J1E-MC-JZEA Statistical Analysis Plan Version 1

A Phase 1 Study of LY3434172, a Bispecific Antibody Monotherapy in Advance Solid Tumors

NCT03936959

Approval Date: 29-Apr-2019

1. Statistical Analysis Plan: J1E-MC-JZEA
A Phase 1 Study of LY3434172, a Bispecific Antibody Monotherapy in Advanced Solid Tumors

LY3434172

Study J1E-MC-JZEA is a multicenter, nonrandomized, open-label, dose-escalation Phase 1 study of intravenous LY3434172 in patients with advanced solid tumors.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol J1E-MC-JZEA
Phase 1

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

Approval Date: 29-Apr-2019 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

Table of Contents

Figure **Page**

3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to 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 assess the safety and tolerability of LY3434172, thereby identifying a recommended Phase 2 Dose (RP2D) to be administered to patients with advanced solid tumors.

4.2. Secondary Objectives

- to assess the pharmacokinetics (PK) of LY3434172 in patients with solid tumors
- to assess the preliminary antitumor activity of LY3434172

4.3. Tertiary/Exploratory Objectives

- to characterize tumor tissue and blood biomarkers relevant to LY3434172, including but not limited to immune cells/immune functioning, mechanism of action of study drugs, cancer-related pathways, and disease state
- to explore the association among biomarkers, doses, concentrations, and clinical outcomes
- to assess the immunogenicity of LY3434172 in patients with advanced solid tumors
- to assess progression-free survival (PFS) and overall survival (OS) of patients receiving LY3434172 administered as monotherapy

5. Study Design

5.1. Summary of Study Design

CCI [redacted]

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The dose escalation will employ a modified toxicity probability interval 2 (mTPI2) method along with PK/pharmacodynamic analysis to identify an RP2D. The RP2D will be determined based on the number of observed dose-limiting toxicities (DLTs) and PK/pharmacodynamic data. The RP2D may be below the maximum tolerated dose (MTD), which may not necessarily be reached during the dose escalations.

The DLT observation will include the observation period (Cycle 1, 42 days) for Cohort A1 (Cycle 1, 28 days); for Cohorts A2 to A5 (A2 to A6 if Cohort A6 is opened; Cycle 1 and 2, 42 days); and for Cohorts A7 and A8. Once the DLT period is completed for respective Cohorts A1 to A5/6, up to approximately 12 to 15 additional patients may be added to 2 dose levels selected from Cohorts A4 and A5/6 (Figure JZEA.5.1).

6. A Priori Statistical Methods

6.1. Sample Size Determination

The sample size determination is described in Section 10.1 of Protocol JZEA.

6.2. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) or its designee.

Sponsor standard tables, figures, and listings (TFLs) and supporting programs and software (eg, SAS®) will be utilized for all analyses where a suitable standard exists. Data derivations in this SAP are defined based upon current sponsor reporting standards at the time of writing, and may be updated at the time of analysis in order to maintain accordance with the most current sponsor standards at that time.

Unless otherwise noted, **summaries of continuous variables** will include a mean, median, standard deviation, minimum, and maximum. When appropriate, lower and upper quartiles will also be presented.

Unless otherwise noted, **summaries of categorical variables** will include the frequency and percentage (relative to the population being analyzed) of each category.

Unless otherwise stated, data will be summarized by dose escalation cohorts that will indicate the assigned treatment regimen and dose schedule for LY3434172.

In addition, safety data may be summarized by the same treatment regimen and dose schedule, and efficacy data may be summarized by the same indication and treatment regimen.

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

6.2.1. Populations

The following population will be defined for this study:

Entered population: will include all patients who sign the informed consent document.

Enrolled/safety population: will include all patients who received any quantity of study treatment (LY3434172), regardless of their eligibility for the study. The safety and efficacy evaluation will be performed based on the first dose of study treatment a patient actually received. This population will be used for all dosing/exposure, safety, and efficacy analyses.

Dose-limiting toxicity–evaluable population: will include all patients from the study who have completed the DLT observation period (Cycle 1) or discontinued treatment before the end of the DLT observation period but with a documented DLT assessment. Exposure and safety summaries may be repeated for this population.

Pharmacokinetic population: will include all enrolled patients from whom a valid assay result (according to laboratory guidelines) has been obtained.

