Statistical Analysis Plan Version 1 J1C-MC-JZDA

A Phase 1a/1b Study of LY3415244, a Bispecific Antibody in Patients with Advanced Solid Tumors

NCT03752177

Approval Date: 24-Oct-2018

1. Statistical Analysis Plan: J1C-MC-JZDA
A Phase 1a/1b Study of LY3415244, a Bispecific Antibody in Patients with Advanced Solid Tumors

LY3415244

Study J1C-MC-JZDA is a multicenter, nonrandomized, open-label, dose-escalation Phase 1a study followed by Phase 1b cohort expansion of intravenous LY3415244 in patients with advanced solid tumors.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol J1C-MC-JZDA
[Phase 1a/1b]

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

Approval Date: 24-Oct-2018 GMT

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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

Phase 1a: To assess the safety and tolerability of LY3415244 in patients with advanced solid tumors, thereby identifying a recommended Phase 2 Dose (RP2D) to be administered to patients in the Phase 1b portion of the study.

Phase 1b: To assess the safety and tolerability of the RP2D dose of LY3415244 in patients with advanced solid tumors.

4.2. Secondary Objectives

Phase 1a: To assess the pharmacokinetics (PK) of LY3415244.

Phase 1b:

- to assess the PK of LY3415244 in patients in each of 4 expansion cohorts.
- to assess early antitumor activity of LY3415244 in patients in each of 4 expansion cohorts.

4.3. Tertiary/Exploratory Objectives

Phase 1a and 1b:

- to characterize tumor tissue and blood biomarkers relevant to LY3415244, 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 between biomarkers and clinical outcomes
- to assess the immunogenicity of LY3415244
- to assess overall survival (OS) of patients receiving LY3415244 administered as monotherapy

5. A Priori Statistical Methods

5.1. Sample Size Determination

The sample size determination is described in Protocol J1C-MC-JZDA (JZDA), Section of Sample Size Determination.

5.2. 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.

In Part 1a, unless otherwise stated, data will be summarized by dose escalation cohorts which will indicate the assigned treatment regimen and dose schedule for LY3415244.

In Part 1b, unless otherwise stated, data will be summarized by expansion cohorts.

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, treatment regimen, and dose schedule by combination of the Phase 1a and 1b part.

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

5.2.1. 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 (LY3415244), 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 (DLT)-Evaluable Population (for Phase 1a): will include all patients from Phase 1a portion of the study who have completed 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 will be repeated for this population.

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

5.2.2. Definitions and Conventions

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

Table JZDA.5.1. 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

5.3. 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.

5.4. 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.

5.5. 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.

5.6. Multiple Comparisons/Multiplicity

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

5.7. 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 (CRF) will be listed.

Important protocol deviations that potentially compromise the data integrity and patients' safety will be summarized for 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 another document within the study Trial Master File.

5.8. Patient Characteristics

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

5.8.1. Demographics

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

5.8.2. 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.

5.8.3. Prior Therapies

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

The patients who received any prior anti-PD-1 and/or anti-PD-L1 therapies will be listed.

5.8.4. Historical Illnesses

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

5.9. Treatment Compliance

LY3415244 will be intravenously administered only at the investigational sites. As a result, patient compliance will be ensured. If there are any cases deemed as not compliance, they will be reported as protocol deviations.

5.10. 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, and dose adjustment reason of the use will be summarized and listed.

5.11. 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.

5.12. Safety Analyses

All patients who receive any quantity of LY3415244 will be evaluated for safety and toxicity. Details of the analyses are described in the following subsections.

5.12.1. 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.

Relative dose intensity will be calculated as:

100% x (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 increase, dose delays, treatment interrupted and the corresponding reasons for dose adjustments for each cohort.

5.12.2. Dose-Limiting Toxicity and DLT-Equivalent Toxicities

The definition of the DLTs and the DLT-equivalent toxicities (DETs) is specified in Protocol J1C-MC-JZDA (JZDA), Section of Dose-Limiting Toxicity Determination.

Dose limiting toxicities will be summarized and listed for DLT-evaluable population.

Dose limiting toxicities-equivalent toxicities (DETs) will also be listed and summarized for safety population.

5.12.3. 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 Term [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 the 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 AE (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, hospitalizations

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.

5.12.4. 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 there are a sufficient number of events for this to be deemed useful.

5.12.5. 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 v4.0 (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.

5.12.6. 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.

5.12.7. Electrocardiograms

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

5.13. 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) 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. Modified RECIST (Byrne and Nowak 2004) will be applied for patients with pleural mesothelioma. For the patients with both pleural mesothelioma and solid tumors, Modified RECIST will be applied to pleural mesothelioma and RECIST 1.1 will be applied to the solid tumors.

Two sets of analyses will be provided, with 1 set based on RECIST 1.1 and the other set based on RECIST 1.1 with confirmatory scan for disease progression. The notation "ir" will be used to denote the analyses based on RECIST 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.

5.13.1. Tumor Measurement

For the patients with solid tumors only (assessed by RECIST 1.1), the tumor size is the sum of the uni-dimensional measurements for each lesion.

For the patients with pleural mesothelioma only (assessed by modified RECIST), the tumor size is the sum of the 6 pleural unidimensional measurements (2 positions, each with 3 levels).

For the patients with both pleural mesothelioma (assessed by modified RECIST) and solid tumors (assessed by RECIST 1.1), the tumor size is the sum of 2 parts, the sum of the 6 pleural unidimensional measurements (2 positions, each with 3 levels) and the sum of the uni-dimensional measurements for each solid lesion.

