

Statistical Analysis Plan I1D-MC-JIAE v4

A Randomized, Double-Blind, Placebo-Controlled Phase 1b/2 Study of LY2228820, a p38 MAPK Inhibitor, plus Gemcitabine and Carboplatin versus Gemcitabine and Carboplatin for Women with Platinum-Sensitive Ovarian Cancer

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1. Statistical Analysis Plan for Protocol I1D-MC-JIAE: A Randomized, Double-Blind, Placebo-Controlled Phase Ib/2 Study of LY2228820, a p38 MAPK Inhibitor, plus Gemcitabine and Carboplatin versus Gemcitabine and Carboplatin for Women with Platinum-Sensitive Ovarian Cancer

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p38 Mitogen-Activated Protein Kinase (MAPK) Inhibitor (LY2228820)

This trial is a Phase Ib dose escalation study followed by a randomized, double-blind, placebo-controlled Phase II study of a p38 MAPK inhibitor administered in combination with gemcitabine/carboplatin to patients with platinum-sensitive ovarian cancer.

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Protocol I1D-MC-JIAE
Phase 1b/2

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to unblinding.

Statistical Analysis Plan (SAP) Version 2 was updated per protocol (c) and approved before the first interim analysis in Phase 2.

The overall changes and rationale for the changes incorporated in Version 2 are as follows:

- Randomization scheme updated: another randomization factor was added.
- Interim analysis for Phase 2 updated: the third interim will examine safety and PK only, and the fourth interim was removed.
- Determination of sample size updated.

Statistical Analysis Plan (SAP) Version 3 was updated and approved before the primary outcome lock and any aggregated unblinding of efficacy data.

The overall change and rationale for the changes incorporated in Version 3 are as follows:

- Added a sensitivity analysis of PFS, with patients who start new anticancer therapy censored at their last assessment prior to doing so.
- Specified that the analysis of OS that will be conducted at the time of final analysis of PFS will serve as a futility interim analysis to inform further conduct of the study, and provided the statistical assumptions for the interim analysis.

Statistical Analysis Plan (SAP) Version 4 was updated and approved after the primary outcome lock and before the final analysis.

- Added a statement in the unblinding plan that topline result from the primary outcome analysis may be shared with sponsor personnel, patients, and site personnel.

4. Study Objectives

4.1. Primary Objective

The primary objective of the Phase 1b portion of this study is to determine the recommended Phase 2 dose of LY2228820 that can be safely administered in combination with gemcitabine and carboplatin.

The primary objective of the Phase 2 portion of this study is to compare the progression-free survival (PFS) in patients treated with LY2228820 plus gemcitabine and carboplatin versus placebo plus gemcitabine and carboplatin.

4.2. Secondary Objectives

The secondary objectives of the study are to evaluate:

- Change in tumor size, CA125 (serum biomarker for ovarian cancer), overall response rate, and overall survival (OS)
- Safety and tolerability of the combination: LY2228820 plus gemcitabine and carboplatin
- Pharmacokinetics (PK) of LY2228820, gemcitabine and its metabolite (dFdU), and carboplatin
- Biomarkers related to p38 MAPK pathway activity and the pathogenesis of ovarian cancer
- Patient-reported outcomes for patients enrolled in the Phase 2 portion of the study.

5. A Priori Statistical Methods

5.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) or its designated third party organization (TPO).

No formal statistical analysis will be performed on the Phase 1b portion of the study in which the primary objective is to assess safety and tolerability of LY2228820 plus gemcitabine and carboplatin. Efficacy analyses for the Phase 2 portion of the study will be conducted on the full analysis set. The analysis populations are defined as below.

- The full analysis population includes patients from Phase 2 portion receiving at least 1 dose of LY2228820/placebo.
- Safety population is defined as all patients who receive at least 1 dose of LY2228820/placebo.
- The PK population consists of patients who have received at least 1 dose of study drug and have had sufficient post-dose samples collected to allow estimation of the PK parameters.
- The pharmacodynamics (PD) population consists of patients who have received at least 1 dose of study drug and have undergone PD assessments at baseline and at least 1 post-baseline visit.