Biomarker population: will include the subset of enrolled patients from whom a valid assay result has been obtained. No imputation will be performed for missing data due to the limitation of small sample size.

6.2.2. Definitions and Conventions

The following definitions and data handling conventions will be used in the analysis.

Table JZEA.6.1. Definitions and Data Handling Conventions

Term	Definition or Rule
Relative 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 cycle, then (date of assessment) – (date of first study drug dose in cycle) +1
	There is no Cycle Day 0. Cycle Day 1 is the date of first dose in that cycle.
Baseline	For change from baseline analyses, baseline value is defined as the last reported measure on or before the first dose date (prior to the dose administration), unless otherwise specified.
Age (years)	Age is based on date of birth and informed consent date. If only a year and month are provided in the date of birth, set day to 15. If only a year is provided, set day to 1 and month to 7 (July).
Duration	Duration (days): (End Date – Start Date + 1) Duration (weeks): (End Date – Start Date + 1)/7 Duration (months): (End Date – Start Date + 1)/30.4375 (Days in months = (1/12)*average number of days in a year) Duration (years): (End Date – Start Date + 1)/365.25 (Average days in a year = 365.25, reflecting the Julian Year of 3 years with 365 days each and 1 leap year of 366 days)
Time-to-Event	The event or censoring time (days) is calculated as: Date of event/censoring – Date of first dose of study drug + 1

6.3. Adjustments for Covariates

Given the small sample size for each tumor type and treatment, no formal analysis investigating the impact of covariates is planned. If data warrant, exploratory analyses may incorporate patient disease characteristics in evaluation of efficacy parameters.

6.4. Handling of Dropouts or Missing Data

Missing data, except for dates, will not be imputed. They will be kept as missing in the data analyses, except for dates when used in calculations of relative study day, for which sponsor reporting standards will be utilized for imputation rules, defined as: Missing start days will be replaced with 1 and missing day/month with 01 JAN. Missing end days will be replaced with the last day of the month, and missing day/month with 31 DEC. The imputation rule may be updated at the time of study reporting if necessary to maintain accordance with most recent sponsor standards. Partial dates should be reported in all listings and not the imputed date.

For time-to-event endpoints, the method for handling missing data will be censoring. Additional sensitivity analyses may be conducted applying different censoring rules if data warrant and will follow sponsor-defined standards.

6.5. Multicenter Studies

Given the small number of patients for each tumor type and treatment, patients across all sites will be grouped together for analysis purposes.

6.6. Multiple Comparisons/Multiplicity

No formal hypothesis testing is planned for this study; thus, there will be no adjustments for multiplicity.

6.7. Patient Disposition

Patient disposition will be summarized and listed for all patients entered into the study. It will include a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated as well as number and percentage of patients completing the study, or discontinuing (overall and by reason for discontinuation of study drug). All patient discontinuation data collected on the case report form will be listed.

Important protocol deviations that potentially compromise the data integrity and patients' safety will be summarized for the safety population. These deviations will include those that can be identified programmatically and those that can only be identified by the clinical research associate during monitoring. Important protocol deviations are described in a separate document within the study Trial Master File.

6.8. Patient Characteristics

Patient characteristics will be summarized and listed for the safety population. Details of the patient characteristics are described in the following sections. Other patient characteristics will be summarized as deemed appropriate.

6.8.1. Demographics

Patient demographics will include sex, race, ethnicity, country, age, age group (<65 years; ≥65 years; <70 years; ≥70 years), height, weight, and body mass index.

6.8.2. Baseline Disease Characteristics

Baseline disease characteristics will include Eastern Cooperative Oncology Group (ECOG) performance status (PS), initial pathological diagnosis, basis for initial diagnosis, disease stage, histopathological grade, tobacco usage (never, current, former), and alcohol use.

6.8.3. Prior Therapies

Prior radiotherapy, surgery, and systemic therapy will be summarized. Prior radiotherapy will be categorized by reason for the regimen (neoadjuvant, adjuvant, neoadjuvant plus adjuvant, advanced/metastatic), and prior surgery will be categorized by intent (curative, palliative). Prior

systemic therapies will be categorized by setting (neoadjuvant, adjuvant, locally advanced, metastatic). Frequency of each specific therapy will be tabulated within each type of regimen and reason for regimen.

