

Statistical Analysis Plan I2V-MC-CXAD

A Phase 1a/1b Study of CXCR4 Peptide Antagonist (LY2510924) Administered in Combination With the Anti-PD-L1 Antibody, Durvalumab (MEDI4736), in Advanced Refractory Solid Tumors

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**1. Statistical Analysis Plan :  
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**LY2510924**

This is a multicenter, nonrandomized, open-label, dose-escalation Phase 1a study of LY2510924 combined with MEDI4736 in patients with advanced refractory solid tumors followed by an open-label 2-expansion-arm Phase 1b study in patients with advanced refractory pancreatic cancer and ovarian cancer.

Eli Lilly and Company  
Indianapolis, Indiana USA 46285  
Protocol I2V-MC-CXAD  
Phase 1

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

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### 3. Revision History

SAP Version 1 was approved prior to the first visit when a subject receives study drug or any other protocol intervention.

## 4. Study Objectives

### 4.1. Primary Objective

#### Dose Escalation

The primary objective of the dose-escalation part of this study is to assess the safety and tolerability of LY2510924 SQ daily in combination with durvalumab by identifying dose-limiting toxicities (DLTs) and the maximum-tolerated dose (MTD) of the combination in patients with advanced (metastatic and/or unresectable) solid tumors.

#### Dose Expansion

The primary objective of the dose-expansion part of this study is to assess the safety of LY2510924 SQ daily in combination with durvalumab in patients with advanced pancreatic and ovarian cancers.

### 4.2. Secondary Objectives

- To characterize the pharmacokinetics (PK) of LY2510924 and durvalumab when co-administered
- To characterize the immunogenicity of durvalumab when administered in combination with LY2510924
- To assess the antitumor activity of the combination of LY2510924 and durvalumab in patients with advanced solid tumors

### 4.3. Exploratory Objectives

The exploratory objective of this study is to examine biomarkers, including pharmacodynamic markers, relevant to LY2510924 and durvalumab, including but not limited to, immune cells/immune functioning, drug targets, cancer-related pathways and the disease state, and to correlate these markers with clinical outcome.



## 5. Summary of Study Design

Study CXAD is a multicenter, nonrandomized, open-label, dose-escalation Phase 1a/1b study of LY2510924 combined with MEDI4736.

This Phase 1a/1b study will be conducted in 2 parts. The first part (Phase 1a) of the study will consist of a dose-escalation assessment of the safety and tolerability of CXCR4 administered with MEDI4736 with advanced refractory solid tumors (Figure CXAD.4.1). The second part (Phase 1b) of the study will be disease restricted to include 2 expansion arms in advanced pancreatic cancer (N=approximately 15 patients) and ovarian cancer (N= approximately 15 patients), all receiving LY2510924 (dose determined from Phase 1a) with MEDI4736.

Dose escalation for LY2510924 in combination with MEDI4736 in Phase 1a will be driven by an adaptive model-based dose-escalation scheme (Neuenschwander et al. 2008) to assist in estimation of DLT rate at recommended dose levels. It provides quantitative guidance on the determination of the dose level and provides a lower underdosing rate and a higher MTD selection rate than traditional 3+3 method. The starting dose level will be 20 mg. Subsequent dose levels will reflect a maximum increment of 10 mg from the prior dose level. If the MTD has not yet been reached at the highest dose level of 40 mg, then additional dose levels may be investigated based on both safety and the available PK data. The dose escalation method is described in details in Attachment 9 of the protocol.

### 5.1. Determination of Sample Size

To determine the MTD of LY2510924, an adequate sample size is required. A sufficient sample size will allow for an accurate evaluation of the relationship between exposure and toxicity, as well as an evaluation of the relationship between exposure and pharmacological effects using descriptive statistics and appropriate modeling techniques, if data warrant.

The actual sample size of the dose escalation (Phase 1a) will primarily be limited by the incidence of DLTs. Under the adaptive scheme, each dose level will enroll 3 patients initially and additional patient cohorts may be enrolled in case of DLT. The anticipated sample size for Phase 1a ranges from approximately 12 to 15 patients, depending on the incidence of DLTs. As shown in protocol Attachment 9, the mean number of patients in simulated trials using this dose escalation method was at most 15 patients. Each expansion arm in Phase 1b will enroll approximately 15 patients. The overall sample size is thus estimated to be approximately 45 patients.

