Statistical Analysis Plan (v1)

A Phase 1a/1b Trial Investigating the CSF-1R Inhibitor LY3022855 in Combination with Durvalumab (MEDI4736) or Tremelimumab in Patients with Advanced Solid Tumors

NCT02718911

Approval Date: 21-Apr-2016

1. Statistical Analysis Plan: I5F-MC-JSCC: A Phase 1a/1b Trial Investigating the CSF-1R Inhibitor LY3022855 in Combination with Durvalumab or Tremelimumab in Patients with Advanced Solid Tumors

LY3022855

Multicenter, nonrandomized, open-label, dose-escalation Phase 1a/1b study of intravenous (I.V.) LY3022855 in combination with I.V. durvalumab (PD-L1 inhibitor) or I.V. tremelimumab (CTLA-4 inhibitor) in patients with advanced solid tumors.

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Indianapolis, Indiana USA 46285

Protocol I5F-MC-JSCC
Phase 1a/1b

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

Approval Date: 21-Apr-2016 GMT

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3. Revision History

Statistical analysis plan (SAP) Version 1 was approved prior to first patient visit.

4. Study Objectives

4.1. Primary Objectives

The primary objectives of this study are:

- to characterize the safety profile and tolerability of each combination, LY3022855 with durvalumab (MEDI4736) and LY3022855 with tremelimumab, in the treatment of patients with advanced solid tumors
- to define a recommended Phase 2 dose (RP2D) for each combination, LY3022855 with durvalumab and LY3022855 with tremelimumab, in the treatment of patients with advanced solid tumors

4.2. Secondary Objectives

The secondary objectives of this study are:

- to document the antitumor activity of each combination, LY3022855 with durvalumab and LY3022855 with tremelimumab, in the treatment of patients with advanced solid tumors.
- to assess the development of antibodies against LY3022855, durvalumab, and tremelimumab (immunogenicity)
- to characterize the single-dose and multiple-dose pharmacokinetics (PK) of LY3022855 in combination with either durvalumab or tremelimumab, and the single-dose and multiple-dose PK of durvalumab and tremelimumab, each in combination with LY3022855

4.3. Exploratory Objectives

- to explore the effects of the combinations of LY3022855 with durvalumab or tremelimumab in the treatment of patients with advanced solid tumors on changes in immune cell subset frequency and activation
- to explore the pharmacodynamic profile of each combination, LY3022855 with durvalumab and LY3022855 with tremelimumab, in the treatment of patients with advanced solid tumors
- to explore cellular and molecular markers potentially associated with safety and antitumor and biological activity of the combination of LY3022855 with durvalumab or tremelimumab, in the treatment of patients with advanced solid tumors

5. Summary of Study Design

Study I5F-MC-JSCC is a multicenter, nonrandomized, open-label, dose-escalation Phase 1a/1b study of LY3022855 in combination with either durvalumab or tremelimumab, in patients with advanced solid malignancies. In Part A, enrollment to the tremelimumab cohorts may potentially start after the enrollment to the durvalumab cohorts. Eligible patients will receive treatment as follows:

- LY3022855 once weekly, in combination with:
  - durvalumab once every 2 weeks
    OR
  - tremelimumab once every 4 weeks; after 6 doses, tremelimumab once every 12 weeks until discontinuation

The study will be conducted in 2 parts:

- Part A – Phase 1a, dose escalation
- Part B – Phase 1b, disease-specific expansion

The following description applies to each combination therapy.

During Part A, patients will be enrolled in a 3+3 design to increasing dose levels, as tolerated. In the event dose-limiting toxicities (DLTs) prevent further dose escalation, exploration of additional dosages between the highest dose tested and the previously identified safe dosage may be explored after further discussion with the investigators, Sponsor, and collaborator. Once a maximum tolerated dose (MTD) has been identified for each combination, enrollment to Part B (5 disease-specific expansion cohorts of 20 patients per cohort) will begin. The non-small cell lung cancer cohort will consist of a minimum of 10 patients with disease refractory to checkpoint therapy and a minimum of 6 patients with disease relapsed on prior checkpoint therapy. Patients in Part B will be treated at the MTD for a given combination, unless otherwise specified by the Sponsor. Upon completion of Part B, which is intended to confirm tolerability of a combination dose, the RP2D will be declared/defined. For patients with melanoma, assignment to the durvalumab or the tremelimumab combination cohort will be made by the Sponsor after consultation with the treating investigator, based upon the patient's medical history as well as the availability of open slots.

