Statistical Analysis Plan: J1F-MC-JZFA (version 2)

A Phase 1a/1b Study of LY3405105 Administered to Patients with Advanced Solid Tumors

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Approval Date: 20-Jul-2020

1. Statistical Analysis Plan: J1F-MC-JZFA: A Phase 1a/1b Study of LY3405105 Administered to Patients with Advanced Solid Tumors

CDK7 Inhibitor (LY3405105)

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Protocol J1F-MC-JZFA
Phase 1

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 16 Nov 2018
Statistical Analysis Plan Version 1 electronically signed and approved by Lilly on date provided below.

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3. Revision History

Statistical analysis plan (SAP) version 1 was approved prior to the first visit when a subject receives study drug or any other protocol intervention.

The SAP version 2 is based on Protocol J1F-MC-JZFA(b), a substantial amendment approved on 02 July 2020.

4. Study Objectives

Table JZFA.4.1. Objectives and Endpoints

Objectives	Endpoints
Phase 1a	
Primary	
• To assess the safety and tolerability of LY3405105, administered as monotherapy to determine the RP2D and schedule in patients with solid tumors	• Safety (including but not limited to): incidence and severity of DLTs, TEAEs, SAEs, deaths, and clinical laboratory abnormalities
Secondary	
• To assess the PK of LY3405105 administered as monotherapy to patients with solid tumors	• AUC/C_{max} of LY3405105
• To document any anti-tumor activity observed with LY3405105 when administered as monotherapy to patients with solid tumors	• Per RECIST v1.1: o ORR o DCR o DoR o TTR o PFS • OS
Exploratory	
• To assess the relationship between biomarkers, LY3405105 exposure, and clinical outcomes	• Results of biomarker analyses • Clinical outcomes data
Phase 1b	
Primary	
• To assess the efficacy of LY3405105	• ORR
Secondary	
• To evaluate the safety and tolerability of LY3405105 when administered as monotherapy to patients with solid tumors	• Safety, including but not limited to incidence and severity of TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE v4.0
• To document any anti-tumor activity observed with LY3405105 when administered as monotherapy to patients with solid tumors across the defined cohorts	• DCR • DoR • PFS • OS • TTR
• To assess the PK of LY3405105 administered as monotherapy to patients with solid tumors across the defined cohorts	• Plasma concentration of LY3405105
Tertiary/exploratory	
• To correlate the clinical activity with molecular subtypes as defined in the protocol	• ORR in relation to molecular subtypes

Abbreviations: AUC = area under the plasma concentration x time curve; C_{max} = maximum concentration; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DLT = dose-limiting toxicity; DoR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TTR = time to response.

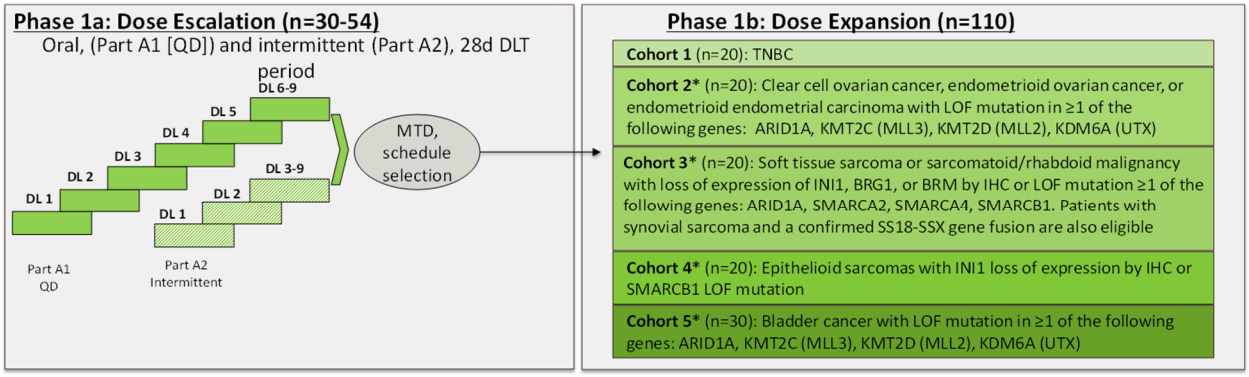
5. Study Design

5.1. Summary of Study Design

Study JZFA is a Phase 1, multicenter, nonrandomized, open-label dose escalation study in patients with advanced solid tumors, followed by dose expansion of oral LY3405105 in patients with advanced selected solid tumors.