The sample size of 15 patients in Phase 1b has been selected to allow adequate assessment of safety at the recommended dose level. It can provide adequate precision for the estimated incidence rate of the following quantities of interest: (1) patients having a specified AE or (2) patients showing a response (PR/CR) to treatment. Example point estimates of incidence rates and corresponding 2-sided 95% confidence intervals (CI) are summarized in **Error! Reference source not found.** The values are provided as a reference for estimation rather than a basis of any decision criteria. The MTD may be revised based on the safety data obtained in Phase 1b (Iasonos and O'Quigley 2013).

**Table CXAD.5.1. Estimated Incidence Rate and Its Two-sided 95% Confidence Interval**

Num. of Cases (N=15)	Est. Rate	95% CI <sup>a</sup>	
		Lower Limit	Upper Limit
0	0.0	0.0	0.22
3	0.2	0.04	0.48
6	0.4	0.16	0.68
9	0.6	0.32	0.84

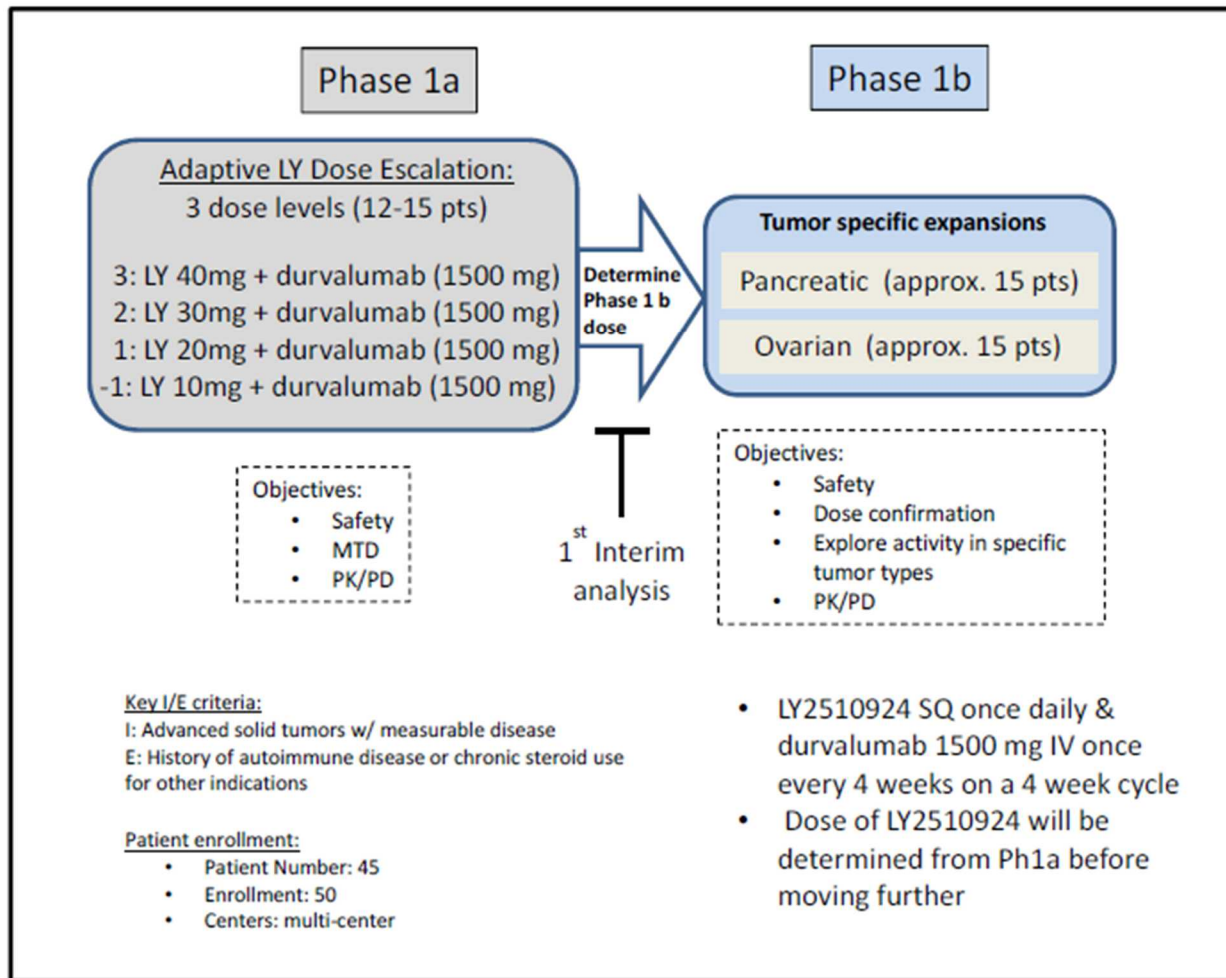
Abbreviations: CI = confidence interval; Est. = estimated; N = number of patients.

a 95% Clopper-Pearson interval for binomial distribution with sample size of 15

## 5.2. Method of Assignment to Treatment

This study is open-label for Phase 1a and Phase 1b. Before each patient's enrollment into the study, an eligibility check must be conducted between the investigational site and the Lilly clinical research personnel to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor will confirm the dose and identification number assignment and cohort/expansion arm for each patient.