Patients who received any prior anti–programmed death 1 (PD-1) and/or anti–programmed death ligand 1 (PD-L1) therapies will be summarized and listed.

6.8.4. Historical Illnesses

Historical illnesses are events in the past that ended before the date on which the informed consent form was signed. Historical illnesses (coded according to the Medical Dictionary for Regulatory Activities [MedDRA]) will be listed for all enrolled patients.

6.9. Treatment Compliance

LY3434172 will be administered intravenously at the investigational sites only. As a result, patient compliance will be ensured. Any cases deemed as not compliant will be reported as protocol deviations.

6.10. Concomitant Therapy

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

For corticosteroids and/or immunosuppressives, the indication, administration route, individual dose, duration, dose adjustment, and reason for use will be summarized and listed.

6.11. Postdiscontinuation Therapy

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

6.12. Safety Analyses

All patients who receive any quantity of LY3434172 will be evaluated for safety and toxicity. Details of the analyses are described in the following subsections.

6.12.1. Extent of Exposure

A summary of exposure will be provided for study drug, including cycle received, cumulative dose, and duration of therapy. Duration of therapy is defined as Discontinuation date – Date of first dose + 1.

A summary of dose intensity will be provided for study drug. Dose intensity expressed in mg/week will be calculated as the actual cumulative amount of drug taken divided by the duration of exposure in weeks. Duration of exposure in weeks is defined as (Date of last dose – Date of first dose + 14)/7 for every 2 weeks (Q2W) dose, and (Date of last dose – Date of first dose + 21)/7 for every 3 weeks (Q3W) dose.

Relative dose intensity will be calculated as:

100% × (actual cumulative dose taken [mg] / planned cumulative dose [mg])

Note that planned dose is the same as actual dose if there is no dose modification or cycle delay.

A summary of dose adjustments will be provided for study drug, including dose omissions, dose reductions, dose increases, dose delays, treatment interrupted, and the corresponding reasons for dose adjustments for each cohort.

6.12.2. Dose-Limiting Toxicities and DLT-Equivalent Toxicities

Definitions of DLTs and DLT-equivalent toxicities (DETs) are provided in Section 7.2.2.2 of Protocol JZEA.

Dose-limiting toxicities will be summarized and listed for the DLT-evaluable population (defined in Section 7.6.1 of Protocol JZEA), and DETs will be listed and summarized for the safety population.

6.12.3. Adverse Events

A listing of all adverse events (AEs) by patient will be presented. This listing will include patient number, AE (reported term and preferred perm [PT]), event start and end dates, Common Terminology Criteria for Adverse Events (CTCAE) grade, relationship to study drug/procedure, seriousness, and outcome. A listing of serious adverse events (SAEs) will be produced using a similar format.

An overall summary will be provided for AEs. The summary will provide counts for all AEs and AEs related to study treatment. Specifically, the number and percent of evaluable patients will be summarized by treatment for each category below:

- patients with at least one treatment-emergent adverse event (TEAE)
- patients with at least one Grade 3 or higher TEAE
- patients with at least one SAE
- patients who discontinued due to AE
- patients who discontinued due to SAE
- patients who died due to AE on study treatment
- patients who died due to AE within 30 days of discontinuation from study treatment

The following summaries will also be produced:

- summary of all preexisting conditions
- summary of TEAEs by PT (any grade and Grade ≥3)
- summary of TEAEs by system organ class (SOC) and PT (any grade and Grade ≥3)
- summary of TEAEs by SOC and PT and maximum grade (1-5)

- summary of treatment-emergent SAEs by SOC and PT (any grade and Grade ≥3)
- summary of AEs as reason for study treatment discontinuation by SOC and PT
- summary of TEAEs leading to dose omissions, reductions, and hospitalization

In addition, immune-related adverse events (irAEs) may be summarized. A list of what is considered an irAE will be defined in a separate document.

6.12.4. Deaths

All deaths recorded in this study will be included as part of the complete AE listing, where appropriate, and listed separately. A summary of deaths may be presented for all patients on therapy if the number of events is sufficient for this to be deemed useful.

6.12.5. Clinical Laboratory Evaluation

All laboratory results will be reviewed using Spotfire® to assess changes over time and differences between cohort/dose levels. Key findings will be summarized in tables and/or illustrated graphically using line plots over time or box plots, for example.

