JZKA SAP v2

Phase 1/2 Study of LY3499446 Administered to Patients with Advanced Solid Tumors with *KRAS* G12C mutation

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4. Study Objectives

4.1. Primary Objective

Primary Objectives	Endpoints
Phase 1 Dose Escalation: • To characterize the RP2D for LY3499446 when administered alone or in combination with either abemaciclib, cetuximab, or erlotinib.	• DLTs • Assessment of safety including, but not limited to, TEAEs, SAEs, deaths, and clinical lab abnormalities per CTCAE v5.0
Phase 2: • To assess the efficacy of LY3499446 alone or in combination with abemaciclib or erlotinib vs. docetaxel in patients with advanced *KRAS* G12C-mutant NSCLC. • To evaluate the efficacy of LY3499446 alone or in combination with cetuximab in patients with advanced *KRAS* G12C mutant CRC. • To evaluate the efficacy of single-agent LY3499446 in patients with advanced *KRAS* G12C-mutant solid tumors (other than NSCLC and CRC).	• Per RECIST v1.1: o ORR (coprimary for NSCLC cohorts; primary for CRC cohorts and Other tumors cohort) o PFS (coprimary for NSCLC cohorts)

Abbreviations: CRC = colorectal cancer; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; NSCLC = non-small cell lung cancer; ORR = overall response rate; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4.2. Secondary Objectives

Secondary Objectives	Endpoints
Phase 1 Dose Escalation: • To characterize the safety and toxicity profile of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib (NSCLC), or cetuximab (CRC) to patients with advanced solid tumors with *KRAS* G12C mutation. • To assess the PK of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab in patients with advanced solid tumors with *KRAS* G12C mutation. • To assess any antitumor activity of LY3499446 administered as monotherapy and in combination with	• Safety as determined by (including but not limited to) TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (Version 5.0) • Plasma concentration of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab • Per RECIST v1.1: ORR, PFS, DoR, DCR

Secondary Objectives	Endpoints
abemaciclib, erlotinib, or cetuximab in patients with advanced solid tumors with *KRAS* G12C mutation.	
Phase 2: • To assess the efficacy of LY3499446 administered as monotherapy or in combination with abemaciclib or erlotinib in patients with NSCLC tumors harboring *KRAS* G12C mutations, and of LY3499446 administered as monotherapy or in combination with cetuximab in patients with CRC tumors harboring *KRAS* G12C mutations, and LY3499446 administered as monotherapy in patients with solid tumors, other than NSCLC and CRC, harboring *KRAS* G12C mutations. • To characterize the safety and toxicity profile of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab to patients with advanced solid tumors with *KRAS* G12C mutation. • To assess the PK of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab in patients with advanced solid tumors with *KRAS* G12C mutation.	• Per RECIST v1.1: o DoR, DCR, TTR, OS (all cohorts) o PFS (CRC cohorts and Other tumors) • Safety as determined by (including but not limited to) TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (Version 5.0) • Plasma concentration of LY3499446 **a**dministered as monotherapy and in combination with abemaciclib erlotinib, or cetuximab

Abbreviations: CRC = colorectal cancer; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DoR = duration of response; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TTR = time to response.

5. Study Design

5.1. Summary of Study Design

Study JZKA is a first in human, multicenter, open-label dose escalation Phase 1 study, followed by a cohort- and disease-specific randomized Phase 2, and a monotherapy Phase 2 expansion in patients with solid tumors harboring *KRAS* G12C mutations other than NSCLC and CRC. Section 5.1.1 describes the Phase 1 study design, and Section 5.1.2 describes the Phase 2 study design.

5.1.1. Phase 1 Study Design

The Phase 1 portion will enroll patients with *KRAS* G12C mutant solid tumors, where patients will be treated with monotherapy, or in combination with abemaciclib, erlotinib, or cetuximab.

Figure JZKA.5.1 illustrates the Phase 1 study design.

Abbreviations: BID = twice daily; DLT = dose-limiting toxicity; N = number of patients; PK = pharmacokinetics; PO = orally; $RP2D_A$ = recommended phase 2 dose in combination with abemaciclib; $RP2D_C$ = recommended phase 2 dose in combination with cetuximab; $RP2D_E$ = recommended phase 2 dose in combination with erlotinib; $RP2D_M$ = monotherapy recommended phase 2 dose.
Note: Dose de-escalation cohorts will only occur if the initial LY3499446 doses are determined to be intolerable. In addition to the LY3499446 dose levels specified in this figure, intermittent dose levels, or alternative schedules may be explored. Similarly, lower doses or alternative schedules of abemaciclib and erlotinib may be explored below the currently approved doses based on emerging safety data. The totality of data including safety, and PK exposure and the incidence of DLT may help guide evaluating alternative dosing and schedule (e.g. CCI).

