Statistical Analysis Plan I7H-MC-JNBA

A Phase 1 Study of LY3164530, a Bispecific Antibody Targeting MET and EGFR, in Patients with Advanced or Metastatic Cancer

NCT02221882

Approval Date: 16-Jun-2014

1. Statistical Analysis Plan: I7H-MC-JNBA: A Phase 1 Study of LY3164530, a Bispecific Antibody Targeting MET and EGFR, in Patients with Advanced or Metastatic Cancer

Anti-MET/EGFR Bispecific Antibody (LY3164530)

This Phase 1 study is a multicenter, nonrandomized, open-label, dose-escalation study of intravenous LY3164530 in patients with advanced or metastatic cancer.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol I7H-MC-JNBA
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 the first visit when a subject receives study drug or any other protocol intervention.

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to determine a recommended phase 2 dose (RP2D) of LY3164530 that may be safely administered to patients with advanced or metastatic cancer.

4.2. Secondary Objectives

The secondary objectives of this study are:

- to characterize the safety and toxicity profile of LY3164530
- to estimate the pharmacokinetic (PK) parameters of LY3164530
- to document any antitumor activity observed with LY3164530.

4.3. Exploratory Objectives

The exploratory objectives of this study are:

- to explore the effect of LY3164530 on pharmacodynamic (PD) markers
- to identify exploratory biomarkers associated with tumor response and/or safety.

5. Study Design

5.1. Summary of Study Design

Study I7H-MC-JNBA (JNBA) is a multicenter, nonrandomized, open label, dose escalation Phase 1 study of IV LY3164530 in patients with advanced and/or metastatic cancer. Eligible patients will receive LY3164530 as an infusion on Days 1 and 15 of each cycle. A cycle will consist of 28 days.

The planned duration of treatment is 2 cycles. Patients who are receiving benefit from study drug may continue to be treated with LY3164530 until 1 or more of the criteria for discontinuation have been fulfilled (Protocol Section 6.3.1).

5.2. Determination of Sample Size

To determine an RP2D of LY3164530 that may be safely administered to patients with advanced or metastatic cancer, an adequate patient 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 pharmacological effects using descriptive statistics and appropriate modeling techniques, if data warrant.

Dose escalation will be driven by a modified toxicity probability interval (mTPI) method. The RP2D will be determined once at least 10 patients, but no more than 20, are treated at a dose level that is at or below the maximum tolerated dose (MTD). The actual sample size for Study JNBA depends on the incidence of dose-limiting toxicities (DLTs) and is anticipated to be approximately 50 patients.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive LY3164530 in this study. Before each patient's enrollment into the study, an eligibility check must be conducted between the investigational site and Eli Lilly and Company (Lilly) clinical research personnel to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the Sponsor will confirm the dose, infusion duration, and identification number assignment for each patient.

6. A Priori Statistical Methods

6.1. General Considerations

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, percentages, and associated SE.

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

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the clinical study report (CSR).

The interpretation of the study results will be the responsibility of the investigator with the Lilly CRP and/or CRS, pharmacokineticist, and statistician. The CRP and/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.

The following data handling conventions will be used in the analysis:

Table JNBA.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. If more than one pre-dose measure is available, they may be averaged if appropriate.
Entered	Patients who sign the informed consent document (ICD).
Enrolled	Patients who have been assigned to a treatment (assigned means they received ≥1 dose for this study).

6.2. Adjustments for Covariates

Adjustment for covariates is not applicable.

6.3. Handling of Dropouts or Missing Data

Missing data will not be imputed.

Patients who withdraw from the study before receiving study drug will be replaced.

In the following situation, patients will be considered non-evaluable and may be replaced to ensure that enough patients complete 1 cycle of therapy at each dose level, unless accrual to that cohort has stopped due to a DLT:

1. Any patient who is discontinued from the study before completing 1 cycle of LY3164530 treatment unless they experience a DLT prior to withdrawal
2. Patients who are not evaluable for PK

6.4. Multicenter Studies

This is a multicenter, non-randomized, open-label study. 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 analyses will be conducted on all patients who have received at least one dose of LY3164530.

Pharmacokinetic analyses will be conducted on patients who have received at least one dose of LY3164530 and have sufficient samples collected to allow the estimation of LY3164530 PK parameters.

Pharmacodynamic analyses will be conducted on patients who have received at least one dose of LY3164530 and have sufficient samples collected to allow the assessment of pharmacodynamics.