For Phase 1a, if investigators have eligible patients who have consented concurrently, more than 3 patients may be entered at a particular dose level provided that accrual has not ceased due to excessive toxicity. This enrollment procedure is allowed because of the advanced disease state of this patient population and the screening involved in defining eligibility. This event should be approved by the sponsor following discussions with the investigators.



Abbreviations: approx. = approximately; I/E = inclusion/exclusion criteria; IV = intravenous; LY = LY2510924; Ph1a = Phase 1a; PK/PD = pharmacokinetic/pharmacodynamic; pts = patients; MTD = maximum-tolerated dose; SQ = subcutaneous.

**Figure CXAD.4.1. CXAD study design.**

## 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/CRS, pharmacokineticist, and statistician. The CRP/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.

The analyses for this study will be descriptive; no p-values will be calculated. Data analyses will be provided by cohort and overall whenever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, standard error, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, percentages, and their standard errors. Exploratory analyses of the data that are not described in the protocol will be conducted as deemed appropriate.

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

The following data handling conventions will be used in the analysis (see [Table CXAD.6.1](#) **Error! Reference source not found.**).

**Table CXAD.6.1. Data Handling Conventions**

Term	Definition or Rule
Relative Study Day	<p>If assessment is on or after date of first dose then  <math>(\text{date of assessment}) - (\text{date of first study drug dose}) + 1</math></p> <p>If assessment precedes first dose of drug then  <math>(\text{date of assessment}) - (\text{date of first study drug dose})</math></p> <p>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.</p>
Baseline	<p>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.</p> <p>For change from baseline within a cycle, baseline value is defined as the measure prior to the first dose of that cycle, unless otherwise specified.</p> <p>If more than one pre-dose measure is available, they may be averaged if appropriate.</p>
Entered	Patients who have signed the informed consent form directly or through their legally acceptable representatives.
Enrolled	Patients who have been assigned to a study treatment and have received at least one dose of study treatment.

## 6.2. Handling of Dropouts or Missing Data

Missing data, except dates, will not be imputed. Historical data such as historical diagnosis, historical illness, pre-existing conditions and prior therapies should be collected in a sufficiently informative way. For example, in order to be considered as a historical illness, events occurring in the same year as study entry should have at least 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; all previous treatments for cancer should have at least known date, month, and year for the end date, in order to determine if inclusion criteria is met. When dates need to be imputed, missing days will be replaced with 15<sup>th</sup> of the month and missing day/month with 01 JULY.

Patients who withdraw from the study before receiving study drug will be replaced and will not be included in the safety or efficacy assessments unless the withdrawal is due to a safety issue that is possibly related to study procedure.

In the following situations, patients will be considered DLT-evaluable; otherwise, patients are considered DLT nonevaluable and may be replaced to ensure that enough patients complete one cycle of therapy at each dose level, unless accrual to that cohort has stopped due to a DLT:

1. Completed the DLT observation period (Cycle 1) and received the scheduled durvalumab dose and at least 75% of LY2510924 doses in Cycle 1;
2. discontinued study treatment or study participation before completing Cycle 1 due to a DLT.

## 6.3. Population for Analysis

Safety and efficacy analyses will be conducted on all patients who have received at least one dose of the study treatment(s), regardless of whether they are deemed evaluable for the assessment of a dose level.

Pharmacokinetic (PK) analyses will be conducted on patients who have received at least one dose of the study treatment(s) and have sufficient samples collected to allow the estimation of LY2510924 and MEDI4736 PK parameters.

Pharmacodynamic (PD) analyses will be conducted on subjects who have received at least one dose of the study treatment(s) and have sufficient samples collected to allow the assessment of PD.