Figure JZKA.5.1 Illustration of Phase 1 study design.

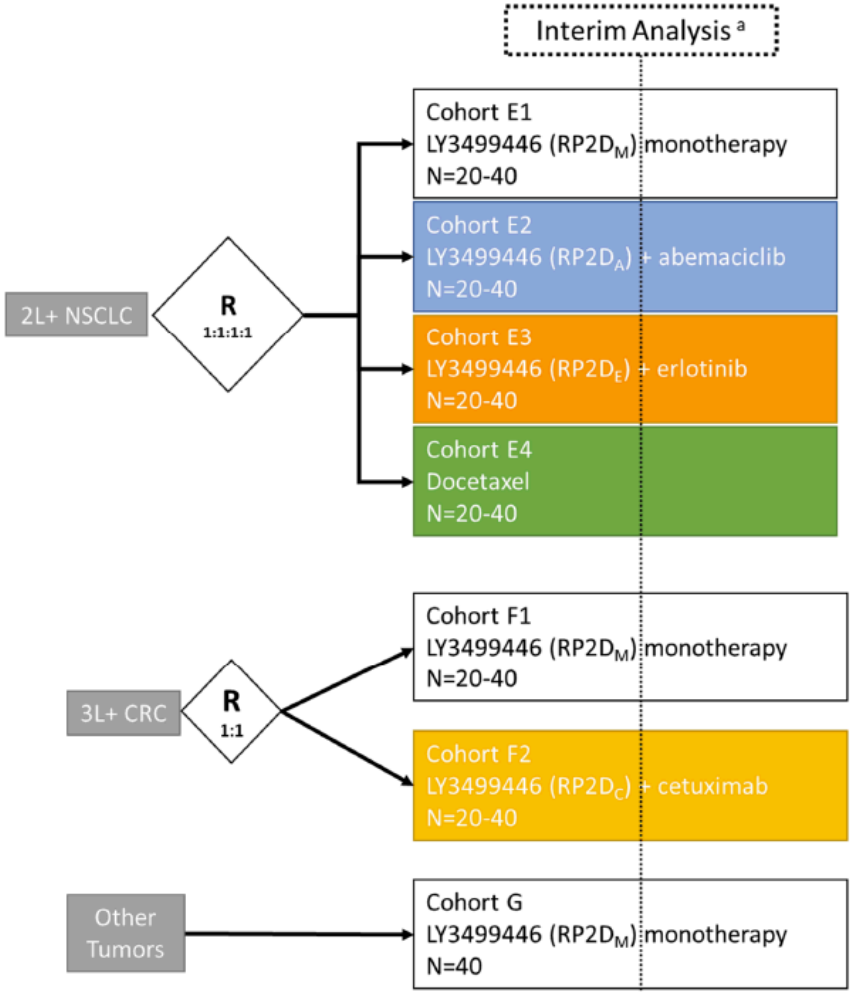
5.1.2. Phase 2 Study Design

Once a recommended phase 2 dose (RP2D) is established, patients with *KRAS* G12C mutant NSCLC will be randomized across 4 cohorts to evaluate for efficacy and safety to select the optimal regimen for further development. This part is a randomized, controlled, Phase 2 design.

For patients with *KRAS* G12C mutant CRC, patients will be randomized to either LY3499446 alone or in combination with cetuximab during the Phase 2 part.

For patients with *KRAS* G12C mutant solid tumors (other than NSCLC or CRC), an expansion cohort of LY3499446 monotherapy will proceed to assess the potential for efficacy once RP2D of LY3499446 monotherapy is established.

Figure JZKA.5.2 illustrates the Phase 2 study design.



Abbreviations: 2L+ = 2 or more lines of therapy; 3L+ = 3 or more lines of therapy; CRC = colorectal cancer; N = number of patients; NSCLC = non-small cell lung cancer; R = randomization; $RP2D_A$ = recommended phase 2 dose in combination with abemaciclib; $RP2D_C$ = recommended phase 2 dose in combination with cetuximab; $RP2D_E$ = recommended phase 2 dose in combination with erlotinib; $RP2D_M$ = monotherapy recommended phase 2 dose.