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

5.13.2. 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 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 (ORR) 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.

Disease control rate (DCR) is defined as the number of patients with stable disease, confirmed partial response or confirmed complete response (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.

5.13.3. 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 Kaplan-Meier (KM) method (Kaplan and Meier 1958) and summary statistics including median and 95% CI will be presented.

5.13.4. Progression-Free Survival

Progression-free survival (PFS) 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 JZDA.5.2 lists rules for determining date of progression or censor for PFS.

Table JZDA.5.2. 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 post baseline radiological tumor assessment available and death reported after 2 consecutively missed tumor assessment interval 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 interval 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)

Abbreviations: PD = partial disease.

Notes: (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, (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 KM method. Median PFS and 95% CI as well as PFS rates (and 95% CI) at 12, 18, 24 weeks will be presented.

5.13.5. 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. It 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 KM method and summary statistics including median and 95% CI will be presented.

5.13.6. Immuno-Related Efficacy Analysis Variables

Study JZDA will use RECIST 1.1 with confirmatory scan for disease progression. Detailed application of RECIST 1.1 with confirmatory scan for PD can be found in Protocol J1C-MC-JZDA, Section 9.1.1.2.

Immune-related objective response rate (irORR) is defined as the proportion of treated patients achieving a best overall response of CR or PR per RECIST 1.1 with confirmatory scan for PD. Particularly, the best overall response by RECIST 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 it does not require confirmation. For example:

- If the best response by RECIST 1.1 is CR, then the best response by RECIST 1.1 with confirmatory scan for PD is CR.
- If the best response by RECIST 1.1 is PR, SD, or PD, the best response by RECIST 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 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 non-evaluable 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 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 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 duration of response 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.

5.13.7. 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 the patient is known to be alive.

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

5.14. 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 Eastern Cooperative Oncology Group (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.

5.15. Immunogenicity Analysis

Immunogenicity (anti- LY3415244 antibody) incidence will be tabulated, and correlation to drug level, activity, and safety will be assessed, as appropriate, respectively. The measures that will be analyzed include baseline presence and level of anti-drug antibodies (ADA), treatment-

emergent ADA, levels of neutralizing ADA, and incidence and levels of ADA related to infusion-related reactions.

5.16. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic parameter estimates for LY3415244 therapy will be calculated by population PK analysis methods using nonlinear mixed effects modeling. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation. It is possible that other validated, equivalent PK software programs may be used if appropriate, warranted, and approved by Lilly global PK/pharmacodynamic management. In addition, selected PK parameters (based on actual sampling times), including maximum observed drug concentration (C_{max}), time of C_{max} , and area under the concentration versus time curve (AUC) may be calculated by noncompartmental analysis methods and/or model simulations. As an exploratory analysis, PK parameter estimates for minimum observed drug concentration during a dosing interval (C_{min}) at steady state following repeated dose may be evaluated.

Pharmacokinetic/pharmacodynamic analyses will be conducted to explore exposure-response relationships between LY3415244 concentrations in systemic circulation and various pharmacodynamic measures, such as selected safety outcomes, receptor occupancy, and biomarkers.

5.17. Biomarker Analysis

Biomarkers related to treatment, immune functioning, mechanism of action of study drugs, and/or cancer will be collected and reported. In addition, the relationship between biomarkers and clinical outcome will be assessed. Biomarker relationships by tumor type, changes in biomarker levels at baseline and over time, and differences among dose levels or exposure will be explored as possible. The pharmacodynamic effect from all patients undergoing pharmacodynamic assessments will be explored.

5.18. Interim Analysis

In the Phase 1a dose-finding portion of the study, safety, PK, and biomarker data (if available) will be reviewed on a cohort-by-cohort basis during the study, until the maximum tolerated dose 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 relayed to the sites prior to patients being treated on 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.

An interim analyses will be performed after all patients in Phase 1a have completed the DLT evaluation period. The Lilly study team will evaluate the data from the interim safety and

PK/PD analyses before opening the dose expansion cohorts in Phase 1b. In this interim analyses, early antitumor activity may also be explored.

An expansion-specific safety and efficacy interim analysis will be conducted approximately 24 weeks (6 months) after the last patient enters/starts study treatment (LPET) for each of the expansion cohorts. These interim analyses may be combined if they are expected to occur within approximately a month of each other. Interim analyses may also be combined with any prespecified safety review or reporting (ie, Trial Level Safety Reviews, Development Safety Update Reviews, or Investigator Brochure update reviews). The expansion-specific safety and efficacy primary analyses will be conducted approximately 52 weeks (12 months) after LPET for each of the expansion(s).

The final overall analysis of Study JZDA will coincide with the safety and efficacy primary analysis of the last expansion.

If it is deemed that enough data have been obtained to assess the primary and secondary objectives, a clinical study report might be created before the last patient visit. In this case, all data until the data-cutoff date will be used for the analysis of safety, efficacy, PK, and 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 after data-cutoff date will not be created.

5.19. Additional Reports to Support 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 which 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 fewer than 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 (eCRF), if available, or if information for both primary and secondary endpoints has been observed.

6. References

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Leo Document ID = 2e7a7e98-04bb-443e-bb4a-55a389bd674d

Approver: PPD
Approval Date & Time: 24-Oct-2018 18:10:07 GMT
Signature meaning: Approved