## 6.4. Patient Disposition

A detailed description of patient disposition will be provided. It will include summaries of the number and percentage of patients entered into the study, enrolled in the study, completing the study, and reasons for discontinuation from study treatment, as well as discontinuation from the study. Patients completing the study are defined as patients who received one cycle of study treatment or discontinued prior to doing so due to an AE classified as a DLT in Phase 1a and patients who received two cycles of study treatment in Phase 1b. All patients entered in the study will be included in the summary. Reason for discontinuation from both study treatment

and the study will be listed by the pre-determined categories. If the reason for discontinuation is adverse event (AE) or death, the associated AE or cause of death will be reported.

Screen failures will be listed and summarized if appropriate.

## 6.5. Patient Characteristics

Patient characteristics will be summarized and listed for all patients enrolled and will include:

- Patient demographics, including age, sex, race, ethnicity, screening height and weight, and screening body mass index (BMI).
- Baseline disease characteristics, including initial pathological diagnosis, basis for initial diagnosis, disease stage at initial diagnosis and Eastern Cooperative Oncology Group (ECOG) performance status.
- Prior disease-related therapies including systemic, radiotherapy, and cancer surgeries, if known, including dose, best response, date of progression.
- Historical substance consumption such as alcohol and tobacco use.

Other patient characteristics will be summarized and listed as deemed appropriate.

## 6.6. Treatment Compliance

### 6.6.1. *LY2510924 Compliance*

Patient compliance with LY2510924 will be assessed on Day 1 of each cycle (excluding Cycle 1). Compliance will be assessed by direct questioning, review of diary, and counting any returned vials. Patients are considered significantly noncompliant if <75% of expected study drug is taken in a visit interval. Deviations from the prescribed dosage regimen should be recorded on the CRF. On those study days that PK collection is scheduled, patients will wait to self-administer LY2510924 until they are in the clinic. For more details refer to Protocol Section 7.6.1.

### 6.6.2. *MEDI4736 Compliance*

MEDI4736 will be administered intravenously at the investigational site, under the direction of the investigator. As a result, a patient's compliance with study drug administration is ensured. Patients should attend scheduled clinic visits and must comply with study criteria under their control. Deviation(s) from the prescribed dosage regimen should be recorded on the CRF.

## 6.7. 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 listed and summarized using the preferred name by cohort and overall for all patients on therapy. If the concomitant medication use is due to an adverse event (AE), the associated National Cancer Institute's (NCI) Common terminology Criteria for Adverse Events (CTCAE) Version 4.0 term will be listed.

## 6.8. Safety Analyses

All patients who receive at least one dose of LY2510924 or durvalumumab will be evaluated for safety and toxicity. The National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0) will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all adverse events (AEs) and other symptoms.

Safety analyses will include summaries of the following:

- adverse events, including severity and possible relationship to study drug
- DLTs at each dose level
- dose adjustments
- laboratory values
- vital signs
- ECG readings
- transfusions

### 6.8.1. Extent of Exposure

Study drug exposure information will be summarized by cohort and overall for patients on therapy, including cycles received per subject, duration on therapy, and cumulative dose.

Dose adjustment information will be summarized by cohort and overall for patients on therapy, including dose reductions, dose delays, dose omissions, dose increases, and the reasons leading to dose adjustments.

Dose intensity, defined as the actual amount of drug taken per week, and relative dose intensity, defined as the actual amount of drug taken/planned amount of drug taken $\times$ 100%, will also be summarized by cohort and overall.

### 6.8.2. Dose Limiting Toxicity

Dose limiting toxicities (DLTs) will be summarized and listed by cohort and overall for the safety population.

DLT-equivalent toxicities will also be summarized and listed by cohort and overall for the safety population.

### 6.8.3. Adverse Events

AE terms and severity grades will be assigned by the investigator using CTCAE Version 4.0. Any minor version of CTCAE Version 4.0 (for example, CTCAE Version 4.03) may be used for this study. In addition, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. AEs will be reported using a unified CTCAE/MedDRA reporting process:

- The CTCAE v4.0 term reported by the investigator will be mapped to the MedDRA preferred term (PT) and system organ class (SOC) of the corresponding MedDRA lowest level term (LLT), unless the reported CTCAE term is “Other-specify”.

- If the reported CTCAE term is “Other-specify” the MedDRA LLT, PT and SOC mapped from the verbatim AE term will be used
- All listings and summaries will use the CTCAE terms when available or the MedDRA LLT, along with the MedDRA PT resulting from this process.

A treatment emergent adverse event (TEAE) is defined as any AE that begins on or after the day of the first dose of study treatment or any pre-existing condition that increases in CTCAE grade on or after the day of the first dose of study treatment, and prior to the end of the short-term (safety) follow-up. Comparisons of pre-existing conditions to treatment events at the LLT level will be used in the treatment-emergent computation.