[a] An interim analysis will take place after approximately 20 patients have been enrolled within each cohort.

Figure JZKA.5.2. Illustration of Phase 2 study design.

5.2. Determination of Sample Size

This study will consist of 2 segments, a Phase 1 dose escalation, and a Phase 2 evaluation of clinical activity. The Phases 1 and 2 segments will each evaluate both monotherapy and combination regimens.

Phase 1 segment

The dose escalation phase will initially evaluate doses in sequentially opened cohorts, with the possibility to explore additional immediate doses or schedules. Dose escalation will implement

An interim analysis will be conducted within each cohort once approximately 20 patients have been enrolled in each arm and evaluated for response per RECIST v1.1. Patients who do not complete an on-treatment or poststudy treatment assessment will be considered nonresponders for analysis purposes and will not be replaced. After the interim, enrollment will continue in the remaining arms until at least 20 additional patients are enrolled in each treatment arm.

With a 1-sided significance level of 0.10, we have 80% statistical power to detect a 20% difference in response rate (assuming LY3499446 monotherapy: 35% versus control: 15%) with approximately 40 patients per arm. With the same 1-sided significance level of 0.10, we have >99% statistical power to detect a 40% difference in response rate (assuming LY3499446 combination: 55% versus control: 15%) with approximately 40 patients per arm.

For the single-arm Cohort G, with a 1-sided significance level of 0.10, we have 85% statistical power to detect a response rate difference of 10%, assuming a historical control rate of 5% and a response rate of 15% under the alternative.

5.3. Method of Assignment to Treatment

The Phase 2 part of study JZKA will implement a randomization design to mitigate the selection bias in allocating patients with NSCLC or CRC to either monotherapy or combination therapies. Patients enrolled into the Phase 2 NSCLC and CRC cohorts will be stratified by the following factors:

- NSCLC patients
    - Lung only metastases versus others
    - Co-occurring mutations KRAS G12C + P53 (KP) versus KRAS G12C + KEAP1 or KRAS G12C + LKB1 (KL) versus others (K)
- CRC patients
    - Sidedness of the tumor (right versus left)
    - Sites of metastases (1 versus 2 versus >2)

Randomization will occur using an Interactive Web Response System (IWRS). Assignment to treatment groups will be determined by a computer-generated random sequence.

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 (e.g., TAFFY, BEACH) 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 and analysis populations are outlined in Table JZKA.6.1.

Table JZKA.6.1. Data Handling Conventions and Analysis Populations

Term	Definition or Rule
Relative Study Day	The **study day of a safety event or assessment** will be calculated as: • the difference between the date of the event or assessment and the date of first dose plus 1 for all events or assessments occurring on or after the day of first dose. For example, if an event occurs on 08JUN2017 and the date of first dose was 06JUN2017, the study day of the event is 3. • the difference between the date of the event or assessment and the date of first dose for all events or assessments occurring before the day of first dose. For example, if an event occurs on 05JUN2017 and the date of first dose was 06JUN2017, the study day of the event is -1.
	The **study day of an efficacy event or assessment** will be calculated as: • the difference between the date of the event or assessment and the date of randomization plus 1 for all events or assessments occurring on or after the date of randomization. • the difference between the date of the event or assessment and the date of randomization for all events or assessments occurring before the date of randomization.
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.

Term	Definition or Rule
Baseline	The **baseline value of a safety assessment** is the last value observed prior to the first dose. This may occur on the day of first dose.
	The **baseline value of an efficacy assessment** is the last value observed prior to the date of randomization. If a patient's first assessment occurs after randomization but prior to the first dose, this assessment will be used as the baseline.
Entered	All participants who sign informed consent
DLT evaluable	All patients enrolled in the dose escalation phase (Phase 1) who either complete 3 weeks of follow-up and at least 80% of treatment doses or discontinue treatment prior to 3 weeks due to a DLT.
Randomized (ITT)	(Phase 2 portion only). All patients with either CRC or NSCLC who are randomized to a treatment regimen, regardless of whether they take any study drug.
PK evaluable	All enrolled patients who have at least 1 postbaseline evaluable PK sample.
Safety	All participants who take at least 1 dose of study treatment. Participants will be included in the treatment group corresponding to their initial dose of study treatment, even if it is not the treatment to which they were assigned. In the event of a treatment error, participants will be analyzed according to the treatment they actually received. "Enrolled" population also refers to the "Safety" population in this study.
Per-Protocol	ITT (randomized) patients who received any study therapy and did not have any important protocol deviations that could potentially affect the efficacy conclusion.
Phase 1	All patients assigned to a treatment cohort during the dose escalation (Phase 1) portion of the study.
Phase 2	All patients randomized to treatment during the Phase 2 portion of the trial (NSCLC and CRC cohorts), regardless of whether the cohort to which they are assigned is closed during or at the end of the Phase 2 portion of the study or continues to Phase 3. All patients enrolled to the "Other Tumors" cohort (nonrandomized).
Screen Failures	Patients who have signed informed consent, do not meet eligibility criteria and are not enrolled.