All tests of treatment effects will be conducted at a 1-sided alpha level of 0.2, unless otherwise stated. All confidence intervals (CIs) will be given at a 2-sided 90% level, unless otherwise stated.

Starting from protocol (c), an additional stratification factor is included for patient randomization (see Section 8.1.2 of the protocol). For patients who were randomized to Phase 2 before the approval of protocol (c), the value of maintenance therapy as a part of or after a first line platinum regimen for these patients will be derived to “not collected.” Patients who consent to protocol (c) will be randomized using the following stratification factors: time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months), Eastern Cooperative Oncology Group (ECOG) performance status (0 and 1 versus 2) and maintenance therapy as a part of or after a first line platinum regimen (yes versus no).

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

Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be justified and described in this plan. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR).

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

This study will be considered complete following final validation and authorization to “lock” the database after the protocol-specified objectives have been met. The Lilly clinical research physician (CRP) will notify investigators in the event of study closure.

The following definitions for endpoints only applies to the Phase 2 part of the study, other than safety endpoints.

5.1.1. Primary Endpoints

The primary outcome of this trial is PFS, which is the time from the date of randomization to the date of objective progression or the date of death due to any cause, whichever is earlier. The censoring is taken in the following order:

- If a patient does not have a complete baseline disease assessment, then the PFS time will be censored at the enrollment date, regardless of whether or not objectively determined disease progression or death has been observed for the patient; otherwise,
- If a patient is not known to have died or have objective progression as of the data inclusion cutoff date for the analysis, the PFS time will be censored at the last complete objective progression-free disease assessment date.

5.1.2. Secondary Endpoints

Secondary endpoints in this trial include change in tumor size (CTS), CA125 (ovary cancer serum biomarker), response rate (RR), and overall survival (OS).

Change in tumor size: the log ratio of tumor size at the end of Cycle 2 to tumor size at baseline will be calculated for each patient. Tumor size is the sum of tumor measurements across all target tumors at a given evaluation (Response Evaluation Criteria In Solid Tumors [RECIST] criteria).

CA125: log-transformed CA125 data will be analyzed using a mixed-effect model repeated measures analysis.

Overall survival: the time from the date of randomization to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cutoff date for the analysis, OS will be censored for that analysis at the date the patient was last known to be alive.

Response rate: the total number of patients with a best response of confirmed complete response (CR) or partial response (PR), based on RECIST version 1.1, divided by the total number of randomized patients.

5.1.3. Safety Endpoints

Safety measures that will be used in this trial include adverse events (AEs) from the time of study entry until at least 30 days after discontinuation of study therapy.

Any clinically significant findings from electrocardiograms (ECGs), labs, vital sign measurements, or other procedures that result in a diagnosis should be reported by the investigator as AEs. All AEs will be graded at each visit according to Common Terminology

Criteria for Adverse Events (CTCAE) Version 4.0, along with the investigator's assessment of the potential relatedness of each AE to protocol procedure, studied disease state, study drug, and/or drug delivery system.

5.1.4. Health Outcomes

Both time to worsening (TTW) and changes from baseline in dimensions of the health-related quality of life (HRQoL) using FACT-O will be assessed in this trial.

5.2. Patient Disposition

A detailed description of patient disposition will be provided. 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). The patient-level completion is defined as follows: Phase 1b: patient who experiences a dose-limiting toxicity, or completes PK sampling set. Phase 2: patient who is dead due to any cause, or patient who is alive and on study at conclusion, but off treatment. Reasons for patients who are not completed will be summarized. A summary of all important protocol violations will be provided. Important violations from the protocol will include protocol inclusion/exclusion criteria violations, informed consent violations, prohibited concomitant medications and initiation of post-study drug therapy prior to documented, confirmed disease progression. Number and percentage for each category will be summarized for each treatment arm.