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 discontinuing treatment and/or 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 collected. If known, reason(s) for discontinuation will be given. Discontinuations due to AE or death will be summarized with cause of death further partitioned into AE, study disease, or other cause and summarized.

- All clinically relevant and programmatically identifiable protocol deviations will be summarized by pre-determined categories (for example, inclusion/exclusion criteria, non-compliance with protocol procedures, drug dosage/intervention, use of excluded treatments, informed consent/assent process, continuing after meeting withdrawal criteria, or other).

All patients entered into the study will be accounted for in the summary disposition tables. Patients entered into study are patients who signed main informed consent. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins will be specified.

6.8. Patient Characteristics

Patient characteristics for the treated population will include a 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 Eastern Cooperative Oncology Group (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 and etc.
- Concomitant medications.

6.9. Treatment Compliance

LY3164530 will be administered intravenously at the investigational site, under the direction of the investigator. As a result, a patient's compliance with study drug administration is ensured.

Potential discontinuation of a patient due to study noncompliance (not attending the scheduled visits; see Protocol Attachment 1) will be presented overall as well as for each cycle.

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 summarized by cohort and overall for all enrolled patients. The Lilly WHO Drug Version Dec 2012 B2 or higher will be used to code therapy.

6.11. Efficacy Analyses

The study was not designed to make an efficacy assessment. However, any tumor response data and duration of treatment will be tabulated.

6.12. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

6.12.1. Pharmacokinetic/Pharmacodynamic (PK/PD) Analyses

Pharmacokinetic analyses will be conducted on patients who have been exposed to study drug and have had samples collected.

Pharmacokinetic parameter estimates for LY3164530 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}\infty}$ of LY3164530. Other noncompartmental parameters, such as $t_{1/2}$, CL, and volume of distribution (V), may be reported. Additional exploratory analyses will be performed if warranted by the data, and other validated PK software programs may be used if appropriate and approved by Lilly Global PK/PD 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 and temporal linearity. Log-transformed C_{max} and AUC estimates will be assessed to estimate ratios of geometric means and the corresponding 90% confidence intervals (CIs).

Provided that the data allows, PD and immunogenicity data from all patients may be analyzed using linear and/or nonlinear fixed and mixed effects models as appropriate. Pharmacodynamic and immunogenicity data will be summarized by dose, drug concentrations, and time from dose. Potential PD markers and immunogenicity versus time data will be presented graphically for each patient and summarized by dose. Absolute and/or percent change from baseline for the PD markers may also be evaluated. Data may be log-transformed prior to summarizing if necessary. The interpatient and intrapatient variability of the PD markers and immunogenicity responses may also be assessed where appropriate. Baseline measurements may be evaluated as potential covariates to assess their relationship to relevant PD responses.

In addition to a standard noncompartmental assessment, and provided that the data allows, the LY3164530 concentration-time data may be evaluated by model-based approaches as warranted. Additional analyses, such as exposure-response modeling using the efficacy endpoints, may also be explored.

Additional exploratory analyses may be performed if warranted by the data.

6.12.2. Biomarker Analyses

Protocol Sections 5.3.4 and 8.2.3 provide a description of the biomarker samples that may be collected and the rationale for their collection in the study.

Exploratory biomarker assessments in this study will focus on identifying markers and/or marker signatures that may indicate the patients most likely to respond or be resistant to LY3164530. In archived and/or pre-treatment tissue samples, biomarker data related to the MET and EGFR pathways and cancer pathobiology may be analyzed to assess any potential associations with response to LY3164530. These analyses may include, but are not limited to, MET and EGFR protein expression, circulating biomarkers (for example, TGFa, HGF, extracellular cleaved domain of MET [MET ECD]), somatic mutation status, and/or copy number variations of MET and EGFR and pathway-related genes (for example, KRAS, BRAF) or genes related to cancer pathobiology. In addition, tumor sample based gene signature(s) may be defined and evaluated to explore whether they are associated with response to LY3164530.

In all analyses, adjustments may be made to account for other baseline patient characteristics, safety, and PK/PD data. Unless otherwise stated, statistical analyses results will be considered exploratory and will not consider multiple comparison adjustments. In the event of emergence of important and relevant scientific findings, this SAP may be updated to allow further analyses on biomarkers and antitumor activities.