The number of patients who experienced a TEAE, SAE, or TEAE possibly related to study drug, will be summarized. TEAEs will be summarized by SOC, by PT terms of decreasing frequency within SOC, and by maximum CTCAE grade and “Any grade” categories. Immune-related AEs may be tabulated if deemed appropriate.

Historical illnesses are defined as events which ended before completion of the screening visit. Pre-existing conditions are defined as AEs that begin but do not resolve prior to the first dose of study drug is administered. The pre-existing conditions will be presented by patient and can be combined with the adverse event listing, so that the history of the pre-existing conditions/adverse events can be traced. Historical illnesses and pre-existing conditions will be summarized and listed by cohort and overall for all patients on therapy.

#### **6.8.3.1. Adverse Events of Special Interest for Durvalumab**

AESIs for durvalumab include infusion-related reactions and immune-related AEs: colitis; pneumonitis; hepatotoxicity: ALT/AST increases/hepatitis/hepatotoxicity; neuropathy/neuromuscular toxicity; endocrinopathy; dermatitis; nephritis; and pancreatitis.

#### **6.8.4. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events**

A summary of deaths will be presented by cohort and overall. Reasons for death will be summarized separately for deaths on therapy, within 30 days of discontinuation of study therapy and after 30 days of discontinuation of study therapy. Other listings include:

- Listing of Deaths
- Listing of Serious Adverse Events
- Listing of Subjects who Discontinued due to Adverse Events of Death

#### **6.8.5. Clinical Laboratory Evaluation**

Laboratory data (including abnormal laboratory data) will be listed by cycle for all patients on therapy. In addition to the investigator-reported AEs, relevant hematology and chemistry laboratory values will be graded according to CTCAE v4.0. These abnormal lab parameters with derived CTCAE grades will be summarized by visit and cohort.



### **6.8.6. Vital Signs and Other Physical Findings**

All vital signs data, height and weight will be summarized and listed by visit/time points and cohort for patients on therapy.

### **6.8.7. Electrocardiograms**

Electrocardiogram (ECG) data will be summarized by visit and parameter for patients on therapy. Any abnormal ECG data will be listed by patient. Number and percentage of subjects with AEs that could be associated with abnormal ECGs will be presented, if appropriate.

If available, the number of patients meeting the following criteria with respect to QTc will be presented for maximum on-study value:

- QTc, >480 to 500 msec, and >500 msec and delta QTc >30 to 60 msec, and >60 msec.

All instances when a patient met the above criteria will be listed. Maximum absolute and change from baseline QTc data will be summarized as a continuous variable. Frequency of patients with Normal ( $\leq 480$  msec) or High ( $>480$  msec) QT/QTc interval at baseline and post baseline nominal time points will be summarized by shift table. Summaries of other ECG parameters (for example, RR, PR, and QRS) will be presented, if appropriate. A QT-concentration analysis of change from baseline in QTcF versus serum concentration may be performed, if deemed appropriate.

Lilly will review ECG data and monitor cardiac events/deaths during the course of the study.

## **6.9. Pharmacokinetic Analyses**

The sampling schedule for drawing blood samples for LY2510924 and Durvalumab for determination of LY2510924 and Durvalumab concentrations is provided in Attachment 4 of the protocol. Serum concentrations of Durvalumab prior to infusion ( $C_{min}$ ) and post-end of infusion will be summarized using descriptive statistics. Pharmacokinetic parameters for LY2510924 will be computed by standard noncompartmental methods using Phoenix<sup>TM</sup> WinNonlin<sup>®</sup> or equivalent program on a computer that meets or exceeds the minimum system requirements for this program. The primary parameters for analysis will be area under the concentration-time curve (AUC) of LY2510924. Other noncompartmental parameters, such as time of half-life ( $t_{1/2}$ ), apparent clearance (CL/F), and apparent volume of distribution (V/F) may be reported.

Population PK analyses for LY2510924 may be conducted using a population PK approach as deemed necessary by Global PK/PD management. Planned PK analyses are specified in separate standalone NCA and popPK/PD analysis plans as appropriate. 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 equivalent pharmacokinetic/graphing/scripting software programs may be utilized if appropriate, warranted, and approved by Global PK/PD management for generating PK and PK/PD tables, figures, and listings. Upon completion of quality control and quality review procedures, all documentation will be collected and filed in a Lilly-approved repository. All PK and PK/PD analysis, and creation of table, figures, and listings will be the

responsibility of Lilly Global PK/PD & Pharmacometrics group based on applicable functional Standard Operating Procedures and software approved by this group's management.