Any abnormal results of clinical laboratory tests will be listed for all patients on therapy and, where appropriate, the calculated CTCAE grades using CTCAE version 4.0 (or higher) will be given. Calculated CTCAE grades will also be summarized by cohort/dose level for laboratory parameters where CTCAE grades are available. A shift table of baseline grade by maximum postbaseline grade will be produced.

6.12.6. Vital Signs and Other Physical Findings

All vital sign results will be reviewed using Spotfire to assess changes over time and differences between cohorts/dose levels. Key findings will be summarized in tables and/or illustrated graphically using line plots over time or box plots, for example.

Any significant physical examination findings and results will be listed.

6.12.7. Electrocardiograms

Any abnormal electrocardiogram data based on local testing will be listed and summarized for the safety population. Further exploratory analyses may be conducted as warranted.

6.13. Efficacy Analyses

All efficacy analyses will be performed on the safety population. This study is not designed to perform hypothesis testing on efficacy; however, all efficacy data will be listed and summarized.

Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al. 2009) will be applied as the primary criteria for assessment of tumor response. Local tumor imaging (investigator assessment with site radiological reading) will be used.

Two sets of analyses will be provided, with 1 set based on RECIST version 1.1 and the other set based on RECIST version 1.1 with confirmatory scan for disease progression. The notation “ir”

(immune-related) will be used to denote the analyses based on RECIST version 1.1 with confirmatory scan for disease progression; it does not indicate that any of the assessments based on irRECIST, irRC, or iRECIST will be used in the study or analyses.

6.13.1. Tumor Measurement

Tumor size is the sum of the uni-dimensional measurements for each lesion. Change in tumor size is defined as the percent change in tumor size from the baseline evaluation to the postdose evaluation at each assessment.

Individual changes in the tumor size over time will be presented graphically by waterfall and spider plots within a tumor type.

6.13.2. Objective Response Rate and Disease Control Rate

Objective response rate (ORR) and disease control rate (DCR) are summary measures of best overall response (BOR) as defined by RECIST version 1.1. Best overall response is derived from time point responses. All time point responses observed while on study treatment and during the short-term follow-up period will be included in the derivation. Patients' responses after objective progression or start of new anticancer therapy are excluded from the determination of best response. Best overall response of complete response (CR) and partial response (PR) should be confirmed by repeated assessment at least 4 weeks following the initial observation. Each patient's BOR will be categorized as CR, PR, stable disease (SD), partial disease (PD), or not evaluable (NE). If appropriate, the best overall tumor response may be calculated by Lilly using all available lesion measurement data to confirm the investigator assessments.

Objective response rate will be estimated by dividing the total number of confirmed responders (CR+PR) by the number of enrolled patients who have received any quantity of study treatment. Patients who do not have any postbaseline tumor response assessments for any reason are considered NE and will be included in the denominator when calculating the response rate.

Disease control rate is defined as the number of patients with SD, confirmed PR, or confirmed CR (CR+PR+SD) divided by the number of enrolled patients who have received any quantity of study treatment.

The estimates of ORR and DCR along with exact 95% confidence interval (CI) will be reported.

6.13.3. Time to Response

Time to response (TTR) is the time from the date of first study treatment until the first evidence of a confirmed CR or PR. If a patient did not experience a confirmed CR or PR, the TTR will be censored at the treatment starting date.

Time to response will be estimated using the Kaplan-Meier (KM) method (Kaplan and Meier 1958) and summary statistics including median and 95% CI will be presented.

6.13.4. Progression-Free Survival

Progression-free survival is defined as the time from the date of first dose until the date of the first observed radiographic documentation of progression or death due to any cause, whichever is earlier.

Table JZEA.6.2 lists rules for determining date of progression or censor for PFS.

Table JZEA.6.2. Rules for Determining Date of Progression or Censor for Progression-Free Survival

Situation	Event/Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate radiological assessment or date of first dose (whichever is later)
unless		
No baseline radiological tumor assessment available	Censored	Date of first dose
No adequate postbaseline radiological tumor assessment available and death reported after 2 consecutively missed tumor assessment intervals following enrollment	Censored	Date of first dose
New anticancer treatment started	Censored	Date of adequate radiological assessment prior to start of new therapy or date of first dose (whichever is later)
Tumor progression or death documented immediately after 2 or more consecutively missed tumor assessment intervals following last adequate radiological tumor assessment or enrollment (whichever is later)	Censored	Date of last adequate radiological assessment or date of first dose (whichever is later)

Abbreviation: PD = partial disease.