5.3. Patient Characteristics

Patient demographics including age, gender, screening height and weight will be summarized using descriptive statistics. Other baseline disease characteristics that will be summarized include:

- Time from first-line platinum-based therapy to relapse
- Pathological diagnosis
- Disease stage at the time of initial diagnosis
- Pre-existing conditions
- Prior cancer therapies
- Concomitant drugs
- Eastern Cooperative Oncology Group performance status

5.4. Concomitant Therapy

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

5.5. Treatment Compliance

The number of dose omissions, reductions, delays, the number of cycles received, and dose intensity will be summarized for all treated patients per treatment arm.

5.6. Primary Analyses

For the primary endpoint of PFS, the hazard ratio (HR) will be estimated from survival data on all randomized patients using a Cox proportional hazards model with assigned study treatment arm as fixed effect along with cofactors for time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months), ECOG performance status (0 and 1 versus 2) and maintenance therapy as a part of or after a first line platinum regimen (yes versus no versus not collected).

The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curve as well as survival rates at various time points for each treatment group. The stratified log-rank test will be used to compare PFS distributions between treatment groups in Phase 2, using the three randomization factors described above as the stratification factors.

5.6.1. Sensitivity Analysis

A sensitivity analysis using the same statistical methods as the primary analysis will be conducted, with patients who do not have documented progressive disease per RECIST 1.1 criteria prior to the initiation of post-study treatment therapy censored at the last adequate radiological assessment date prior to start of new anticancer therapy or the enrollment date, whichever is later.

5.7. Efficacy Analyses

The primary objective of the Phase 1b portion of this study is to determine the recommended Phase 2 dose of LY2228820 that can be safely administered in combination with gemcitabine and carboplatin. Thus, no formal efficacy analysis is planned for this part of the trial. Any antitumor activity observed will be reported.

The primary objective of the Phase 2 portion of this study is to compare the PFS in patients treated with LY2228820 plus gemcitabine and carboplatin versus placebo plus gemcitabine and carboplatin. To support the primary efficacy analysis, additional efficacy analyses will be performed on change in tumor size, CA125 (serum biomarker for ovarian cancer), overall response rate, and OS.

CA125 data will be log-transformed first and analyzed using a mixed-effect model repeated measures analysis with treatment, time, and treatment-by-time interaction as fixed effects, along with cofactors for time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months), ECOG performance status (0 and 1 versus 2), and maintenance therapy as a part of or after a first line platinum regimen (yes versus no versus not collected). The baseline will be modeled as an observation with a single treatment group.

The log ratio of tumor size at the end of Cycle 2 to tumor size at baseline will be calculated for each patient. Patients who discontinue early but have a post-baseline assessment will not be included. This measure presumably follows a normal distribution and will be compared between treatment groups using a t-test. Analysis of variance will be used to assess the effect of baseline factors on the change in tumor size.

The overall response rate (ORR) is estimated as the total number of patients with a best response of CR or PR, based on RECIST version 1.1, divided by the total number of randomized patients. The efficacy endpoint of overall response rate and its exact 90% confidence interval will be estimated for each treatment arm. The proportion in each treatment arm will be compared using the Chi-square test.

The efficacy analysis on OS will be conducted after all the patients have had the opportunity to have been followed for at least 2 years. The HR will be estimated from survival data on all randomized patients using a Cox proportional hazards model using assigned study treatment arm as fixed effect, along with cofactors for time from completion of first line platinum-based therapy to relapse (6 to 12 months versus over 12 months), ECOG performance status (0 and 1 versus 2) and maintenance therapy as a part of or after a first line platinum regimen (yes versus no versus not collected).

Additional exploratory analyses may be performed as deemed appropriate.

5.8. Pharmacokinetic/Pharmacodynamic Analyses

5.8.1. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on the pharmacokinetic population as mentioned in section 5.1.