This initial Phase 1 study of LY3405105 consists of a once daily (QD) continuous (Phase 1a/Part A1) and Monday, Wednesday, and Friday (MWF) or Tuesday, Thursday, and Saturday (TTS) intermittent (Phase 1a/Part A2) dose escalation phase and an expansion phase (Phase 1b) of LY3405105 given as a monotherapy in 5 tumor expansion cohorts (Cohorts 1 through 5) as shown in Figure JZFA.5.1. Based on available human pharmacokinetics (PK) exposure data, the intermittent dosing schedule (Part A2) will no longer be pursued in the study. The dose escalation will determine the maximum tolerated dose (MTD) as well as the recommended Phase 2 dose (RP2D).

Figure JZFA.5.1 illustrates the overall study design, Section 5.1.1 describes the dose escalation phase and Section 5.1.2 describes the dose expansion phase.



Abbreviations: ARID1A = AT-rich interactive domain-containing protein 1A; BRG1 = Brahma-related gene 1; BRM = Brahma; DL = dose level; DLT = dose-limiting toxicity; ICH = International Conference on Harmonization; INI1 = integrase interactor 1; KDM6A (UTX) = lysine demethylase 6A; KMT2C (MLL3) gene = lysine methyltransferase 2C; KMT2D (MLL2) gene = histone-lysine-methyltransferase 2D; LOF = loss of function; MTD = maximum tolerated dose; n = approximate number of patients per group; QD = once daily; SMARCA2 = SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2; SMARCA4 = SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4; SMARCB1 = SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1; SS18 = SS18 subunit of BAF chromatin remodeling complex; SSX = SSX family member; TNBC = triple-negative breast cancer.

Figure JZFA.5.1. Illustration of study design.

5.1.1. Dose-Escalation Phase

Monotherapy Dose Escalation (Phase 1a) will start first, with a starting dose of LY3405105 1 mg orally (PO) QD (Part A1) and 2 mg PO intermittently every MWF or TTS (Part A2) on a 28–day cycle. Based on available human PK exposure data, the intermittent dosing schedule (Part A2) will no longer be pursued in the study. The Bayesian model-based toxicity method called N-CRM (Neuenschwander et al. 2008) will be used to inform the dose levels in each cohort. The dose-escalation method is further described in Section 7.1.1.2 in the protocol.

Each dose level will enroll a minimum of 3 patients (but no more than approximately 6 patients per dose level). At the RP2D, up to 10 patients may enroll to further assess the safety and tolerability of the dose selected prior to advancing to the Phase 1b of the study. Part A2 will enroll the first patient after 7 days if no toxicity concerns are found. Part A2 may enroll the second patient and Part A1 will enroll the first patient to that regimen. Additional patients in Parts A1 and A2 will be enrolled once the preceding patient in the same dose level has completed 7 days of therapy. Subsequent dose levels will enroll patients based on the safety from the previous dose level, any available PK and pharmacodynamic (PD) data, and discussion with investigators. This decision is made between the investigators and the Eli Lilly and Company (Lilly) clinical research physician/clinical research scientist (CRP/CRS).

Lilly and the investigators will discuss safety and available PK/PD results after each dose level for Phase 1a of the study, and dose-escalation decisions will be made prior to starting enrollment to the next dose level. Lilly will send written notification to the investigator site to specify the dose and dosing schedule before patients may be enrolled in the next dose level. Intermediate and/or higher dose levels, as well as alternative schedules of administration, will be explored if deemed necessary after discussion between Lilly and investigators, taking into account patient safety and PK/PD data.