Note: 1) If there are multiple dates associated with 1 radiological tumor assessment, the assessment date will be set to the first date when the overall response is PD and the last date otherwise; 2) Symptomatic deteriorations (ie, symptomatic progressions, which are not radiologically confirmed) will not be considered as progressions; and 3) A radiological tumor assessment is considered adequate if its response is among CR, PR, SD, or PD.

Progression-free survival will be estimated using the KM method. Median PFS and 95% CI as well as PFS rates (and 95% CI) at 12, 18, and 24 weeks will be presented.

6.13.5. Duration of Response

The duration of response (DoR) time is defined only for responders (patients with a confirmed CR or PR). It is measured from the date of first evidence of CR or PR to the date of the first observed radiographically documented PD or the date of death due to any cause, whichever is earlier. For clarity, the start date should be determined by the initial assessment of CR or PR, not the date of confirmation of CR or PR. Start date is calculated as date of progression or death – date of first response evaluation of CR or PR + 1.

Duration of response will be censored according to the same rules as PFS, with the addition of the following rule: if a patient begins postdiscontinuation therapy, DoR will be censored on the day of the last response evaluation prior to the initiation of postdiscontinuation therapy.

Duration of response will be estimated using the KM method and summary statistics including median and 95% CI will be presented.

6.13.6. Immuno-Related Efficacy Analysis Variables

Study JZEA will use RECIST version 1.1 with confirmatory scan for disease progression. Detailed application of RECIST version 1.1 with confirmatory scan for PD can be found in Section 9.1.1.2 of Protocol JZEA.

Immune-related objective response rate (irORR) is defined as the proportion of treated patients achieving a BOR of CR or PR per RECIST version 1.1 with confirmatory scan for PD—particularly, the BOR by RECIST version 1.1 with confirmatory scan for PD closely related to confirmed response by RECIST. Immune-related objective response rate further captures responses after unconfirmed PD and does not require confirmation. For example:

- If the best response by RECIST version 1.1 is CR, then the best response by RECIST version 1.1 with confirmatory scan for PD is CR.
- If the best response by RECIST version 1.1 is PR, SD, or PD, the best response by RECIST version 1.1 with confirmatory scan for PD is the best response over the initial assessment (prior to PD by RECIST) and the confirmation stage.

Overall, the best response by RECIST version 1.1 with confirmatory scan for PD should be the same or better than the best response by RECIST criteria. In addition, patients who do not have any postbaseline tumor response assessments for any reason are considered NE and will be included in the denominator when calculating the response rate.

Immune-related disease control rate (irDCR) is defined as the number of patients with immune-related stable disease (irSD), immune-related complete response (irCR), or immune-related partial response (irPR) divided by the number of enrolled patients who have received any quantity of study treatment.

Immune-related time to response (irTTR) is the time from the date of first study treatment until the first documented irCR or irPR.

Immune-related PFS (irPFS): The date from the treatment start date to the time of PD assessed by RECIST version 1.1 with confirmatory scan for PD.

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

Immune-related duration of response (irDoR): The irDoR is defined from the date of first documented irCR or irPR (responder) to the date of irPD or the date of death due to any cause, whichever is earlier.

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

6.13.7. Overall Survival

Overall survival is defined as the time from first study treatment until death due to any cause. If the patient is not known to have died at the data inclusion cutoff date for the analysis (or is lost to follow-up), OS data will be censored on the last date on which the patient was known to be alive.

Overall survival will be estimated using the KM method. Median OS along with 95% CI as well as OS rates (and 95% CI) at 1 and 2 years will presented.

6.14. Subgroup Analyses

Subgroup analyses of efficacy endpoints may be performed for each of the potential prognostic subgroup variables listed below.

- sex (male; female)
- age (<65 years; ≥65 years; <70 years; ≥70 years)
- baseline ECOG PS (0; 1)
- ethnicity (White; East Asian; others)
- smoking status (never; current; former)
- prior lines of therapy (such as first line, second line, third line, and beyond)

Other subgroups may be added as deemed necessary.

