Statistical Analysis Plan I6X-MC-JBDA

A Phase I Study of LY3009120 in Patients with Advanced or Metastatic Cancer

NCT02014116

Approval Date: 11-Nov-2013

1. Statistical Analysis Plan: I6X-MC-JBDA: A Phase I Study of LY3009120 in Patients with Advanced or Metastatic Cancer

LY3009120

This Phase I study is a multicenter , nonrandomized, open-lable, dose-escalation study followed by dose-confirmation of oral LY3009120 in patients with advanced or metastatic cancer.

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Protocol I6X-MC-JBDA
Phase 1

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3. Revision History

SAP Version 1 was approved prior to first patient visit.

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to determine a recommended Phase 2 dose of LY3009120 that may be safely administered to patients with advanced and/or metastatic cancer.

4.2. Secondary Objectives

The secondary objectives of this study are:

- to characterize the safety and toxicity profile of LY3009120.
- to estimate the pharmacokinetic (PK) parameters of LY3009120.
- to document any antitumor activity observed with LY3009120.

4.3. Exploratory Objectives

The exploratory objectives of this study are:

- to explore pharmacodynamic (PD) biomarkers.
- to explore biomarkers related to the safety and efficacy of LY3009120.

5. A Priori Statistical Methods

5.1. Endpoint Definitions

5.1.1. Safety Endpoints

All patients who receive at least 1 dose of LY3009120 will be evaluated for safety and toxicity. Safety measures that will be used in the study include adverse event (AE), dose limiting toxicity (DLT), clinical laboratory test results, vital signs and electrocardiograms (ECG). In addition, after each cohort, the toxicity-band method will be used to summarize the posterior distribution of probability of a DLT.All AEs will be classified and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

Dose Limiting Toxicity:

Dose-limiting toxicity (DLT) is defined as an adverse event (AE) during Cycle 1 for a patient enrolled in Part A (Dose Escalation) that is possibly related to the study drug and fulfills any one of the following criterion using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0:

- ≥CTCAE Grade 3 non-hematological toxicity. Exceptions will be made for:
  - Nausea, vomiting, diarrhea, or constipation that can be controlled with appropriate care. Grade 3 and Grade 4 nausea, vomiting, or diarrhea should be considered DLT if persisting more than 48 hours despite maximum supportive intervention.
  - Grade 3 elevations of ALT and/or AST lasting fewer than 8 days, without evidence of other hepatic injury, in the setting of preexisting hepatic metastasis and baseline elevation of these values, may not be considered a DLT if agreed by the study investigator and Lilly CRP.
- CTCAE Grade 4 hematological toxicity of >5 days duration.
- Grade 4 thrombocytopenia of any duration
- Grade 3 thrombocytopenia with bleeding
- Grade 3 febrile neutropenia
- 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).

Investigators, together with the Lilly CRP, can declare a DLT if a patient is experiencing increasing toxicity during treatment, and it becomes clear that it is not going to be possible to complete the treatment without exposing the patient to excessive risk.

DLT-Equivalent Toxicity:

A DLT-equivalent toxicity is defined as an AE occurring between Day 1 and Day 28 of any cycle (other than Cycle 1) for a patient enrolled in Part A or in any cycle for a patient enrolled in

Dose Confirmation: Part B (including Cycle 1) that would have met the criteria for DLT if it had occurred during Cycle 1 for a patient enrolled in Part A.

Maximum Tolerated Dose (MTD):

For the purpose of this study, the MTD is defined as a safe dose that has the highest probability of DLT in the targeted toxicity interval (20 to 35%). A safe dose means that the probability of DLT larger than 35% is below 25%.

5.1.2. Efficacy Endpoints

The study was not designed to make an efficacy assessment. However, any tumor response data will be tabulated according to study part and patient cohort.

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

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5.2. Analysis Sets

Safety and efficacy analysis will be performed on all patients who receive at least 1 dose of study drug.

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

Pharmacodynamic (PD) analyses will be conducted on patients who have received at least 1 dose of the study drug and had PD assessments.