5.1.2. Dose Expansion Phase

After all patients in the dose-escalation phase (Phase 1a) have completed the dose-limiting toxicity (DLT) evaluation period or discontinued, an interim safety and PK/PD analysis will be conducted before opening the dose expansions (Phase 1b). The N-CRM method along with PK/PD analysis will be used to identify a monotherapy RP2D for investigation in the dose expansion phase. The monotherapy RP2D may be below the MTD.

Phase 1b dose expansion will include LY3405105 monotherapy in patients with multiple tumor types and will enroll approximately 20 patients in Cohorts 1 through 4. Cohort 5 will enroll approximately 30 patients. Patients in Cohorts 2 through 5 will be identified by the treating investigator based on local immunohistochemistry or molecular testing results.

6. A Priori Statistical Methods

6.1. General Considerations

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

Sponsor standard tables, figures, and listings (TFLs) and supporting programs and software (eg, TAFFY, BEACH, Spotfire) 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.

In general, continuous variables will be presented using the mean, standard deviation, coefficient of variation, median, minimum, maximum, and number of patients with an observation (n). For categorical variables, the population size (N), the number of patients with events (n), and the percentage of patients with events are usually reported.

All confidence intervals (CIs) will be given at a 2-sided 95%, unless otherwise stated.

The data handling conventions will be used in the analysis are outlined in Table JZFA.6.1.

Table JZFA.6.1. 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.
Entered	Patients who have signed the informed consent form.
Enrolled	Patients who have been assigned to study treatment and received at least 1 dose of any study drug. Enrolled population is the same as the safety population.
Screen Failures	Patients who have signed informed consent, do not meet eligibility criteria and are not enrolled.

Any change to the data analysis methods described in the protocol/SAP will require an amendment ONLY if it changes a principal feature of the protocol/SAP. Any other change to the

data analysis methods described in the protocol/SAP and the justification for making the change will be described in the clinical study report (CSR). Additional exploratory analyses will be conducted as deemed appropriate.

6.2. Handling of Dropouts or Missing Data

Missing data, except dates, will not be imputed. Historical data such as historical diagnosis, historical illness, preexisting conditions and prior therapies should be collected in a sufficiently informative way. For example, in order to be considered as historical illness, events occurring in the same year as study entry should have at least a known month and year for the end date, while events occurring in previous years should have at least a known year for the end date. The start dates and end dates for adverse events and concomitant medications will be imputed following the most recent Sponsors' standards. Partial dates should be reported in all listings and not the imputed date.

6.3. Patient Disposition

A detailed summary of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, and treated as well as number and percentage of patients completing the study (patients who receive 1 cycle of study dose or are evaluable for DLT for Phase 1a and patients who have at least 1 postbaseline tumor assessment for Phase 1b), or discontinuing (overall and by reason for discontinuation of LY3405105). Reason for discontinuation from both the study treatment and the study will be summarized by pre-determined categories.

A listing of primary reasons for study treatment and study discontinuation will also be provided.

6.4. Patient Characteristics

Patient demographics (including age, sex, screening height, weight, body mass index, race, ethnicity, and country) will be reported using descriptive statistics. The summary will include the number of patients for each treatment group and the total across treatment groups.

The following baseline disease characteristics will be summarized by treatment arm: Eastern Cooperative Oncology Group (ECOG) performance status, initial pathological diagnosis, and basis of initial pathological diagnosis.

Patient preexisting condition, historical illness, prior anti-cancer therapies, and other baseline characteristics such as biomarker and genetic alterations at baseline will be summarized as deemed appropriate.

6.5. Treatment Compliance

Study treatment compliance will be assessed as the proportion of dose that is actually taken, relative to what is expected, after accounting for protocol-defined dose adjustments. The actual dose taken will be derived from the difference between the total number of tablets/capsules dispensed and returned over the course of the patient's treatment.