6.13. Safety Analyses

All patients who receive at least 1 dose of LY3164530 will be evaluated for safety and toxicity. Adverse event (AE) terms and severity grades will be assigned by the investigator using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03.

Safety analyses will include summaries of the following:

- Adverse events, including severity and possible relationship to study drugs
- Dose delays and dose adjustments
- Laboratory values
- Vital signs
- Dose-limiting toxicities at each dose level
- Electrocardiogram readings
- Deaths on treatment and within 28 +/- 5 days of treatment discontinuation

Hospitalizations and transfusions during the study treatment period or during the 28 +/- 5 days - day postdiscontinuation follow-up period will be summarized.

Dose Limiting Toxicity

Dose-limiting toxicity is defined as an AE during Cycle 1 that is considered by the investigator to be at least possibly related to LY3164530 and fulfills any one of the following criterion using the NCI CTCAE Version 4.03:

- ≥ Grade 3 non-hematological toxicity. Exceptions will be made for:

  - nausea, vomiting, diarrhea, and constipation that can be controlled with treatment. Grade 3 and Grade 4 nausea, vomiting, or diarrhea should be considered DLTs if persisting more than 48 hours despite supportive intervention.
  - Grade 3 rash that resolves with treatment to ≤ Grade 2 within 8 days
  - Grade 3 or 4 asymptomatic electrolyte abnormalities that respond to standard treatment
  - 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. Baseline elevation of these values may not be considered a DLT if agreed by the study investigator and Lilly CRP/CRS.
- Grade 4 neutropenia or leukopenia, of >7 days duration.
- Grade 4 thrombocytopenia of any duration.
- Grade 3 thrombocytopenia with bleeding.
- Any febrile neutropenia.
- Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (eg, any toxicity that is possibly related to the study drug that requires the withdrawal of the patient from the study during Cycle 1).

DLT-Equivalent Toxicities

A DLT-equivalent toxicity is defined as an AE occurring in Cycle 2 and beyond that would have met the criteria for a DLT if it had occurred during Cycle 1.

Dose Escalation Method

Dose escalation will be driven by an mTPI method (Ji and Wang 2013) (Appendix 1). A 3+3 design is commonly used in Phase 1 trials due to its simple, intuitive, and pre-specified escalation rules. However, the 3+3 method has been criticized for being conservative because the method is dictated by the observed DLT rate without acknowledging the variability arising from small cohort size.

Like the 3+3 design, the mTPI method incorporates pre-specified escalation rules. In contrast, the mTPI method is based on quantitative models that incorporate uncertainty into the decision rules, thereby allowing more aggressive dose escalation. In the mTPI method, the number of patients in each cohort is not fixed, but a minimum of 3 patients are required for this study at each dose (unless the rule in the table indicates to deescalate the dose due to unacceptable toxicity [DU]). If 3 to 6 patients are enrolled in a cohort, the escalation rule parallels a traditional 3+3 design. However, the stay/de-escalation rule of the mTPI is more aggressive than the 3+3 design. For instance, with 2 to 3 DLTs per 6 patients enrolled, the mTPI would recommend staying at the current dose, whereas the 3+3 design would recommend de-escalation. Figure JNBA.6.1 provides the mTPI escalation rules for any cohort size up to 20 patients.

In Figure JNBA.6.1, the number of patients dosed at a given dose level are shown in the columns (x-axis), while the number of DLTs experienced are shown in the rows (y-axis). The rules in this figure will be used for each dose level evaluated; the patient numbers and DLTs do not carry over from cohort to cohort. By locating the intersection of the number of patients dosed and the number of DLTs, 1 of 4 pre-defined rules is used:

- E: Escalate the dose
- S: Stay at the same dose
- D: Deescalate the dose
- DU: Deescalate the dose due to unacceptable toxicity. The dose cannot be re-escalated to this dose level at a future point in the escalation.

If agreed upon by the investigators and Sponsor (for instance, if PK/PD data suggest that increasing the dose further is not expected to yield additional benefit), a more conservative rule may be applied. For instance, if the rule indicates "E" to escalate, the dose may remain at the current dose level or be deescalated to a lower level.

As shown in Figure JNBA.6.1, if 1 of 3 patients experiences a DLT, the decision (located in column 3 row 1) is "S", stay at the same dose. Therefore, the next patient must be treated at the same dose level. If 1 of 6 patients experience a DLT, the decision (located at column 6 row 1) is "E", escalate the dose. However, if 2 of 3 patients experience a DLT the decision is "D" and the dose must be deescalated.