5.3. Statistical Methods

5.3.1. Sample Size Considerations

The total sample size for Parts A and B is estimated to be approximately 80 patients. In Part A, the sample size is estimated to be approximately 30 to 35 patients depending on the relationship between exposure and toxicity as well as the relationship between exposure and pharmacodynamic effects. A total of approximately 45 patients has been selected in the dose-confirmation phase to ensure an adequate sample size for assessing the safety, PK, and preliminary efficacy signals. The sample size of 15 for each confirmation cohort provides a reasonable power to explore preliminary signals of efficacy. If we assume that a true overall response (complete response [CR] + partial response [PR]) rate less than 10% indicates inadequate anti-tumor activity, then at a one-sided type 1 error rate of 5%, the sample size of 15 will provide 73% power if the true overall response rate is 30% or higher.

5.3.2. Dose Escalation Method

In this study, the escalation will start from the lowest planned dose, the maximum allowed dose increment is 100%, and each new dose level will have a minimum of 3 patients enrolled to it. The Bayesian model-based toxicity band method (Neuenschwander et al 2008) that incorporates prior expectations about the dosetoxicity curve will be fitted to the data at the end of each cohort to recommend a dose for the next cohort. The toxicity band method is a Bayesian model-based design with built-in escalation with overdose control mechanism. After each cohort, the toxicity band model will utilize data from all available cohorts to make dose recommendation, based on the model based posterior probability of a DLT at each dose, and the overdose control criteria. The toxicity band method will stop if the pre-specified maximum number of subjects is reached or the recommended next dose has been taken by 9 patients.

During the escalation, the investigators and Lilly CRP will consider both the model recommendation and the observed DLT rate at each cohort to determine the next dose level and determine when to stop the escalation. Dose levels for each cohort will not exceed those recommended by the toxicity band model. Dose escalation will take into account PK and PD information when available. Additional patients may therefore be enrolled at a specific dose level to characterize PK/PD.

Intermediate or higher dose levels will be explored if deemed necessary after discussion between the sponsor and investigators. The JBDA toxicity band model has the ability to accommodate additional dose levels naturally.

Details regarding the JBDA toxicity band design are provided in Protocol Attachment 10.

5.3.3. Treatment Compliance

Patient compliance with study drug will be assessed at each visit by direct questioning, patient's diary examination and counting returned capsules. Deviation(s) from the prescribed dosage regimen should be recorded on the case report form (CRF).

The patient must take ≥75% of the intended doses to be deemed compliant with study drug

administration. Similarly, a patient may be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication. Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP before making the final determination for discontinuation.

5.3.4. Interim Analyses

During Part A, patient safety will be assessed prior to each dose escalation to ensure nothing precludes administration of larger doses to future study patients. In addition to reviewing AEs and laboratory measurements, available PK/PD profiles of LY3009120 will be reviewed per cohort. Based on these interim results, modifications (eg, reductions in dose increment or changes in dosing schedule) to the dose-escalation strategy or other design elements may be made to ensure patient safety. The study investigators and the Lilly CRP will make the determination regarding dose escalation based upon their review of the safety/tolerability data and the PK data from the previous cohorts. In addition, an interim review will be conducted prior to proceeding to Part B including safety, PK, and PD. All relevant data will be reviewed to confirm the estimation of the MTD. The decision to proceed to Part B will be made following discussions between the investigators and Lilly clinical research personnel.

During Part B, interim analyses may be conducted in each cohort to review available safety, PK, PD, and efficacy data once enrollment to that particular cohort (A, B, or C) has completed and all evaluable patients in that cohort have either completed 3 cycles of therapy or discontinued from the treatment.

5.4. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company. The analyses for this study will be descriptive, except for possible exploratory analysis as deemed appropriate. Data analyses will be provided by dose groups and for all study patients combined wherever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, and percentages. Missing data will not be imputed.

The interpretation of the study results will be the responsibility of the investigator with the Lilly CRP or CRS, pharmacokineticist, and statistician. The CRP or CRS and statistician will also be responsible for the appropriate conduct of an internal review for both the final study report and any study-related material to be authorized by Lilly for publication.