Abbreviations: CRC = colorectal cancer; DLT = dose-limiting toxicity; ITT = intent-to-treat; NSCLC = non-small cell lung cancer; PK = pharmacokinetic(s).

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. Additional exploratory analyses will be conducted as deemed appropriate.

6.2. Adjustments for Covariates (Phase 2 Only)

As supportive analysis, the primary PFS endpoint in Phase 2 will also be analyzed adjusting for potential prognostic factors, including all stratification factors and variables identified for subgroup analyses. See Section 5.3 for a list of stratification factors for the NSCLC and CRC cohorts.

6.3. 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.

General rules for imputing dates related to AE or concomitant therapy:

- Onset date of an AE or start date of a concomitant therapy:
    - If only the day is missing, the date will be set to:
        - First day of the month that the event occurred, if the onset yyyy-mm is after the yyyy-mm of first study treatment.
        - The day of the first study treatment, if the onset yyyy-mm is the same as yyyy-mm of the first study treatment.
    - If both the day and month are missing, the complete date will be set to:
        - January 1 of the year of onset, if the onset year is after the year of the first study treatment.
        - The date of the first dose, if the onset year is the same as the year of the first study treatment.
- Resolution date of an AE or end date of a concomitant therapy:
    - If only the day is missing, the date will be set to the last day of the month of the occurrence.
    - If both the day and month are missing, the date will be set to December 31 of the year of occurrence. If a date is completely missing, then the AE will be considered treatment-emergent. In case of additional therapies, the therapy will be considered concomitant.

General rule for imputing other dates: If a date variable is needed for an analysis, use the following general rule to impute incomplete date:

- If the date has no missing year and month but the day is missing, then assign Day 1 to the day.
- If the date has no missing year, but has missing month, then assign January to the month.

However, after imputation, check if the imputed date is logically consistent with other relevant date variable(s) and make appropriate correction if necessary. For example, if a visit start date

was May 10, 2008 and a tumor assessment date was May xx, 2008 (missing day) but it was known that it occurred after that visit, then after imputation, the tumor assessment date became May 01, 2008. In this case, the imputed tumor assessment date should be compared to the visit start date and then corrected to be the visit start date, May 10, 2008.

Safety analysis: The following rule for missing data processing will apply for safety analysis:

- Missing classifications concerning study medication relationship will be considered as related to study medication (both components).
- If the AE onset date is missing or partial, the date will be compared as far as possible with the date of first dose of study medication when determining whether or not the AE is present at baseline. In this case, the AE will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first dose of study medication.

Time-to-event analysis: All censored data will be accounted for using appropriate statistical methods. See Section 6.11 for details.

6.4. Multicenter Studies

The Phase 1 portion of study JZKA is multicenter and open-label.

The NSCLC and CRC cohorts in Phase 2 portion of study JZKA is multicenter, open-label and randomized. Investigative center was not a stratification factor because the large number of investigative centers would break down the intended balance within each combined stratification level by the stratified randomization method. It will not be included as a covariate in any covariate-adjusted analysis because the large number of investigative centers in this study cannot be practically incorporated into such analysis.

The "Other Tumors" cohort (other than NSCLC and CRC) in Phase 2 portion of study JZKA is multicenter and open-label.

6.5. Multiple Comparisons/Multiplicity

Comparative analyses will be done for Phase 2, Cohorts E1 through E4 (NSCLC), and separately for Phase 2 Cohorts F1 and F2 (CRC). Formal multiple comparison adjustment will be done for the NSCLC cohorts only relative to the active control arm.