In the mTPI, the cohort size is not fixed. However, each cohort in this study will contain a minimum of 3 patients, unless the escalation rules dictate that the dose should be deescalated due to unacceptable toxicity ("DU"). Doses can be escalated, deescalated, and re-escalated following the rules in Figure JNBA.6.1. If the dose decision was "DU," the dose cannot be re-escalated to that level.

This study is designed to identify a dose level with a dose-limiting target toxicity rate of 30%. In reality, the exact target toxicity rate is almost never achieved for a dose. To this end, instead of using a single target rate, the mTPI method considers an equivalence interval (EI) around the target toxicity rate. For this study, the EI is calibrated to be (28.7%, 30.1%), resulting in the rules in Figure JNBA.6.1. If the observed toxicity rate exceeds 40% and the model is still recommending "S", the Sponsor, in discussion with the investigators, may choose to deescalate.

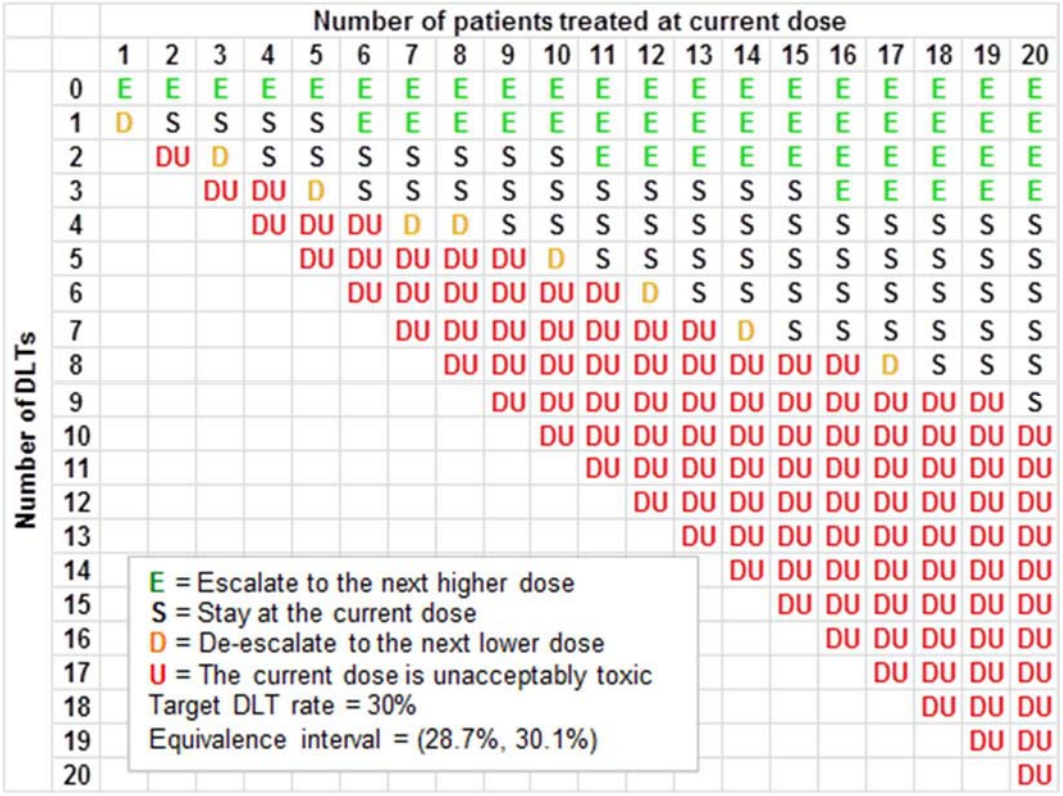

Figure JNBA.6.1. Dose-finding spreadsheet of the modified toxicity probability interval method.

The beginning dose level will be 300 mg. The dose will be escalated by a maximum increment of 100%. If the beginning dose level is determined to be unacceptably toxic, a -1 dose level may be explored.

The exact increment will be determined by the investigators and Lilly CRP/CRS, and may be less than the maximum increment allowed in the protocol. Safety data will be the primary criteria for both the decision to dose-escalate and for selecting the dose to be administered in the next cohort. In addition, if available at the time of the dose escalation decision, PK (maximum plasma concentration [C_{max}], area under the plasma concentration-time curve [AUC], and CL) and/or PD results will be used as secondary/supporting data for dose escalation. No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly CRP or CRS; the decision will be documented in writing. Intrapatient dose escalations are not permitted.

