period
- discontinuations due to AEs during the DSUR reporting period

6.9. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized by treatment group and by Medical Dictionary for Regulatory Activities (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 Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may be excluded if a 5% threshold is chosen.
- adverse event reporting is consistent with other document disclosures for example, the clinical study report (CSR), manuscripts, and so forth.

7. References

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

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