The PK parameters for LY2228820 will be computed by standard noncompartmental methods. The C_{max} , AUC, half-life, apparent volume of distribution (V_d/F), apparent clearance (CL/F), and other relevant parameters (such as intercycle accumulation) that can be calculated from the data will be reported. Parameters will be calculated following administration on Day 1 and on Day 10 of Cycle 1 as well as on Day 10 of Cycle 2 for the Phase 1b portion; on Day 3 and on Day 10 of Cycle 1 for the induction part of the Phase 2 portion, and on Day 3 of Cycle 7 for the maintenance part of the Phase 2 portion.

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 Global Pharmacokinetic management.

Providing that data allow in the Phase 1b portion, the pharmacokinetic parameter estimates (C_{max} and AUC) for LY2228820 will be evaluated statistically to delineate the effects of dose proportionality using the methods described previously (Smith et al. 2000). Least-square estimates of geometric means and their corresponding 90% confidence intervals will be provided by dose and with the dose-normalized ratio of geometric means and confidence interval.

The primary PK parameters for gemcitabine, its metabolite (dFdU), and carboplatin that will be used to detect potential drug–drug interaction are the maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from zero to the last measurable time [$AUC_{(0-t_{last})}$], area under the plasma concentration-time curve from 0 to 24 hours [$AUC_{(0-24hr)}$], and area under the plasma concentration-time curve from time 0 to infinity [$AUC_{(0-\infty)}$]. The AUC

values will be calculated by the linear/log trapezoidal method, in which the linear trapezoidal method will be employed up to the t_{\max} , and the log trapezoidal rule will be used for concentrations beyond t_{\max} . Descriptive statistics will be reported for other secondary PK parameters (for example, t_{\max} , CL/F, Vd/F, and terminal elimination half-life).

The 90% CI for the AUC and C_{\max} ratios will be computed to assess the potential effect of LY2228820 on gemcitabine and carboplatin. The ratios will be calculated for the Phase 2 portion for gemcitabine, its metabolite (dFdU), and carboplatin on Day 3 of Cycle 1 in the LY2228820 arm versus the placebo arms.

The 90% confidence interval for the AUC and C_{\max} ratios will be computed to assess the potential effect of gemcitabine and carboplatin on LY2228820. The ratios will be calculated for the Phase 2 portion for LY2228820 on Day 3 of Cycle 1 versus Day 3 of Cycle 7.

In addition to a standard noncompartmental assessment, the plasma LY2228820 data will also be analyzed using nonlinear mixed effect modeling (as implemented in nonlinear mixed effects model [NONMEM]).

All available plasma data from all patients may be analyzed to determine the compartmental pharmacokinetics parameters and between and within patient variability. The drug–drug interaction may also be assessed using this approach using the typical covariates approach.

5.8.2. Pharmacodynamic Analysis

The pharmacodynamic population will be analyzed as mentioned in Section 5.1. Pharmacodynamic data will be documented in the study report by dose. Absolute and percentage change from baseline for PD markers may be summarized by providing the mean, standard deviation, median, minimum, and maximum for each cohort. Data may be log-transformed prior to summarizing if necessary. The interpatient variability in human PD response may also be assessed where appropriate.

5.9. Health Outcome/Quality of Life Analyses

Findings of the FACT-O and compliance with completing the questionnaire will be summarized for all treated patients for the given time points: baseline, each treatment cycle, and discontinuation visit. Frequency distributions, including measures of central tendency and variability, will be calculated for individual items and for the total scale. The TTW variables, including TTW in TOI, will be analyzed using the same methods utilized for other time-to-event variables. All randomized patients with a baseline assessment will be included in the TTW analysis. Clinically important difference thresholds will be used to define the proportion of patients that improve, remain stable, or worsen. The FACT-O scores will be summed at baseline and for each visit in order to calculate changes from baseline mean scores. These data will be compared between the 2 treatment arms. The scores will include the FACT-O total and subscale scores and TOI-O. All randomized patients with baseline and at least 1 post-baseline measure will be included in the change from baseline analysis. Other exploratory analyses may be performed, including longitudinal modeling (for example, repeated measures models and the impact of covariates) and subgroup analysis (for example, age ≤ 70 versus > 70 years, and

subgroups based on ECOG performance status, tumor response status, PFS, and OS). Individual responses, using an a priori responder definition (that is, the individual patient PRO score change over a predetermined time period that should be interpreted as a treatment benefit) will be displayed using the cumulative distribution function of responses between treatment groups.