6.6. Use of an "Efficacy Subset" of Patients

The Phase 1 portion of study JZKA aims to characterize the RP2D for LY3499446 when administered alone or in combination with either abemaciclib, cetuximab, or erlotinib. Patients that are used for dose recommendation and final MTD determination by the mTPI-2 method must be **DLT-evaluable** (see Table JZKA.6.1 for the population definitions). DLT non-evaluable patients may be replaced to ensure sufficient number of patients are tested for DLT at any given dose level.

Safety analyses for study JZKA are based on the **safety population**.

Efficacy analyses for study JZKA will be done based on the following populations:

- For non-randomized cohorts (cohorts in Phase 1 and Cohort G in Phase 2), the **safety population** will be used.
- For randomized cohorts (NSCLC and CRC cohorts in Phase 2), the **intent-to-treat (ITT) population** will be used.

Per-protocol analyses for study JZKA will be performed based on the **per-protocol population** *only if* study JZKA is intended for registration.

6.7. 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 (Phase 1: patients who receive 1 cycle of study dose or are evaluable for DLT; Phase 2: patients who die while on study (either on treatment or during long-term follow-up), or still on study at study completion), or discontinuing (overall and by reason for discontinuation of LY3499446). Reason for discontinuation from both the study treatment and the study will be summarized by predetermined categories.

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

6.8. Patient Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target patient population. A summary of baseline patient and disease characteristics, historical diagnoses, pre-existing conditions, and prior therapies will be reported using descriptive statistics.

6.9. Treatment Compliance

Study treatment compliance for LY3499446, abemaciclib, and erlotinib will be assessed as the proportion of treatment that is actually taken, relative to what is expected, after accounting for protocol-defined dose adjustments. Study treatment taken will be derived from the difference between the total number of capsules/tablets dispensed and returned over the course of the patient's treatment. The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by treatment arm.

Docetaxel and cetuximab will be intravenously administered only at the investigational sites, so patient compliance is ensured.

6.10. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use

- Dates of administration including start and end dates

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

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.

6.11. Efficacy Analyses

6.11.1. Efficacy Definitions

The following definitions for efficacy endpoints will be used:

Overall response rate (ORR) is the proportion of patients who achieved a CR or PR out of all patients treated. Tumor responses will be measured and recorded using RECIST v1.1 guidelines (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 sample method that was used at baseline. Confirmation of CR or PR is required per RECIST v1.1.

Disease control rate (DCR) is defined as the proportion of patients who achieved a best overall response (BOR) of confirmed CR, confirmed PR, or 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.

Duration of response (DOR) is defined as the time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or objective progression is observed, per RECIST v1.1 criteria, or the date of death from any cause in the absence of objectively determined disease progression or recurrence. Duration of SD will be calculated only for patients with the best response of SD. It is measured from the date of start of treatment to the date of first progression of disease or the date of death due to any cause, whichever is earlier. For each patient who is not known to have died or to have had a progression of disease as of the data-inclusion cut-off date, duration of SD 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) will be defined as the time from study enrollment (for non-randomized cohorts)/the time from randomization (for randomized cohorts) to the first observation of a PD overall response or death without documented disease progression per RECIST v1.1 criteria. Patients not known to have either of these events will be censored. A full description of censoring rules is described below:

PFS Event/Censoring Scheme

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 tumor assessment, per RECIST v1.1 criteria, or date of randomization (whichever is later)[a]
Unless		
No baseline radiologic tumor assessment available	Censored	Date of randomization
No adequate postbaseline tumor assessment available and death reported after 2 scan intervals following randomization[a,b]	Censored	Date of randomization
Tumor progression or death documented immediately after 2 or more scan intervals following last adequate tumor assessment or randomization (whichever is later)[a,b]	Censored	Date of last adequate tumor assessment, per RECIST v1.1 criteria, or date of randomization (whichever is later)[a]
New therapeutic anticancer treatment started and no tumor progression or death within 14 days	Censored	Date of last adequate radiological assessment prior to start of new therapeutic anticancer therapy +14 days, or date of randomization, whichever is later[a]

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SD = stable disease.

[a] Adequate tumor assessment per RECIST v1.1 criteria refers to an assessment with one of the following responses: CR, PR, SD, or PD.

[b] Refer to the statistical analysis plan for the definition of 2 scan intervals, including any adjustment for scan window.

Overall survival (OS) is defined as the time from study enrollment (for non-randomized cohorts)/the time from randomization (for randomized cohorts) to death from any cause. Patients alive at the end of the study, who have withdrawn from the study, or who are lost to follow up will be censored on their last known alive date.