Exploratory analyses of the data not described below will be conducted as deemed appropriate.

5.5. Patient Disposition

All patient discontinuations (treatment and study) will be documented, and the extent of each patient's participation in the study will be reported. If known, a reason for their discontinuation will be given. All patients entered in the study will be accounted for in the summary of

disposition. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins will be specified.

All significant protocol deviations will be listed by pre-determined categories (e.g., inclusion/exclusion criteria, noncompliance with protocol procedures, drug dosage/intervention, use of excluded treatments, informed consent/assent process, continuing after meeting withdrawal criteria, or other).

5.6. Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics
- Baseline disease characteristics
- Prior disease-related therapies
- Concomitant medications.

Other patient characteristics will be summarized as deemed appropriate.

5.7. Efficacy Analyses

The study was not designed to make an efficacy assessment. However, any tumor response data will be tabulated according to study part and patient cohort. A listing of best overall reponse will be provided by part and cohort. A summary of best overall response will be summarized by dose (Part A) and overall by study part. The percentage of patients with a confirmed response, defined as a complete response (CR) or partial response (PR), will be provided along with a 90% exact confidence interval for the response percentage. The objective response rate is defined as:

(# patients with confirmed CR or PR) / (# patients dosed with study drug)

5.8. Safety Analyses

All patients who receive at least 1 dose of LY3009120 will be evaluated for safety and toxicity.Adverse event terms and severity grades will be assigned by the investigator using CTCAE, Version 4.0).

Safety analyses will include summaries of the following:

- adverse events, including severity and possible relationship to study drug
- dose adjustments
- laboratory values
- vital signs
- DLTs at each dose level
- ECG readings

In addition, after each cohort, the toxicity-band method will be used to summarize the posterior distribution of probability of a DLT.

5.8.1. Study Drug Exposure

Study drug exposure information will be listed by patient and summarized by dose (Part A) and overall by study part.

Number of capsules taken for each capsule strength will be listed, and the actual dose taken (mg) will be calculated for each cycle and all scheduled days within cycle for each patient.

A patient is said to have received a cycle if they received any of the doses in the cycle. The number of cycles given per patient will be summarized. Any dose adjustments will be characterized by presenting cycle delays, dose reductions, dose delays, and dose omissions, including reasons.

Dose intensity is defined as the percentage of the actual cumulative dose (mg) with respect to the planned cumulative dose (mg). Dose intensity will be listed per cycle and overall for all patients on therapy. Note that the denominator is based only on the assigned dose at the beginning of the cycle and not any additional prescribed reductions that may occur during the cycle.

Compliance for the study can be calculated by summing the doses across all cycles and dividing by the sum of the assigned dose for each cycle.

5.8.2. Dose Limiting Toxicity

Dose limiting toxicities (DLT) will be listed for all patients on therapy in Part A. DLT-equivalent toxicities will also be listed for all patients on therapy in Parts A and B. A Toxicity Band method (described in Protocol Appendix 10) will be used to assist the decisions related to dose escalation and determination of the MTD.

5.8.3. Adverse Events

CTCAE v4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the CTCAE v4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the CRF. This collection is in addition to verbatim text used to describe the AE. In addition to collecting the AE verbatim, the CTCAE term, and the CTCAE severity grade, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

The investigator decides whether he or she interprets the observed AEs as either related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terminologies are defined:

- **Related**: a direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly Related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Unrelated**: without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures all "related" and "possibly related" AEs and SAEs

will be defined as related to study drug.