In Cohort 1 only, the first patient is required to complete a full cycle (28 days) before subsequent patients can be dosed. Subsequent patients in Cohort 1 can be dosed concurrently. Beginning with Cohort 2, patients within a cohort can be dosed concurrently.

The decision to stop dose escalation will be primarily driven by the appearance of DLTs and the rules in Figure JNBA.6.1. However, if PK/PD data suggest that increasing the dose further is not expected to yield additional benefit, escalation may cease.

6.13.1. Recommended Phase 2 Dose Determination

The RP2D will be a dose at which at least 10 patients, but no more than 20, have been enrolled. The RP2D will be agreed upon following discussion between the investigators and the Lilly CRP or CRS and will include an assessment of safety, PK, and PD data. At the RP2D, the intersection of the number of patients dosed and the number of DLTs at that dose level on the mTPI grid should indicate "S" or "E".

6.13.2. Extent of Exposure

For doses less than 1000 mg, LY3164530 will be administered intravenously over approximately 60 minutes on Days 1 and 15 of each 28-day cycle. The Sponsor may instruct sites to extend the infusion time for up to 3 hours for doses ≥1000 mg. The assigned dose and duration of infusion of LY3164530 will be provided by the Sponsor on a patient registration form. Subsequent doses and/or infusion times should be adjusted as described in Protocol Section 7.2.5.

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 by patient.

The number of dose reductions, dose delays, and number of cycles received will be summarized for all treated patients by cohorts. The number of patients with any dose reductions and delays will be presented overall as well as for each cycle by cohorts.

6.13.3. Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 will be used to grade all AEs and other symptoms. Minor updates to the CTCAE Version 4.03 from the NCI will not necessitate a protocol amendment, and the use of an updated CTCAE Version 4.03 will not be considered a protocol violation. For AEs without matching terminology within the NCI-CTCAE v 4.03 criteria, the investigator will be responsible for selecting the appropriate System Organ Class (SOC) 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).

A treatment-emergent adverse event (TEAE) is defined as (i) adverse event that occurred after the administration of at least one 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. All analysis of AEs will be done according to the MedDRA hierarchy and the investigator assigned CTCAE term will be used as the assigned LLT, except where "other-specify" has been chosen, in which case the LLT will come from the centrally mapped verbatim description of the event. Event worsen in severity is supported by higher CTCAE grade observed after first dose of study treatment for the corresponding MedDRA Lower Level Term (LLT). Treatment-emergent adverse events (AEs) will be aggregated and summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT).

The number of patients who experienced a TEAE, SAE, TEAE related to study drug, died, or discontinued from the study due to an AE will be summarized. Treatment-emergent adverse events will be summarized by SOC, by decreasing frequency within SOC, and by maximum CTCAE severity grade, including the total of patients with maximum severity grade ≥3.

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

Deaths and other SAEs 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 28 days of last dose of study drug/last visit. All SAEs will be summarized by preferred term.

6.13.5. Clinical Laboratory Evaluation

Laboratory data (including chemistry, hematology, and coagulation) will be summarized for all patients on therapy. Relevant hematology and chemistry laboratory values will be graded according to CTCAE Version 4.03. The grades will be summarized by the maximum grade over the entire study for all patients on therapy.

Abnormal laboratory results will be summarized for all patients on therapy by cycle. To the extent that they can be assessed according to CTCAE Version 4.03 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.

6.13.6. Vital Signs and Other Physical Findings

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

6.13.7. Electrocardiograms

For each patient, 12-lead ECGs will be obtained according to the Study Schedule (Protocol Attachment 1). All ECGs will be analyzed for safety and categorical analysis will be provided including:

1. Number and percentage of individuals with abnormal ECG findings.
2. Number and percentage of individuals with AEs that could be associated with prolongation of cardiac repolarization or proarrhythmia, for example, palpitations, dizziness, syncope, cardiac arrhythmias and sudden death.

Categorical analysis of the following ECG parameter may be performed at day 1 and day 15 of each cycle and the short term follow up visit at the time points outlined in the protocol and changes will be compared to baseline (that is, Cycle 1, Day 1 pre-dose). Such analysis will be triggered only as needed. If triggered, the analysis will include the number and percentage of individuals with:

1. Absolute QT/QTc values >450 ms, >480 ms, and >500 ms; as well as the number and percentage of individuals with change from baseline >30 ms and >60 ms.
2. PR changes from baseline ≥50% if baseline value is <200 ms and ≥25% of baseline value is ≥200 ms.
3. QRS changes from baseline ≥50% if baseline value is <110 ms and ≥25% of baseline value is ≥110 ms.