6.6. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary. All concomitant medications will be summarized for the safety population using the preferred name.

6.7. Efficacy Analyses

Tumor response data will be tabulated, and further exploratory analyses will be conducted as warranted, grouping patients by tumor type, for the safety population.

6.7.1. Efficacy Definitions

The following definitions for efficacy endpoints will be used:

Overall response rate (ORR) is the proportion of patients who achieved a complete response (CR) or partial response (PR) out of all patients treated. Tumor responses will be measured and recorded using the appropriate guidelines (Response Evaluation Criteria in Solid Tumors [RECIST 1.1; Eisenhauer et al. 2009]). To confirm objective responses, all lesions should be radiologically assessed, and the same radiologic method used for the initial response determination should be repeated at least 4 weeks following the initial observation of an objective response, using the same method that was used at baseline.

Disease control rate (DCR) is defined as the proportion of patients who achieved a best overall response (BOR) of confirmed CR, confirmed PR or stable disease (SD) out of all patients treated. Best response is determined from a sequence of responses assessed. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. A minimum timeframe of 6 weeks is required for a BOR of SD.

Duration of Response (DoR) will be calculated only for responders. It is measured from the date of first evidence of a confirmed response to the date of first progression of disease or the date of death due to any cause, whichever is earlier. For patients who are not known to have died or to have had a progression of disease as of the data-inclusion cut-off date, DoR will be censored at the date of last objective response assessment prior to the date of any subsequent systemic anticancer therapy.

Progression-free survival (PFS) is defined as the time from the date of start of treatment to the first date of radiologically documented PD or the date of death due to any cause, whichever occurs first. For patients who are not known to have died or progressed as of the data-inclusion cut-off date, PFS time will be censored at the date of the last objective progression-free disease assessment prior to the date of any subsequent systemic anticancer therapy.

Time to Response (TTR) is defined as the time from the date of start of treatment to the date measurement criteria for confirmed CR or PR (whichever is first recorded) are first met. For patients who are not known to have achieved CR or PR as of the data-inclusion cut-off date, TTR will be censored at the date of the last objective disease assessment prior to the date of any subsequent systematic anticancer therapy.

Overall survival (OS) is defined as the time from the date of start of treatment to the date of death due to any cause. For patients who are alive, lost to follow-up, or withdrawn from the study at the time of analysis, OS will be censored at the last date the patient is known to be alive.

6.7.2. Efficacy Analyses

Reported lesion data (target/non-target or measurable/nonmeasurable), investigator assessment of response, all time-to-event endpoints will be listed for all patients. The following efficacy summaries will be provided:

- overall response rate and DCR will be presented with exact 95% CI;
- time to event endpoints, including PFS, DoR, TTR, and OS will be summarized descriptively using the Kaplan-Meier method for Phase 1b only; and
- best percent change in tumor size will be presented using a waterfall plot. All patients with at least 1 pre and postdose target lesion measurement will be shown in the plot.

In Phase 1b dose expansion cohorts, Bayesian models will be used to estimate the posterior probability of activity in terms of ORR (with non-informative prior).

6.8. Safety Analyses

All safety summaries and analyses will be based upon the safety population. Details of the analyses are described in the following sections.

6.8.1. Extent of Exposure

LY3405105 will be administered PO QD or 3 times a week (TIW [MWF or TTS]) on a 28-day cycle. Based on available human PK exposure data, the intermittent dosing schedule (Part A2) will no longer be pursued in the study.

The actual cumulative dose taken of LY3405105 will be derived from the difference between the total number of tablets/capsules dispensed and returned over the course of the patient's treatment taking into account the dose strengths (1 mg and 5 mg).

The duration of therapy for the QD schedule will be calculated as last dose date-first dose date+1. The duration of therapy for the TIW schedule will be calculated as last dose date-first dose date+(28/[4×3]).

A summary of exposure will be provided for each study drug, including cycle received, cumulative dose, and duration of therapy.