6.11.2. Efficacy Analyses for Phase 1

There is no primary efficacy endpoint for the Phase 1 portion of the study, as the primary objective is to determine an RP2D, based on the incidence of DLTs and totality of data (including, but not limited to, PK, target occupancy, and clinical response data). Antitumor activity of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab will be evaluated (secondary objective).

6.11.3. Efficacy Analyses for Phase 2

6.11.3.1. Primary Analyses

The primary analysis will be an evaluation of whether any of the treatment regimens are likely to provide a clinically relevant level of activity. This will be based on an evaluation of the ORR within each treatment arm, and evaluation of PFS in the NSCLC cohorts. Primary efficacy assessment will be based on an independent review of imaging data. Comparative analyses will be done for Phase 2, Cohorts E1 through E4 (NSCLC), and separately for Phase 2 Cohorts F1 and F2 (CRC).

At the first interim analysis (approximately 20 patients enrolled in each arm), a determination will be made whether any of the treatment arms may be dropped due to limited clinical activities. An integrated benefit-risk assessment from other data such as DOR, PK, target occupancy, tolerability, and safety will also be used to determine if a treatment arm should be stopped early due to futility. Otherwise, approximately 20 additional patients will be randomized or enrolled to each of the remaining treatment arms to confirm the efficacy signals. Analysis of the Phase 2 ORR and PFS will be performed after all patients randomized to an arm have had the opportunity of having at least 3 months (for ORR evaluations) or 6 months (for PFS evaluations) of follow-up. An updated analysis will be performed when DoR and PFS data are mature (e.g., 60% PFS events are observed).

Enrollment may be discontinued due to futility if the response rate (confirmed and unconfirmed) in the first 20 patients enrolled in any one arm is less than:

- 20% for arms E1, E2, or E3, and
- 10% for arms F1 or F2

6.11.3.2. Secondary Analyses

Assessments of PFS (CRC and Other Tumors cohorts), DoR, DCR, TTR and OS (all cohorts) in Phase 2 will be performed as secondary analyses. Data from Phase 1 subjects will be summarized within each treatment cohort, but comparisons between cohorts will not be made. Data from Phase 2 subjects will be summarized within treatment arms. Comparisons between treatment arms will be made within tumor type. Survival rates at various time points (e.g., at 3, 6, 9, and 12 months), 75%, median, and 25% survival times will be reported, including differences between arms and their 95% confidence interval.

Progression-free survival will be compared between treatment arms using a stratified log-rank test, stratified by the randomization strata. The corresponding HR between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by randomization strata. Progression-free survival curves, median PFS, and PFS rates at various time points with 95% confidence interval for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958).

Symptomatic deterioration (i.e., symptomatic progression that is not confirmed per RECIST v1.1) will not be considered as tumor progression.

6.12. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

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

Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of the study drug and have sufficient samples collected to allow the estimation of LY3499446 PK parameters.

Pharmacokinetic parameter estimates for LY3499446 will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be maximum concentration and area under the concentration-time curve ($AUC_{[0\text{-tlast}]}$, $AUC_{[0\text{-}\infty]}$) of LY3499446. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

Additional analyses such as population PK analyses may also be conducted if deemed appropriate. Other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global PK management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

Pharmacokinetic/pharmacodynamic analyses may be conducted to explore exposure-response relationships between LY3499446 concentrations in systemic circulation and various pharmacodynamic measures or clinical outcomes.

Plasma concentrations of erlotinib, abemaciclib and its metabolites, and serum concentrations of cetuximab at different time points will be summarized by descriptive statistics.

6.13. Safety Analyses

All patients who receive at least 1 dose of any study therapy will be evaluated for safety and toxicity.

Safety analyses will include summaries of the following:

- DLTs at each DL
- AEs, including severity and possible relationship to study drug
- DLT-equivalent AEs, including severity and possible relationship to study drug
- SAEs, including possible relationship to study drug
- AEs leading to dose adjustments
- discontinuations from study treatment due to AEs or death
- treatment-emergent abnormal changes in laboratory values
- treatment-emergent abnormal changes in vital signs and ECGs

6.13.1. Extent of Exposure

The following exposure-related variables will be reported using summary statistics (number of patients, mean, and standard deviation) by treatment group:

- exposure: duration of treatment; number of cycles received; number of patients completing ≥1 cycle, ≥2 cycles, …, ≥6 cycles, and mean, SD; number of patients with dose adjustments: dose reduction, dose delay, and dose omission;
- reasons for dose adjustments

The following exposure-related variables will be reported using summary statistics (number of patients, mean, SD, median, 1st and 3rd quartiles, minimum, and maximum) by treatment group:

- dose intensity: cumulative dose; weekly dose intensity; relative dose intensity, overall weekly dose intensity, overall relative dose intensity

Details of study drug administration will be included in patient listings.