All AEs and SAEs, regardless of relatedness to study drug or protocol procedures, occurring during the follow-up visit (Visit 801) must be reported to Lilly or its designee. Following Visit 801, along-term follow-up will begin for dermatological assessment. Dermatological assessment will be performed every 2 months up to 6 months post-treatment discontinuation (long-term followup Visits 802, 803, and 804), after which the patient will be discontinued from the study, unless there is an ongoing AE or SAE that is possibly related to study drug. In this instance, the patient should be followed in subsequent follow-up visits, until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. During the longterm follow-up period (V802 to V804), ongoing or new AEs/SAEs possibly related to study drug(s) or protocol procedures are required to be reported. After V804, if an additional follow-up period is necessary, new or ongoing AEs and new SAEs are not required to be reported, unless the investigator feels the events were related to either study drug, drug delivery system, or a protocol procedure.

Treatment emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened in severity after the administration of at least one dose of study therapy, regardless of causality. New adverse events reported after Visit (801) will not be considered as a TEAE. With version4 CTCAE v4.0, the CTCAE codes are MedDRA LLT codes.

MedDRA mapping is applied to adverse event data as it is received. MedDRA versions may be upgraded as frequently as twice in a year. Therefore, different MedDRA versions may be used in this trial, based upon when the adverse event information is received, however, the safety information will be summarized and listed in preferred terms of the most current version of MedDRA at the time of reporting. Safety information collected with previous versions of MedDRA will be updated at the preferred term (PT) and system organ class level to the most currentversion in the locked database. The version used in any reports will be documented.

Specific tables and listings needed include:

- List of DLTs and DLT-equivalent toxicities
- List of pre-existing conditions and AEs
- List of serious AEs
- List of deaths
- Summary of AEs
- Summary of TEAEs
- Summary of related TEAEs
- listing of discontinuation due to AE or death
- summary of TEAE by maximum CTCAE grade
- summary of related TEAE by maximum CTCAE grade.

A separate listing of vomiting adverse events with dosing information included will also be produced.

5.8.4. Eye and Dermatological Safety Monitoring
A listing will be provided for Eye and Dermatological Safety assessment.

5.8.5. Deaths
All deaths in this study will be listed.

5.8.6. Laboratory Parameters
Abnormal laboratory results will be listed by dose, patient and cycle (using SI units [International System of Units]). Relevant hematology, chemistry and urinalysis laboratory values will be graded according to CTCAE v4.0.

5.8.7. Vital Signs
Vital sign data will be listed by patient and cycle.

5.8.8. Electrocardiograms
Electrocardiogram (ECG) data will be listed for each patient.

5.8.9. Other Data
CT lot numbers will be listed for all patients on therapy.

5.9. Pharmacokinetic Analyses
Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of the study drug and have had samples collected.

Pharmacokinetic parameter estimates for LY3009120 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be maximum concentration (Cmax) and area under the concentration-time curve ($AUC_{0-tlast}$, $AUC_{0-\infty}$, or $AUC_{\tau,ss}$,) of LY3009120. Other noncompartmental parameters, such as time of half-life ($t_{1/2}$,), apparent clearance (CL/F), and apparent volume of distribution (V/F) may be reported. 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.

Pharmacokinetic parameter estimates will be evaluated to delineate effects of dose proportionality log-transformed Cmax and AUC estimates will be assessed to estimate ratios of geometric means and the corresponding 90% confidence intervals (CIs).

5.10. Pharmacodynamic Analyses
Pharmacodynamic data from all patients undergoing PD assessments will be analyzed.

Biomarker data from all patients undergoing biomarker assessments will be analyzed by appropriate statistical methods. These data may include, but are not limited to IHC, genetic mutations that are hypothesized to be related to safety, efficacy, drug disposition or pathways associated with the mechanism of action of LY3009120.

5.11. Pharmacokinetic / Pharmacodynamic Analyses

The PK data will be combined, and analyses may be conducted to determine a relationship between exposure and clinical PD effect (eg, phospho-ERK, p27, and/or Ki67 protein expression in tumors), data permitting. This model may be used to help reassess the dose cohort escalation and schedule as the study progresses. If deemed necessary, PK/PD modelling may be employed to evaluate variability in exposure, pharmacologic effects, and safety parameters.

6. References

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0., NCI, NIH, DHHS. 2009. Publish date: 29 May 2009.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Frod 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.

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. *Stat Med*. 2008;27(13):2420-2439.