A summary of dose intensity will be provided for each study drug. Dose intensity (per day) is calculated as total actual dose taken/duration of therapy (day). Relative dose intensity is calculated as 100 × (actual dose intensity per day/planned dose intensity per day).

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

A summary of dose adjustments will be provided for each study drug, including dose omissions, dose reductions, cycle delays, and the corresponding reasons for dose adjustment.

6.8.2. Adverse Events

Adverse event (AE) verbatim terms will be provided by the investigators and then will be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) Lower Level Term (LLT) dictionary Version 21.0 (or higher). The investigator will use Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (NCI 2009) to assign AE severity grades.

Preexisting conditions are defined as AEs that begin but do not resolve prior to the first dose of study drug in each study period. Preexisting conditions will be presented by patient and can be combined with the listing of AE, so that the history of the preexisting conditions/AEs can be traced.

A treatment emergent adverse event (TEAE) is defined as any AE that begins on or after the day of first dose in the reporting study period or any preexisting condition that increases in CTCAE grade on or after the day of first dose in the reporting study period. The MedDRA LLT will be used in the treatment-emergent computation.

The number of patients who experienced a TEAE, or TEAE at least possibly related to study drug, will be summarized. Treatment-emergent adverse events will be summarized by System Organ Class (SOC), by Preferred Term (PT) of decreasing frequency within SOC, and by maximum CTCAE grade and grade categories (any, Grade 3 or higher).

Adverse events leading to dose adjustments, treatment discontinuation, or death will also be summarized.

Dose-limiting toxicities in Phase 1a and DLT-equivalent toxicities in Phase 1b will be summarized by cohort.

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

All deaths in this study, including the reasons for death, will be listed by treatment. The reasons for death will be summarized, separately for on-therapy, and within 30 days of last dose of study drug.

Serious AEs will be summarized for each treatment by decreasing frequency of PT within SOC. The summary will be provided for events, regardless of study drug causality, and repeated for events deemed by the investigator to be related to study medication.

6.8.4. Clinical Laboratory Evaluation

Listings of laboratory results will be provided. All relevant hematology and chemistry laboratory values will be graded according to CTCAE Version 4. Shift tables showing the change from baseline to the worst grade on study will be presented.

Laboratory analytes below/above quantifiable levels (data in the database recorded as "<x" and ">x") will be reported as such in listings, and imputed to the lower or upper limit of quantification in any summaries or analyses.

6.8.5. Vital Signs and Other Physical Findings

Vital signs measurements, including height, weight, temperature, blood pressure, pulse, and ECOG performance status will be listed and summarized.

6.8.6. Electrocardiograms

Local electrocardiograms (ECGs) will be summarized by cycle and overall. The summary by cycle will classify patients as having normal or abnormal. Adverse events that could be associated with abnormal ECGs will be presented, if appropriate.

Quantitative ECG results including PR, QRS, Bazett's corrected QT (QTcB), Fridericia's corrected QT (QTcF), and RR intervals will be provided in patient listings for absolute and change from baseline. In addition, summaries of outlying corrected QT (QTc) intervals (QTc, QTcB, and QTcF) will be provided. Outlying intervals include absolute values >450 for males, >470 for females, >480 and >500 msec, and change from baseline >30 and >60 msec.

6.9. Pharmacokinetic/Pharmacodynamic Analyses

Unless stated otherwise, the Lilly pharmacokineticist will be responsible for the PK/PD analyses.

Pharmacokinetic parameter estimates for LY3405105 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be maximum concentration (C_{max}) and area under the concentration-time curve ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$). Other noncompartmental parameters, such as half-life ($t_{1/2}$), apparent clearance (CL/F), apparent volume of distribution (V/F), and renal clearance of LY3405105 may be reported. Additional exploratory analyses will be performed if warranted by data and other validated PK software programs (for example, NONMEM) may be used if appropriate. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

Pharmacokinetic parameter estimates will be evaluated to delineate effects of dose proportionality. Log-transformed C_{max} and AUC estimates will be assessed to estimate ratios of geometric means and the corresponding 90% CIs.