6.13.2. Adverse Events

The most current version of MedDRA at time of analysis will be used when reporting AEs by MedDRA terms. Unless otherwise specified, when summarized by PT, AEs will be presented in decreasing frequency of PT; when summarized by System Organ Class (SOC) and PT, AEs will be presented in decreasing frequency of PT within SOC. If more than 1 AE is recorded for a patient within any SOC or PT term, the patient will only be counted once on the most severe grade and the closest relationship to treatment.

6.13.2.1. Overall Summary of Adverse Events

An overall summary of AEs will be provided to summarize the following categories using frequency counts and percentages:

- patients with at least 1 TEAE, treatment-emergent serious adverse event (TE-SAE), Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 and above
- patients with AEs that led to death (on study, within 30 days after treatment discontinuation)
- patients with AEs that led to discontinuation and SAEs that led to discontinuation

The summary will be provided for regardless of study drug causality, and repeated for events deemed by the investigator to be related to study treatment. Comparison between the treatment groups will be performed using Fisher's exact test.

6.13.2.2. Treatment-Emergent Adverse Events

The following summaries of TEAEs will be provided (*repeat for events deemed by the investigator to be possibly related to study medication, and repeat for events grade 3 and above; †include consolidated summary):

- by PT*†
- >5% in any treatment arm by PT*†
- by SOC and PT*
- by maximum CTCAE grade and by PT*†

A patient listing of all AEs will be provided.

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

Reasons for deaths (study disease, AE [any study drug-related, investigational drug-related, procedural related]) will be summarized separately for 1) all deaths, 2) on study treatment deaths, within 30 days after treatment discontinuation, and more than 30 days after treatment discontinuation.

Serious adverse events will be summarized by SOC and PT, by PT and repeated for events deemed by the investigator to be possibly related to study medication, with consolidated summary performed if needed. A listing of SAEs will be produced.

In addition, the following analyses will be performed (*repeated for events deemed by the investigator to be possibly related to study medication, †include consolidated summary):

- adverse events leading to death by PT†
- adverse events leading to study treatment discontinuations by PT†
- adverse events leading to study treatment dose modification by PT†
- adverse events of special interest by PT* (if applicable)
- liver injury/failure
- listing of deaths
- listing of AESIs

6.13.4. Clinical Laboratory Evaluation

The severity of laboratory results will be classified according to CTCAE Version 5.0. The shifts in CTCAE toxicity grading from baseline to worst grade postbaseline (first dose up to 30 days after the last dose of study treatment) will be produced.

A patient listing of all laboratory data will be provided with a flag for values outside of the laboratory normal range as well as investigator site, patient identifier, age, gender, race, and visit.

6.13.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

A summary of ECOG performance status at each scheduled time point will be provided. Actual value and change from baseline for vital sign measurements will be summarized at each assessment time point using summary statistics. Electrocardiogram (ECG) measurements will be summarized at each assessment time point using summary statistics. Listings of ECOG performance status, vital signs, ECG data will be provided.

6.14. Subgroup Analyses

Efficacy analyses will be performed for the following potential prognostic subgroup variables:

- All baseline stratification factors
- age (<65 years versus ≥65 years)
- race (White versus Asian versus Other)
- gender (females versus males)
- ECOG performance status (0 versus 1)

If a level of a factor consists of fewer than 20% of randomized patients, analysis within that level will be omitted. The treatment effect within each subgroup will be summarized, and, separately, across subgroups with a test of interactions of subgroups with treatment performed. Estimated HRs and CIs for the within subgroup analyses will be presented as a forest plot along with p-values for tests of interactions between subgroup variables and treatment.

Other subgroup analyses not specified in the SAP may be performed as deemed appropriate. If any safety analyses identify important imbalances between arms, subgroup analyses of these endpoints may be performed.