### **6.10. Biomarker Analyses**

Exploratory biomarkers will be summarized and assessed for correlations with clinical outcomes. Biomarker relationships by tumor type, changes in biomarker levels at baseline and over time, and differences among dose levels or exposure will be explored as possible.

### **6.11. Pharmacokinetic/Pharmacodynamic Analyses**

The relationship between LY2510924 exposure and selected efficacy, safety outcomes, and biomarkers may be explored if relevant.

### **6.12. Immunogenicity Analyses**

Immunogenicity incidence will be tabulated, and correlation to MEDI4736, activity, and safety will be assessed, as appropriate, respectively. The measures that will be analyzed include baseline presence and level of ADA, treatment-emergent ADA, levels of neutralizing ADA, and incidence and levels of ADA related to IRRs.

### **6.13. Efficacy Analyses**

Tumor response data will be tabulated by cohorts. Particularly, the antitumor effect will be summarized by the objective response rate (ORR) and disease control rate (DCR) by cohort and overall. Mean, median, range, and exact 95% confidence intervals (CI) will be provided. Reported lesion measurement data, including sum of target lesions, change and/or percent change from baseline sum and smallest sum (nadir) at each visit will be listed for all patients on therapy. Investigator-determined response by cycle will be listed.

Time-to-event variables, such as progression-free survival (PFS), time to response (TTR), duration of response (DoR) and overall survival (OS) will be listed and summarized. For all time-to-event variables, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curves, medians with 95% CI, and survival rates at various time points if applicable. For Phase 1b, time-to-event variables will be summarized by different cohorts.

#### **6.13.1. Efficacy Analysis Variables (RECIST v.1.1)**

Definition of efficacy analysis variables are listed alphabetically.

**Disease Control Rate** is defined as the proportion of treated patients achieving a best overall response of complete response (CR), partial response (PR), or stable disease (SD) per RECIST v.1.1. Patients who do not have any postbaseline tumor response assessments for any reason are considered non-responders and are included in the denominator when calculating the response rate.

**Note.** Best overall response is the best response recorded from the start of treatment until disease progression, in the order of CR, PR, SD, PD, and NE.

**Duration of Response** is defined from the date of first documented CR or PR that is subsequently confirmed (responder) to the date of objective progression or the date of death due to any cause, whichever is earlier. If a responder is not known to have died or have objective progression, then the patient will be censored at the date of last evaluable tumor assessment.

**Objective response rate** is defined as the proportion of treated patients achieving a best overall response of PR or CR per RECIST v.1.1. Patients who do not have any postbaseline tumor response assessments for any reason are considered non-evaluable and are included in the denominator when calculating the response rate.

**Overall survival** is defined as time from the date of first treatment to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cut-off date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the data-inclusion cut-off date (contacts considered in the determination of last contact date include AE date, lesion assessment date, visit date, and last known alive date).

**Progression-free survival** is defined as the time from the date of first treatment until the date of radiographic documentation of progression (as defined by RECIST v. 1.1) based on investigator assessment or the date of death due to any cause, whichever is earlier.

**Time-to-response** is the time from the date of first study treatment until the first evidence of a confirmed CR or PR.

[Table CXAD.6.2](#) lists rules for determining date of progression or censor for PFS. The censoring is taken in the following order:

- If a patient does not have a baseline disease assessment, then the PFS time will be censored at the treatment starting date, regardless of whether or not objective progressive disease (PD) or death has been observed for the patient; otherwise,
- If a patient is not known to have died or have investigator-assessed PD as of the data-inclusion cut-off date for the analysis, the PFS time will be censored at the date of last postbaseline adequate radiological tumor assessment, or at the date of first treatment if the patient does not have any postbaseline adequate radiological assessment.

**Note.** If there are multiple dates associated with one radiological tumor assessment, the assessment date will be set to the first date when the overall response is PD and the last date otherwise. A radiological tumor assessment is considered adequate if its response is among CR, PR, SD, or PD.

$$\text{PFS (day)} = \text{Date of progression / censor} - \text{date of first treatment} + 1$$

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

Rule	Situation	Date of Progression or Censor	Outcome
1	No baseline tumor assessments	Date of first treatment	Censored
2	No postbaseline assessments and no death	Date of first treatment	Censored
3	No documented progression and no death (with a postbaseline tumor assessment)	Date of last adequate tumor assessment	Censored
4	Patient lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last adequate tumor assessment	Censored
5	Documented progression	Date of documented progression  If a tumor assessment was done on multiple days, use the earliest date for that visit.	Progressed
6	Death without documented progression	Date of death	Progressed
7	Documented progression or death after missing $\geq 2$ consecutive postbaseline tumor assessments	Date of last adequate tumor assessment before missed assessments or date of first treatment, whichever is later	Censored

Note: Progression-free survival and associated outcome is determined by the earliest of the dates above, if more than 1 situation applies.