All patients enrolled to all cohorts of Part A or to the ovarian cancer cohort of Part B will undergo mandatory attempted pretreatment and on-treatment (6-8 weeks after starting study treatment) tumor core needle or excisional biopsies.

Figure JSCC.5.1 presents the overall study design. Figure JSCC.5.2 presents the schema for an individual patient with regard to timing of tumor tissue biopsies.

5.1. Determination of Sample Size

Up to approximately 178 patients (78 [Part A] + 100 [Part B]) may be enrolled in this multicenter, nonrandomized, open-label Phase 1a/1b study of LY3022855.

The sample size for Part A will be determined primarily by the incidence of DLTs prior to establishing the MTDs in Part A. The anticipated sample size for Part A ranges from approximately 12 to 36 patients in the combination of LY3022855 plus durvalumab and approximately 12 to 42 patients in the combination of LY3022855 plus tremelimumab. In each cohort of Part B, approximately 20 patients will be enrolled. Patients in Part A (dose-finding) who receive all doses of study treatment for Cycle 1 (DLT-evaluation period) or who are discontinued from the study due to DLTs will be considered evaluable for the assessment of a dose level. Nonevaluable patients in Part A may be replaced to ensure that enough patients complete 1 cycle of therapy at each dose level for Part A, unless accrual to that cohort has stopped due to a DLT. The sample size of Part B has been selected to allow adequate assessment of safety and tolerability of LY3022855 in combination with durvalumab or tremelimumab at the recommended dose level and can provide adequate precision for the estimated incidence rate of the following quantities of interest: (1) patients having a specified adverse event (AE), or (2) patients showing a response (partial response [PR]/complete response [CR]) to treatment. Example point estimates of incidence rates and corresponding 2-sided 95% confidence intervals (CI) are summarized in Table JSCC.5.1. The values are provided as a reference for estimation rather than a basis of any decision criteria. The RP2D may be revised based on the safety data obtained in Part B (Iasonos and O'Quigley 2013).

Table JSCC.5.1. Estimated Incidence Rate and 2-Sided 95% CI

Number of Cases (N=20)	Estimated Incidence Rate	95% CI[a]	
		Lower Limit	Upper Limit
0	0.0	0.0	0.17
5	0.25	0.09	0.49
10	0.50	0.27	0.73
15	0.75	0.51	0.91

Abbreviations: CI = confidence interval; N=number of patients.
a 95% Clopper-Pearson interval for binomial distribution with sample size of 20.

5.2. Method of Assignment to Treatment

In Part A of dose escalation (Phase 1a), patients who meet all criteria for enrollment will be assigned to receive protocol-defined treatment in this study. 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 for each patient.

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.

In Part B of disease-specific expansion (Phase 1b), a patient who meets all criteria for enrollment will be assigned (by the Sponsor) to a treatment cohort, based on the patient's diagnosis at baseline.