6.10. Biomarker Analyses

Biomarkers related to treatment, immune response, mechanism of action, and/or cancer will be measured and analyzed. The association of biomarker and clinical outcomes will be assessed via single-marker and/or multi-marker analyses.

6.11. Protocol Violations

All significant protocol violations will be summarized by pre-determined categories (eg, inclusion/ exclusion criteria, noncompliance with protocol procedures, drug dosage/intervention, use of excluded treatments, informed consent/assent process, continuing after meeting withdrawal criteria, or other). These violations will include deviations which can be identified

programmatically and those which can only be identified by the clinical research associate (CRA) during monitoring.

6.12. Interim Analyses

Because this is a dose-finding study, data will be reviewed on a dose level-by-dose level basis during the dose escalation, until the MTDs are determined. The purpose of these dose level-by-dose level reviews is to evaluate the safety data at each dose level and determine if a DLT has been observed that would suggest MTD has been met or exceeded. The investigators and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data (and PK/PD data were available) as described in the protocol.

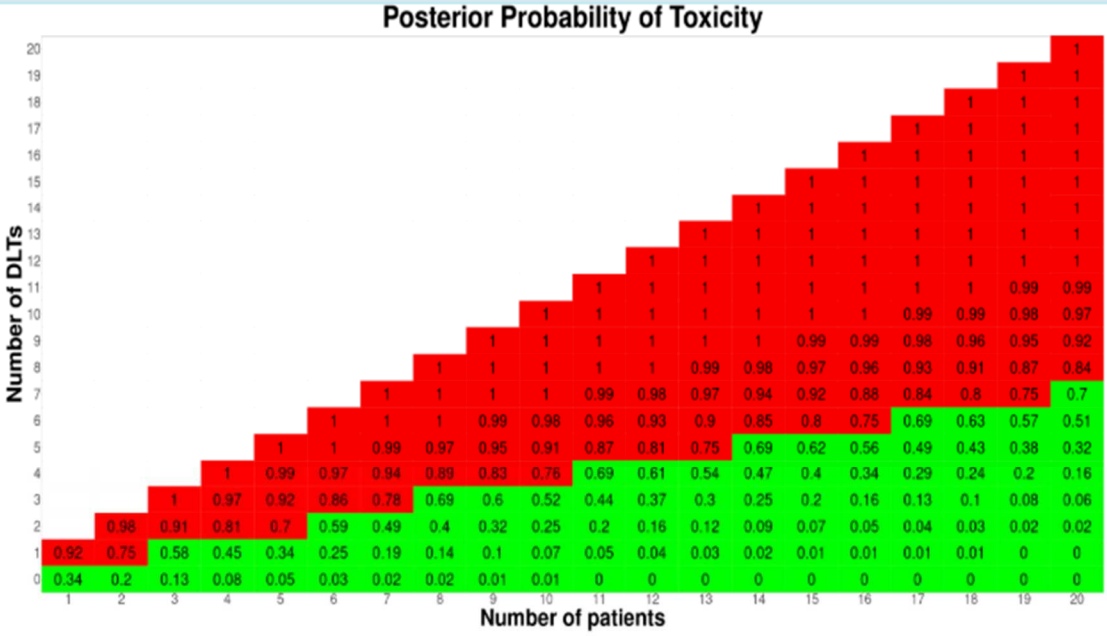
For Phase 1a, after all patients who are deemed evaluable for the assessment of dose levels complete DLT evaluation period or MTD is determined, an interim analysis for safety and PK will be conducted.