6.15. Protocol Violations

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

The Per-Protocol population is a subset of the ITT population and consists of the randomized and treated patients who do not have an important protocol deviation (IPD, that is, clinically important and potentially impact efficacy evaluations). The Trial Issue Management Plan (TIMP) details the IPDs and indicates which deviations are programmable or not.

6.16. Interim Analyses and Data Monitoring

In the Phase 1 portion of this study, data will be reviewed for safety on a cohort-by-cohort basis during the study, until the MTDs (or the highest DLs if MTDs are not reached) are determined for each treatment part. The purpose of these cohort-by-cohort reviews is to evaluate the safety data at each DL 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 as described in this protocol. Before opening of the randomized Phase 2 portion of this study, a formal interim analysis including all Phase 1 data will be performed to conclude the safety profiles and RP2Ds.

The Phase 2 portion of Study JZKA comprises more than 3 cohorts and may warrant additional considerations to ensure patient safety.

Lilly has systematic and robust internal processes in place that ensure safety surveillance of development compounds in line with expectations of Regulatory Agencies. This includes processes with clearly described roles and responsibilities that are owned by Lilly's Global Patient Safety organization. These processes are designed to monitor the evolving safety profile (i.e., review of cumulative SAEs and other important safety information) by designated cross-functional teams in a timely manner at predefined intervals or on an ad-hoc basis. In addition, a dedicated process may be used to perform unblinded comparisons of event rates for SAEs, as necessary.

This system ensures that the accumulating safety data derived from individual and multiple trials across a development program are reviewed on a regular basis and that important new safety information such as the need for protocol modification or other relevant safety-related material is identified and communicated to regulators and investigators appropriately and in a timely fashion. An internal review of aggregate safety data occurs on at least a quarterly basis or more frequently, as appropriate. Any serious adverse reactions (SARs) are reported within the required timeline for expedited reporting.

In addition to annual periodic safety updates and to further inform investigators, a line listing reports of SUSARs is created and distributed to investigators on a biannual (twice yearly) basis. Any significant potential risk/safety concerns that are being monitored, as well as any results being reported in other periodic reports for the compound, SAC decisions, and other significant safety data (for example, nonclinical, clinical findings, and removal of SARs) are included in the report.

In the Phase 2 portion of this study, a safety review will be performed after the first 20 patients across all cohorts (NSCLC, CRC, and Other Tumors) are enrolled and treated for 1 cycle, and then every 6 months afterward.

In the Phase 2 portion of this study:

- For the NSCLC cohorts, an interim analysis of safety and efficacy is planned after approximately 20 patients in each cohort are treated and have completed 2 cycles or have discontinued before the first postbaseline tumor assessment. At this first interim analysis, the totality of data (including, but not limited to, safety and preliminary efficacy) will be used to determine if any of the treatment cohorts (E1, E2, E3) may be dropped due to limited clinical activities relative to the active comparator (E4). After the data cutoff date of this interim analysis, approximately 20 additional patients will be randomized to each of the remaining treatment arms to confirm the efficacy signals. Enrollment will be paused until the interim analysis has been completed.
- For the CRC cohorts, an interim analysis of safety and efficacy is planned after approximately 20 patients in each arm are treated and have completed 2 cycles or have discontinued before the first postbaseline tumor assessment. Enrollment will be paused until the interim analysis has been completed. Depending on the preliminary efficacy

signal and totality of data, 1 arm may be dropped for futility and an additional 20 patients will be enrolled into the remaining arm. If no meaningful difference in efficacy or safety is observed in between the 2 arms, 40 additional patients may be randomized at a 1:1 ratio, leading to approximately 80 total randomized patients (40 in each arm). Depending on the magnitude of clinical response observed in terms of durable objective responses, Study Protocol JZKA may be amended to provide for a more robust assessment of benefit/risk in this setting.

- For the Other Tumors cohort, an interim of safety and efficacy is planned after approximately 20 patients are treated and have completed 2 cycles or have discontinued before the first postbaseline tumor assessment. The trial will continue to enroll an additional 20 patients for the final analysis.

The interim analyses may be combined if they are expected to occur within a similar timeframe; interim analyses may also be combined with any prespecified safety review or annual reporting (such as an update to the IB or Development Safety Update Review, etc.).

6.17. 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
- Listing of Subjects Who Died During the Reporting Period

Clinical 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
- Listing and Summary of Study Drug Adjustment

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

6.18. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

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

- An adverse event is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

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

[CTCAE] Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 5.0, DCTD, NCI, NIH, DHHS. 2017.

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