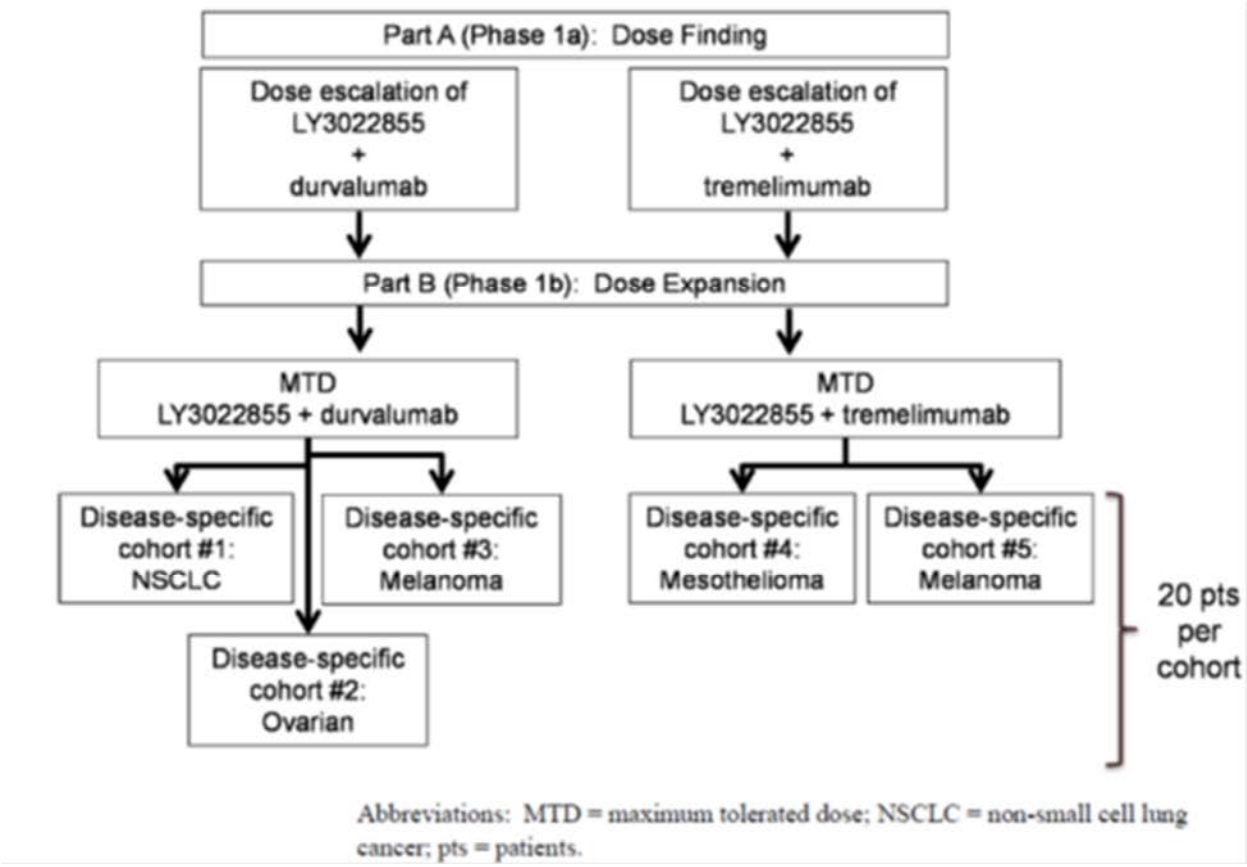

Figure JSCC.5.1. Illustration of Study JSCC study design.

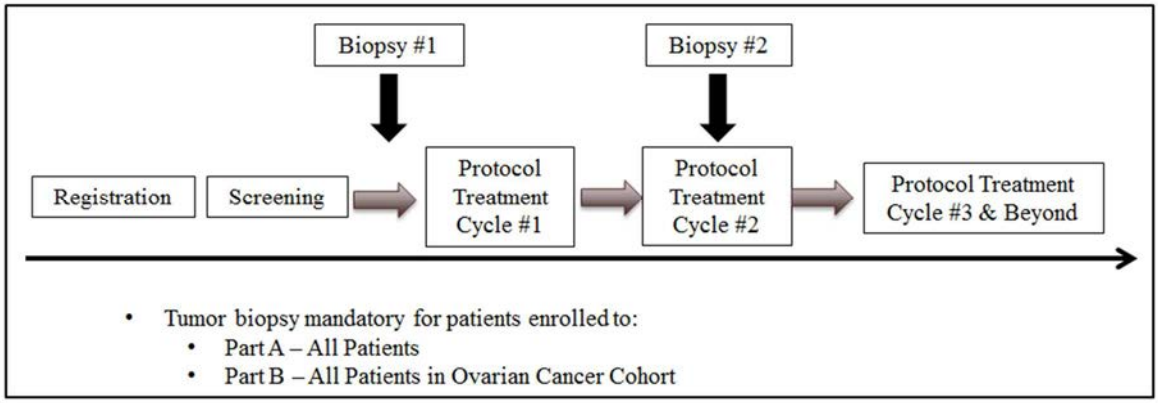

Figure JSCC.5.2. Schema for an individual patient with regard to timing of tumor tissue biopsies.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly). The interpretation of the study results will be the responsibility of the investigator with the Lilly clinical research physician (CRP)/clinical research scientist (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 treatment whenever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients and percentages. 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 JSCC.6.1).

Table JSCC.6.1. Data Handling Conventions

Term	Definition or Rule
Relative Study Day	If assessment is on or after date of first dose then (date of assessment)-(date of first study drug dose)+1
	If assessment precedes first dose of drug then (date of assessment) – (date of first study drug dose)
	There is no Study Day 0. Study Day 1 is the date of first dose and Study Day -1 is the day before the first dose.
Baseline	For change from baseline analyses, baseline value is defined as the last reported measure on or before the first dose date (prior to the dose administration), unless otherwise specified. 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.
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 1 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, 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. When dates need to be imputed, missing days will be replaced with 15th of the month and missing day/month with 01 July.