For Phase 1b, a safety review will be performed after the first 20 patients across all cohorts are enrolled and treated for 1 cycle, and then every 6 months afterward. The purpose of this safety review is to evaluate the safety and tolerability for each expansion cohort and determine if a dose-limiting equivalent toxicity (DLET) has been observed. For the first 20 patients enrolled into Phase 1b, if in 7 patients or more DLETs are observed, accrual may be temporarily paused, and the available data from Phase 1a and Phase 1b will be analyzed to potentially modify the RP2D or the study. Considerations for stopping recruitment should be given after discussion with the investigator and the Sponsor.

Continuous monitoring for safety and efficacy will occur in Phase 1b and if aggregate data suggest that continued enrollment is unlikely to alter the outcome or present an unreasonable risk to patients, enrollment into any one or all Cohorts 1 through 5 may be stopped.

Bayesian Toxicity Monitoring Plan (U-Design [WWW], version 1.3): Assuming the maximum permissible probability of toxicity is 0.3, the probability threshold for declaring excessive toxicity is 0.7, we may stop the trial if the posterior probability $P(\theta > 0.3|n, x) \geq 0.7$, where θ is the true toxicity rate, n is the current number of patients, and x is the number of DLETs. A precalculated decision table by posterior probability of toxicity (assuming a beta(0.5, 0.5) prior) is shown in Figure JZFA.6.1. From the precalculated table, if the number of patients with DLETs observed among 5, 10, 15, and 20 treated patients is greater or equal to 2 (40%), 4 (40%), 6 (40%), and 7 (35%), respectively, based on the totality of data, accrual may be paused and the available data from Phase 1a and Phase 1b will be analyzed to potentially modify the RP2D or the study.

Table TM: Decision Table by Posterior Probability of Toxicity



Notes:
*1.red denotes the posterior probability of toxicity $Pr(\theta > \theta_{max} \mid Data)$ is larger than θ_T= **0.7** .*
2.green on the opposite.

Figure JZFA.6.1. Bayesian toxicity monitoring decision table.

If it is deemed that enough data are obtained to assess the primary objective and the secondary objectives, a CSR 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 PD biomarkers. All data defined in the protocol will continue to be collected from patients on treatment after the data-cutoff date. These data may be reported separately and the analyses on all patients including these data may not be performed.

6.13. Annual Report Analyses

The following reports are needed as requested for annual reporting purposes.

- Development Safety Update Report:
  - Cumulative Subject Exposure by Age Group and Sex,
  - Cumulative Subject Exposure by Racial Group,
  - Estimated Cumulative Subject Exposure,
  - Exposure Information,
  - Listing of Discontinuations Due to AE During the Reporting Period, and
  - Listing of Subjects Who Died During the Reporting Period.

- Clinical Investigator's Brochure (IB):
  - Listing and Summary of Serious Adverse Event (SAE),
  - Listing and Summary of Death,
  - Listing and Summary of TEAE (and by maximum CTCAE grade),
  - Listing and Summary of Patient Disposition, and
  - Listing and Summary of Study Drug Adjustment.

Other reports may be requested if deemed appropriate for the IB.

6.14. 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

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs will be summarized by: MedDRA PT within treatment group.
- An AE is considered 'Serious' whether or not it is a treatment-emergent adverse event (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,
  - the number of participants who experienced each event term, and
  - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- Adverse event reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

In addition, a participant flow will be created that will describe how many enrolled 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 if the patient is observed until event (PD or death) or the patient had discontinued study treatment and is in follow up at the time of the final analysis. Patients who withdraw consent or are lost to follow-up before the final analysis, or who

are still on treatment at the time of the final analysis will be identified as not completing the study.

7. References

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. https://doi.org/10.1016/j.ejca.2008.10.026

[NCI] National Cancer Institute. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0, DCTD, NCI, NIH, DHHS. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Published: 29 May 2009. Accessed July 15, 2020.

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. *Stat Med*. 2008;27(13):2420–2439. https://doi.org/10.1002/sim.3230

U-Design resources page. U-Design website. Available at: https://udesign.laiyaconsulting.com/phase-2-trial/bayesian-efficacy-toxicity-mon/bayesian-toxicity-mon. Accessed July 15, 2020.

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