6.14. Protocol Violations

All significant protocol deviations will be summarized by cohorts and by reasons (for example, inclusion/exclusion criteria, noncompliance with protocol procedures, informed consent/assent process etc.).

6.15. Interim Analyses and Data Monitoring

Since this is a dose-escalation study, data will be reviewed on an ongoing basis during the study until the RP2D is determined. The purpose of these ongoing reviews is to evaluate the safety data at each dose level. A review of the data will be completed approximately after 5 patients have been treated for at least 1 cycle at a dose level without a cohort analysis.

An interim analysis will be triggered when 10 patients have been dosed at a given dose level for 1 cycle of treatment to evaluate the safety and tolerability of LY3164530. The interim analysis may include, but are not limited to, an assessment of available safety, PK, and PD data.

Enrollment may continue during the interim analysis and the dose escalation rules as outlined in Figure JNBA.6.1 will continue to be followed.

Additional interim analyses may be triggered and may include, but are not limited to, assessment of available safety, PK, and PD data.

6.16. Annual Report Analyses

The following reports are needed as requested for annual reporting purposes

Clinical Investigator Brochure:

- Summary of SAE (patients on therapy).
- Summary of deaths reported (patients on therapy).
- Summary of Patient disposition.
- Summary of primary reason for treatment discontinuation.
- Summary of treatment-emergent adverse events –by CTCAE category and term.

Development Safety Update Report:

- Cumulative Subject Exposure by Age Group and Sex
- Cumulative Subject Exposure by Racial Group
- Estimated Cumulative Subject Exposure
- Subject Exposure by Gender
- Listing of Patients Who Discontinued Due to Adverse Event
- Listing of Deaths

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 adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events (SAEs) and 'Other' Adverse Events are summarized: by treatment group, by MedDRA preferred term.

- An adverse event flagged as an SAE by the investigator due to meeting one or more of the standard criteria (Protocol Section 8.1.2.1) is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event 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 all treated patients/subjects may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

A participant flow summary will also be produced. This participant flow will describe how many patients completed the study, and for those who did not, the frequency of each reason for not completing. At the time of database lock, any patient who completed one cycle of treatment or discontinued due to an adverse event and completed the required safety and full set of PK assessments during cycle 1 will be considered to have completed the study:

7. References

Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. *Clin Trials*. 2010;7(6):653-663.

Ji Y, Wang SJ. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. *J Clin Oncol*. 2013;31(14):1785-1791.

8. Appendices

Appendix 1. Protocol JNBA mTPI and Simulation

The modified toxicity probability interval (mTPI) method employs a simple beta-binomial hierarchical model. Decision rules are based on calculating the unit probability mass (UPM) of 3 intervals corresponding to under dosing, proper dosing, and over dosing in terms of toxicity. Specifically, the under dosing interval is defined as $(0, p_T-\varepsilon_1)$, the overdosing interval as $(p_T+\varepsilon_2, 1)$, and the proper dosing interval as $(p_T-\varepsilon_1, p_T+\varepsilon_2)$, where ε_1 and ε_2 are small fractions, such as 0.05, to account for the uncertainty around the true target toxicity. A sensitivity analysis reported by Ji et al. (2010) showed that the mTPI design is robust to the specification of ε values.

In addition, ε_1 and ε_2 could take different values to reflect physician preference and the nature of the disease. For advanced diseases with few treatment options, higher toxicity rates might be considered acceptable, implying a specification of $\varepsilon_2>\varepsilon_1$. For less advanced diseases, the 2 ε values could be identical or ε_1 could be $>\varepsilon_2$. The 3 dosing intervals are associated with 3 different dose-escalation decisions. The under-dosing interval corresponds to a dose escalation (E), overdosing corresponds to a dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S).

Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI design calculates the UPMs for the three dosing intervals, and the one with the largest UPM implies the corresponding dose-finding decision. That decision provides the dose level to be used for future patients. For example, if the under dosing interval has the largest UPM, decision E, to escalate, will be executed, and the next cohort of patients will be treated at the next-higher dose level. Ji et al. (2010) show that the decision based on the UPM is optimal in that it minimizes a subsequent expected loss. Under the mTPI design, a trial is terminated when either the lowest dose is above the maximum tolerated dose (MTD) or a pre-specified maximum sample size is reached.