In the following situations of Part A, patients will be considered nonevaluable and may be replaced to ensure that enough patients complete 1 cycle of therapy at each dose level, unless accrual to that cohort has stopped due to a DLT:

1. Any patient who is discontinued from the study before completing 1 cycle of therapy unless they experience a DLT prior to withdrawal
2. Patients who are not evaluable for PK, but who complete 1 cycle of therapy

6.3. Population for Analysis

Safety and efficacy analyses will be conducted on all patients who have received at least 1 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 1 dose of the study treatment(s) and have sufficient samples collected to allow the estimation of LY3022855, durvalumab, and tremelimumab PK parameters.

Pharmacodynamic (PD) analyses will be conducted on subjects who have received at least 1 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, and completing the study (with data indicating completion of study primary and secondary objectives in electronic case report form page of the End of Study), and reasons for discontinuation from study treatment, as well as discontinuation from the study. 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 AE or death, the associated AE or cause of death will be reported.

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

- baseline disease characteristics, including initial pathological diagnosis, basis for initial diagnosis, disease stage at initial diagnosis, and Eastern Cooperative Oncology Group performance status (PS)
- prior disease-related therapies, including systemic, radiotherapy, and cancer surgeries, if known, including dose, best response, and 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

LY3022855, durvalumab, and tremelimumab 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.

6.7. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization drug dictionary. All concomitant medications will be listed and summarized using the preferred name by cohort and overall for all patients on therapy.

6.8. Safety Analyses

All patients who receive at least 1 dose of LY3022855, durvalumab, or tremelimumab 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 AEs and other symptoms.

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- DLTs at each dose level
- dose adjustments
- laboratory values
- vital signs
- electrocardiogram (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 adjustments, including the reasons for dose adjustment, will also be listed, and will be summarized by cohort and overall for patients on therapy.

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×100%, will also be summarized by cohort and overall.

6.8.2. Dose-Limiting Toxicity

Dose-limiting toxicities (DLTs) during Cycle 1 (the DLT-evaluation period) in Part A will be summarized and listed by cohort and overall if appropriate.

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

6.8.3. Adverse Events

Adverse event terms and severity grades will be assigned by the investigator using CTCAE v4. Any minor version of CTCAE v4 (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. Adverse events 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 preexisting condition that increases in CTCAE grade on or after the day of the first dose of study treatment. Comparisons of preexisting conditions to on-treatment events at the LLT level will be used in the treatment-emergence computation.

The number of patients who experienced a TEAE, serious adverse event (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 grade categories. Immune-related AEs may be tabulated if deemed appropriate.

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

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 (counting from the date the decision to discontinue treatment is made) 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

All ECG data will be analyzed for safety, and categorical analysis will be provided if appropriate. These ECG analyses may include the number and percentage of individuals with abnormal ECG findings or ECG parameters at scheduled time points as well as changes from baseline for ECG parameters.

6.9. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of the study drug and have had samples collected. Pharmacokinetic parameter estimates for LY3022855, durvalumab, and tremelimumab will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be maximum concentration (C_{max}) and area under the concentration-time curve ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$) of each of the study drugs. Other noncompartmental parameters, such as time of half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V/F) for each study drug may be reported. Additional exploratory analyses will be performed if warranted by data and other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global Pharmacokinetic 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 parameter estimates will be evaluated to delineate the effects of dose proportionality, target-mediated drug disposition, and drug accumulation. Log-transformed C_{max}

and AUC estimates will be assessed to estimate ratios of geometric means and the corresponding 90% CIs. The potential effect of durvalumab-mediated programmed death-ligand 1 (PD-L1) inhibition and/or tremelimumab-mediated cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibition on the exposure of LY3022855 and the effect of LY3022855-mediated CSR-1 inhibition on the exposure of tremelimumab and/or durvalumab will be assessed using historical monotherapy exposure data for each of the 3 study drugs.

6.10. Pharmacodynamic Analyses

Pharmacodynamic analyses will be conducted on subjects who have received at least 1 dose of the study treatment(s) and have sufficient samples collected to allow the assessment of PD. Characterized profiles of available longitudinal biomarkers for estimable patients will be created and analyzed. Pattern recognition analysis may be applied for the PD biomarkers that indicate the evidence of drug engagement. Those include circulating levels of colony stimulating factor 1 (CSF-1), interleukin-34 (IL-34), cluster of differentiation (CD)$14^{Dim}CD16^{Bright}$ monocytes, free membrane PD-L1, and monocyte markers.

6.11. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/pharmacodynamic analyses for LY3022855 may be conducted as deemed necessary by Global PK/PD management. These analyses may include, but are not limited to, establishing relationships (or lack of) between exposure and PD biomarkers that were explored or confirmed in PD analyses (refer to Protocol Section 10.6).