### **6.13.2. Efficacy Analysis Variables (RECIST v1.1 with confirmatory scan for disease progression)**

For Study CXAD, RECIST v1.1 with confirmatory scan for disease progression (denote it as RECISTc for simplicity) will be adapted to account for the unique tumor response characteristics seen with treatment of immuno-oncology therapy. RECISTc will be applied as detailed in the study protocol, and the resulting data will be included in the clinical database.

**Objective response rate (RECISTc)** is defined as the proportion of treated patients achieving a best overall response of PR or CR per RECISTc. Particularly, the best overall response by RECISTc (denoted as ORRc) closely related to confirmed response by RECIST v1.1. ORRc further captures responses after unconfirmed PD and it does not require confirmation. For example:

- If the best response by RECIST is CR, then the best response by RECISTc is CR.
- If the best response by RECIST is PR, SD, or PD, the best response by RECISTc is the best response over the initial assessment (prior to PD by RECISTc) and the confirmation stage.

Overall, the best response by RECISTc should be the same or better than the best response by RECIST criteria. In addition, patients who do not have any postbaseline tumor response

assessments for any reason are considered non-evaluable and will be included in the denominator when calculating the response rate.

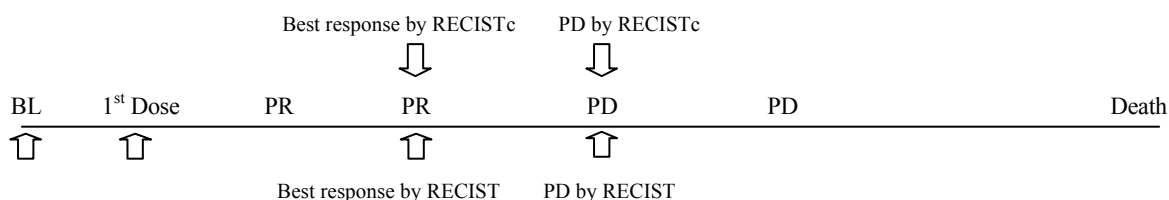
**PFS<sub>c</sub>:** The date from the treatment started date to the time of confirmed PD (PD<sub>c</sub>) assessed by RECIST<sub>c</sub>.

- If the initial PD is confirmed at the very next scan (consecutive PD) then the date of PD<sub>c</sub> is the initial PD date by RECIST v1.1.
- If the initial PD is unconfirmed at the very next scan (non-consecutive PD), then the date of PD<sub>c</sub> is the date of second PD.

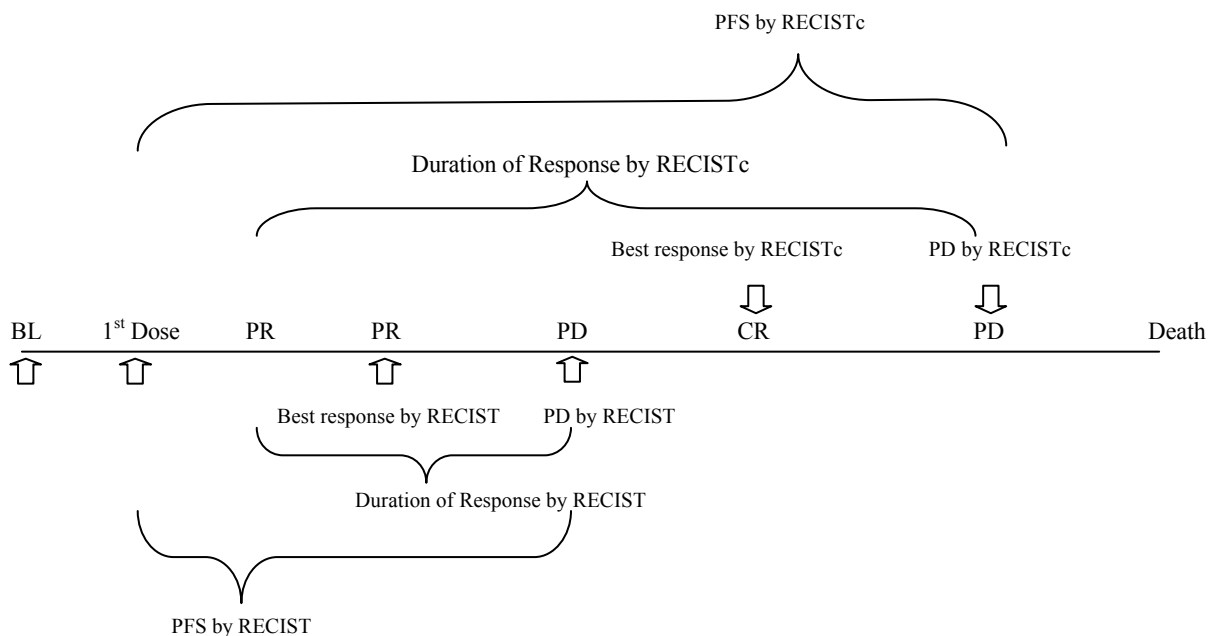
**Duration of response by RECIST<sub>c</sub>:** The duration of response is defined from the date measurement criteria for CR or PR (whichever is first recorded) are first met to the date of PD<sub>c</sub> or the date of death due to any cause, in the absence of an observed PD<sub>c</sub>.