6.15. Immunogenicity Analysis

Immunogenicity (anti-LY3434172 antibody) incidence will be tabulated, and correlation to drug level, activity, PK parameters, and safety will be assessed, respectively, as appropriate. The measures that will be analyzed include baseline presence and level of anti-drug antibodies (ADAs), treatment-emergent ADAs (defined in Section 10.3.3.7 of Protocol JZEA), levels of neutralizing ADA, and incidence and levels of ADA associated with infusion-related reactions.

6.16. Pharmacokinetic/Pharmacodynamic Analyses

Selected PK descriptors (based on actual sampling times), including approximate maximum observed drug concentration (C_{max}) and area under the concentration versus time curve (AUC), will be calculated by noncompartmental analysis methods. As an exploratory analysis, PK descriptor estimates for trough concentrations (minimum observed drug concentration [C_{min}]) at steady state following repeated dose may be evaluated.

In addition, PK parameter estimates for LY3434172 may be calculated by population PK analysis methods using nonlinear mixed effects modeling (NONMEM). The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements for software validation. It is possible that other validated, equivalent PK software programs may be used if appropriate, warranted, and approved by Global PK/pharmacodynamic management.

Following review of the biomarker analyses (see Section 6.17), pharmacodynamic biomarker analysis with tumor type, changes in biomarker levels over time, and association to dose levels or exposure may be explored if applicable. Pharmacokinetic/pharmacodynamic analyses may be conducted to explore exposure-response relationships between LY3434172 concentrations in systemic circulation and relevant pharmacodynamic measures such as soluble PD-1, soluble PD-L1, and interleukin 2 (IL-2) stimulation. Either summary metrics of exposure and effect (for example, individual trough concentrations) or concentration time profiles of exposure and effect could be used for these analyses.

6.17. Biomarker Analysis

Association analysis between selected biomarkers and clinical outcome may be assessed if applicable. If the ORR is ≥10%, the baseline biomarkers that potentially predict better response to LY3434172 may be explored using a single- or multimarker approach. In addition (as discussed in Section 6.16), pharmacodynamic/biomarker analyses related to treatment, immune functioning, mechanism of action of study drugs, and/or cancer may be explored if applicable. Biomarker variations over tumor types, the on-treatment percentage changes in selected biomarker(s) from baseline, and potential correlation between biomarker(s) and different LY3434172 dose levels (or exposure) may be explored if applicable.

6.18. Interim Analysis

In this Phase 1 dose-finding study, safety, PK, and biomarker data (if available) will be reviewed on a cohort-by-cohort basis during the study until the MTD and/or RP2D is determined. The purpose of these cohort-by-cohort data reviews is to evaluate the safety data at each dose level and determine if a DLT has been observed. The decision whether to advance to the next dose level will be made following discussion between the investigators and Lilly and will be communicated to the sites prior to patients being treated in the subsequent cohort.

Safety and available PK data will be reviewed during the study to inform dose escalation, modifications to the dose-escalation strategy, or other design elements.

After all patients in Cohorts 1 to A5/6 have completed the DLT evaluation period or discontinuous treatment, an interim safety and PK/pharmacodynamic analysis will be conducted. In this interim analysis, early antitumor activity may also be explored. Additional enrollment of patients to Cohorts A4 to A5/6 can continue during the interim analysis.

Interim analysis may also be combined with any prespecified safety review or reporting (ie, Trial Level Safety Reviews, Development Safety Update Reviews, or Investigator's Brochure update reviews).

The final overall analysis of Study JZEA will be conducted with the safety and efficacy primary analysis approximately 52 weeks (12 months) after the last enters/starts study treatment. If it is deemed that enough data have been obtained to assess the primary and secondary objectives, a clinical study report may be created before the last patient visit. In this case, all data collected before the data cutoff date will be used for the analysis of safety, efficacy, PK, and pharmacodynamic biomarkers. All data defined in the protocol will continue to be collected from patients on treatment after data-cutoff date and results will be listed. However, summary tables including data collected after the data-cutoff date will not be created.

6.19. Additional Reports to Support the Clinical Trial Registry

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

A participant flow will be created that will describe how many patients completed the study, and for those who did not, the frequency of each reason for not completing. This analysis will be based on study discontinuation, not treatment discontinuation. A patient will be identified as having completed the study on the study discontinuation electronic case report form, if available, or if information for both primary and secondary endpoints has been observed.

7. References

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