Simulation

A small simulation study was conducted to compare the mTPI with 3+3 in identifying the right MTD. Six scenarios were run, each with 1000 simulated trials. As in Study JNBA, the MTD has a target toxicity probability of $P_T=0.3$ and ε_1 and ε_2 are set at 0.013 and 0.001 respectively. The scenarios assumed the true probabilities of six doses as follows: scenario 1= (0.1, 0.2, 0.3, 0.4, 0.5, 0.6); scenario 2= (0.08, 0.16, 0.24, 0.3, 0.38, 0.46); scenario 3= (0.04, 0.08, 0.12, 0.16, 0.2, 0.24); scenario 4= (0.4, 0.5, 0.6, 0.7, 0.8, 0.9); scenario 5= (0.04, 0.08, 0.12, 0.16, 0.2, 0.58); and scenario 6= (0.06, 0.46, 0.53, 0.6, 0.67, 0.74). For all scenarios, the probability of selecting each dose was summarized, the average number of patients treated at each dose and average number of patients experience DLT at each dose. The simulation demonstrates that, in general, mTPI method correctly identifies the MTD more than 3+3 and appears to be as safe as 3+3 method in that it puts a similar percentage of patients on toxic doses.

Scenario	Dose Level	True Prob (tox)	Selection Prob (%)		# of Subjects Treated		# of Toxicities	
			mTPI	3+3	mTPI	3+3	mTPI	3+3
1	1	0.1	4.3	31.5	5.583	4.473	0.534	0.42
	2	0.2	29.5	33.2	10.02	4.617	1.985	0.979
	3	0.3	42.7	19.5	9.306	3.15	2.811	0.983
	4	0.4	18.4	5.7	4.023	1.371	1.624	0.57
	5	0.5	4.5	0.7	0.9	0.381	0.442	0.194
	6	0.6	0.4	0	0.114	0.048	0.07	0.029
2	1	0.08	1.1	21.1	4.5	4.083	0.339	0.295
	2	0.16	15.7	30.6	8.082	4.494	1.237	0.735
	3	0.24	33.1	23	8.832	3.642	2.125	0.902
	4	0.3	31.3	14	5.601	2.28	1.659	0.692
	5	0.38	14.2	4.3	2.325	1.083	0.886	0.409
	6	0.46	4.6	0.1	0.66	0.297	0.305	0.141
3	1	0.04	0	7.1	3.561	3.51	0.146	0.139
	2	0.08	1.7	10.9	4.626	3.81	0.375	0.315
	3	0.12	8.1	16	5.811	3.918	0.743	0.45
	4	0.16	19.1	20.8	6.045	3.723	0.953	0.578
	5	0.2	24.4	14.5	4.776	3.132	0.934	0.654
	6	0.24	46.7	1.2	5.181	1.908	1.251	0.451
4	1	0.4	46.5	22.2	18.318	4.914	7.374	1.931
	2	0.5	5.4	3.1	3.276	1.434	1.64	0.721
	3	0.6	0.5	0	0.408	0.228	0.253	0.139
	4	0.7	0	0	0.021	0.018	0.014	0.012
	5	0.8	0	0	0.003	0	0.003	0
	6	0.9	0	0	0	0	0	0
5	1	0.04	0.4	6.8	3.648	3.51	0.155	0.146
	2	0.08	1.3	11.6	4.398	3.834	0.354	0.314
	3	0.12	6.3	16.7	5.613	3.909	0.657	0.448
	4	0.16	21	20.7	6.171	3.669	0.998	0.604
	5	0.2	55.8	37.6	6.813	3.594	1.32	0.729
	6	0.58	15.2	0.8	3.357	1.788	1.936	1.038
6	1	0.06	59.3	80.9	13.71	5.556	0.809	0.314
	2	0.46	36.7	13.5	13.98	4.461	6.513	2.038
	3	0.53	3.7	1.5	2.067	0.858	1.098	0.481
	4	0.6	0.1	0	0.195	0.102	0.114	0.064
	5	0.67	0	0.1	0.009	0.006	0.004	0.002
	6	0.74	0.1	0	0.015	0.006	0.008	0.004

Abbreviation: mTPI = modified toxicity probability interval.

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