**Graphic Example:**

Scenario 1: The initial PD is confirmed at the next scan (consecutive PD). The efficacy variables by RECIST<sub>c</sub> and RECIST are the same.



Scenario 2: The initial PD is not confirmed at the next scan (non-consecutive PD). The efficacy variables by RECIST<sub>c</sub> and RECIST are different.



In addition, the best response after initial PD may be listed. Other efficacy analysis based on RECIST and/or RECISTc may be performed for exploratory analysis (e.g., in patients who had baseline and at least one post-baseline scan).

#### **6.14. Protocol Violations**

All major protocol violations will be summarized by cohort and reason. These violations will include those defined by, for example:

- Inclusion/Exclusion Criteria
- Dosing
- Noncompliance with other protocol procedures
- Informed consent/assent process

#### **6.15. Interim Analyses and Data Monitoring**

Data will be reviewed on a cohort-by-cohort basis during Phase 1a of the study, until the MTD is determined. The purpose of these cohort-by-cohort 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 in consultation with collaborator (AstraZeneca) will make the determination regarding dose escalation based upon their review of the safety and tolerability data as described in this protocol.

Safety and/or PK data will be reviewed during the study if needed for dose escalation, modifications to the dose escalation strategy or other design elements.

Once MTD is determined for Phase 1a, an interim analysis including safety and PK will be performed prior to opening Phase 1b.

In Phase 1b, if a DLT-equivalent toxicity occurs in one third or more of patients during Cycle 1 (with a minimum of 6 patients enrolled, unless two events occur prior to 6 patients being enrolled), a data review will be performed to determine whether to continue at the current LY2510924 dose or whether the dose of LY2510924 should be reduced.

In Phase 1b, a safety review may occur for each expansion arm approximately 2 months after approximately 8 of the planned patients start study therapy.

If an unplanned interim analysis is deemed necessary, the sponsor will determine if it is necessary to amend the protocol.

Any interim analyses may be combined if they are expected to occur within approximately a month, and interim analyses may also be combined with the ongoing trial-level safety review or annual safety review for annual safety update reporting.

The final analysis and evaluation of the primary objective and the secondary objectives will be performed approximately 6 months after the last patient of each expansion arm starts study therapy, and the final analysis may be conducted separately for each expansion arm. A clinical

study report might be created before the last patient visit. In this case, all data until the data-cutoff date will be used for the analysis of safety, efficacy, PK and PD biomarkers.

## 6.16. Annual Report Analyses

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

Clinical Investigator brochure:

- Summary and Listing of SAE
- Summary and Listing of Deaths
- Summary and Listing of TEAE
- Listing of Subjects Who Discontinued Due to Adverse Event or Death

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 Adverse Event During the Reporting Period
- Listing of Subjects Who Died During the Reporting Period

Other analyses may be requested if deemed necessary.

## 6.17. 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 AEs, provided as a dataset which will be converted to an XML file. Both SAEs and ‘Other’ AEs are summarized by MedDRA preferred term (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
  - the number of events experienced.

- Consistent with [www.ClinicalTrials.gov](http://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.

A participant flow will be created that will describe how many entered 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.



## 7. References

- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2) 228-247.
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- Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST. Confidence interval criteria for assessment of dose proportionality. *Pharm Res*. 2000;17(10):1278-1283.

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