6.12. Immunogenicity Analyses

Immunogenicity data will be summarized, and correlation to drug level (each drug), activity, and safety will be assessed, as appropriate. The measures that will be analyzed include baseline presence and level of anti-drug antibody (ADA), treatment-emergent ADA, levels of neutralizing ADA, and incidence and levels of ADA related to infusion-related reactions.

6.13. Efficacy Analyses

Tumor response data will be tabulated by cohorts (according to Response Evaluation Criteria In Solid Tumors Version 1.1 [RECIST 1.1]). Particularly, the antitumor effect will be summarized by the overall response rate (defined by the total number of responses divided by the number of patients enrolled) and disease control rate (defined by the total number of stable disease + responses divided by the number of patients enrolled) by cohort and overall. Mean, median, range, and exact 95% CI will be provided. A patient is considered to have a tumor response if they achieve a confirmed CR or PR according to RECIST 1.1. Reported lesion measurement data, including sum of target lesions and change and/or percent change form baseline and nadir sum 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, will be listed and summarized. PFS time is defined as the time from the first dose of the study drug to objective progressive disease or death

due to any cause in the absence of disease progression. DoR is defined as the time from the first assessment of any tumor response to progressive disease or death due to any cause, occurring without observed disease progression. Patients not known to have progressed or died while on study will have their PFS and DoR time censored at the date of the last objective progression-free disease assessment. Patients for whom there is no record of progression, death, or postbaseline radiographic assessment will have their PFS time censored on the day of first dose of any study drug. TTR is defined as the time from the first dose of the study drug to the first assessment of confirmed response (CR or PR) by RECIST 1.1. DoR and TTR will be presented for each cohort for patients with a confirmed response (CR or PR). Overall survival is defined as the time from the first dose of study drug until death due to any cause. Patients with no reported death at analysis will be censored at their last reported date alive. For all time-to-event variables, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curves, medians, and survival rates at various time points, with 95% CI if applicable. For Part B, time-to-event variables will be summarized by cohort.

6.14. Tailoring Biomarker Analyses/Companion Diagnostic Analyses

If applicable, efficacy measures may be summarized descriptively within subgroups of patients. Exploratory analyses may be applied to evaluate the association between baseline biomarkers and clinical outcome. If applicable, a subset of potential predictive biomarkers associating with interpretable clinical benefit may be further examined with biological evidence. Biomarker analyses related to the exploratory objectives of this study will be described in a separate SAP.

6.15. Protocol Violations

All major protocol violations will be summarized by parts and/or cohorts and by reasons (for example, inclusion/exclusion criteria, noncompliance with protocol procedures, informed consent/assent process, etc.)

6.16. Interim Analyses and Data Monitoring

Because this is a dose-finding study, data will be reviewed on a cohort-by-cohort basis during the study, until the MTDs are determined for each combination. 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 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.

In Part A, after all patients who are deemed evaluable for the assessment of dose levels complete DLT-evaluation period or MTD is determined, an interim safety and PK analysis may be conducted for each combination for planning next studies.

If it is deemed that enough data are obtained to assess the primary objectives and the secondary objectives, a CSR may 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, pharmacokinetics, and pharmacodynamic biomarkers. After the data cutoff date, all data defined in the protocol will continue to be collected from patients on treatment, listed, and summarized in an updated CSR. However, summary tables containing the data collected after the data cutoff date will not be created; these data may be reported separately and the analyses on all patients, including these data, may not necessarily be performed.

6.17. Annual Report Analyses

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

Clinical Investigator brochure:

- Summary and Listing of SAEs
- Summary and Listing of Deaths
- Summary and Listing of TEAEs
- 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.

6.18. 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 AEs, provided as a dataset that will be converted to an XML file. Both SAEs and 'Other' AEs are summarized by MedDRA PT within treatment group.

- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - 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).
- 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

Iasonos A, O'Quigley J. Design considerations for dose-expansion cohorts in phase I trials. *J Clin Oncol*. 2013;31(31):4014-4021.

Kaplan EL, Meier P. Nonparametric estimation of incomplete observations. *J Amer Stat Assoc*. 1958;53:457-481.

[NCI] National Cancer Institute. 2009. Cancer therapy evaluation program. Common Terminology Criteria for Adverse Events, version 4.0. NCI, NIH, DHHS. May 29, 2009. NIH publication # 09-7473.

Leo Document ID = 8cb72cbd-60dd-46ef-9cb3-7e7a10d1c91f

Approver: PPD
Approval Date & Time: 20-Apr-2016 19:37:41 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 21-Apr-2016 01:48:10 GMT
Signature meaning: Approved