Exploratory analysis may be performed to assess potential relationships between patient reported symptoms and endpoints of interest such as OS and PFS. Compliance with completing the FACT-O will be summarized.

5.10. Safety Analyses

All safety summaries and analyses will be based upon the Safety Population as defined in Section 5.1.

Overall exposure to study drug, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics. The number of patients with any dose adjustment will be presented for entire treatment period as well as for each cycle. The number of patients with dose reductions, dose delays, or dose omissions will also be summarized, as will the reasons for dose adjustments.

An overall summary of AEs will be provided for AEs deemed by the investigator to be possibly related to study medication, and repeated for events regardless of study drug causality. Incidence rates of these events will be compared between treatment arms using Fisher's exact test.

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline or within 30 days of treatment discontinuation.

The number of patients who experienced a TEAE, SAE, or AE related to study drug, as well as those who died or discontinued from the study due to an AE will be summarized by treatment.

Common Terminology Criteria for Adverse Events version 4.0 will be used to report AEs by CTCAE system organ class, terms, and grades.

Laboratory and nonlaboratory CTCAEs will be summarized by CTCAE term and maximum CTCAE grade, including the total for maximum Grade 3 or higher. These summaries will be provided for events regardless of study drug causality, and repeated for events deemed by the investigator to be possibly related to study medication.

Reasons for death will be summarized separately for on-therapy and within 30 days of last dose of study drug/last visit. All SAEs will be summarized by preferred term.

Hospitalizations and transfusions during the study treatment period or during the 30-day post-discontinuation follow-up period will be summarized by treatment group.

Hematology and chemistry lab results will be summarized and presented using Spotfire. Listings will also be provided for abnormal lab results. Listings and summary tables, or Spotfire outputs of the key ECG parameters will be provided for each day/time combination (heart rate, QTcF, QTcB, RR). Changes from baseline and maximal change from baseline will also be summarized. Listing of vital signs will be provided.

5.11. Subgroup Analyses

There are no planned subgroup analyses. However, exploratory analyses may be performed to generate hypotheses about the efficacy of study therapy in certain subgroups tested in future clinical trials.

5.12. Interim Analysis

All interim analyses for Phase 2 will be conducted under the guidance of an internal assessment committee. The study team will assess data continuously during Phase 1b.

5.12.1. Interim Analysis for Phase 1b

Safety data for all patients will be reviewed continuously throughout this component of the study. One interim analysis is planned for the Phase 1b portion of the study and will be conducted for safety and pharmacokinetics after all patients in Phase 1b have completed at least 1 cycle of study treatment. If the combination maximum tolerated dose (MTD) has been identified prior to completion of the interim analysis and patients are available for Phase 2, with investigator and Lilly CRP approval, those patients will be randomized into the Phase 2 component of the study without delay.

5.12.2. Interim Analysis for Phase 2

Three interim analyses are planned for the Phase 2 portion of the study. The first analysis will be conducted for safety and pharmacokinetics when approximately 30 patients in Phase 2 have completed at least 1 cycle of study treatment. The second interim analysis will be conducted for safety and PK when approximately 60 patients in Phase 2 have completed at least 2 cycles of study treatment. Patient enrollment will continue along with the interim analyses. The third interim analysis will be the futility analysis of OS, which will be conducted at the time of the final analysis of PFS, to inform further conduct of the study.

The Phase 2 interim analyses will be conducted using unblinded data under the guidance of an internal assessment committee.

5.12.2.1. The Third Interim Analysis for Phase 2

Assuming an OS hazard ratio of 0.70 (a median OS of 18 months for the control arm [Pfisterer, et al]), it is predicted that approximately a total of 47 OS events would be observed at the time of the futility interim analysis of OS, and approximately a total of 70 OS events would be observed at the time of final analysis of OS. These numbers of events will provide an approximately 70% statistical power to detect superiority of investigational treatment arm (Arm A) over control arm (Arm B) in OS with the use of a log-rank test and a 1-sided type I error rate of 0.20.

If 47 OS events were actually observed and the observed hazard ratio were greater than 0.88 at the time of the futility interim analysis of OS, then the futility boundary would be crossed and the study could be stopped for futility. A Lan-DeMets spending function will be used to control Type II error rate, which has the flexibility to adjust futility boundary according to the actual number of OS events observed at interim analysis, even if that number is different than the predicted one.

5.13. Determination of Sample Size

The primary objective of the Phase 1b portion of this study is to determine the recommended Phase 2 dose of LY2228820 that can be safely administered in combination with gemcitabine and carboplatin. The sample size for this part of the study is customary and not subject to statistical calculations.

The primary objective of the Phase 2 portion of this study is to compare the progression-free survival in patients treated with LY2228820 plus gemcitabine and carboplatin versus placebo plus gemcitabine and carboplatin. The primary analysis will be performed after 79 PFS events have occurred. Assuming a HR of 0.7, this sample size yields at least 77% power with a false-positive rate of 0.2 (1-sided) using a log-rank test. This assumes exponentially distributed PFS times, median PFS of 8.6 months for the control arm, enrollment duration of 12 months, and follow-up time of 18 months after the last patient is enrolled. Assuming 28% censoring rate of the PFS, a total of 110 patients will be randomized (55 patients in each arm) to achieve 79 PFS events at the primary analysis.

6. Unblinding Plan

The purpose of this unblinding plan is to maintain the scientific integrity of the study. Access to study data will be strictly controlled until the final database lock occurs.

The Phase 1b portion of this study is open-label whereas the Phase 2 portion of this study is double-blind.

Randomization during Phase 2 will occur at each patient's baseline visit using an interactive voice response system (IVRS). Assignment to treatment groups will be determined by dynamic allocation using the method of Pocock and Simon. Only a minimum number of Lilly personnel with the IVRS group will have access to the randomization algorithm and treatment assignments before the study is complete.

To preserve blinding of the study, a minimum number of sponsor personnel will see treatment assignments before PFS and OS analyses are completed. A designated study team member in collaboration with the statistician will be responsible for keeping a running log of individuals given access to any unblinded study data. This log will include the person's name, title, date of unblinding, level of unblinding (that is, group or patient), and purpose of unblinding.

Emergency unblinding for AEs may be performed through an IVRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used only if the patient's well-being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IVRS.

The investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately by telephone.

Every effort will be made to blind both the patient and the investigator to the treatment assignment, but the inadvertent unblinding of a patient may occur. A double-blind study design is known to be imperfect because the potential for individual unblinding exists due to treatment-related signs and symptoms. If a patient or investigator is unblinded, the unblinding will not alone be sufficient cause for that patient to be discontinued from study treatment or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasons to have the patient remain on study treatment. For patients to continue on study treatment in the event of unblinding, the investigator must obtain specific approval from a Lilly CRP for the patient to continue in the study.

Patients and investigators will remain blinded to study treatment with no sharing of efficacy information with sites until PFS analyses are completed. Treatment assignment will be blinded in the reporting database except for a minimum number of sponsor personnel required to perform the interim and final analyses. This will ensure unblinded aggregate efficacy results are not available outside of the Assessment Committee until the time of final data analysis of the primary outcome (PFS). The topline result from the primary outcome analysis, stating whether the primary objective of the study was met as determined by the assessment committee, is

documented in the assessment committee meeting minutes and may be shared with sponsor personnel, patients, and site personnel, given that doing so will induce negligible bias to study conduct and data analyses. Patients and investigators may be unblinded to individual treatment assignments after both PFS and OS analyses are completed.

For this study, there are four planned interim analyses (1 for Phase 1b and 3 for Phase 2). During Phase 2, internal procedures require that interim analyses be conducted under the guidance of an Assessment Committee.

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