Statistical Analysis I5F-MC-JSCB Version 2

Phase 1 Study to Identify the Immunomodulatory Activity of LY3022855 (IMC-CS4) in Patients With Advanced, Refractory Breast or Prostate Cancer

NCT02265536

Approval Date: 31-Aug-2017

1. Statistical Analysis Plan: Phase 1 Study to Identify the Immunomodulatory Activity of LY3022855 (IMC-CS4) in Patients with Advanced, Refractory Breast or Prostate Cancer

Confidential Information

LY3022855 (IMC-CS4)

This Phase 1 study is a single-center, open-label, nonrandomized, noncontrolled study of intravenous LY3022855 (IMC-CS4) in patients with advanced, refractory breast or prostate cancer.

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

Approval Date: 31-Aug-2017 GMT

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to first patient visit.

SAP version 2 was approved based on protocol I5F-MC-JSCB(d) dated 10 November 2016.

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to document the immunomodulatory activity of LY3022855 treatment in patients with advanced, refractory breast or prostate cancers, according to the following measures:

- Changes from baseline over time in peripheral blood immune cell subsets, as determined by flow cytometric analysis using an antibody panel, and that may include but not be limited to the following markers: Live-Dead, CD3, CD4, CD8, CD14, CD16, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS.
- Changes from baseline over time in serum cytokines, as determined by Meso Scale Discovery (MSD) multiplex cytokine immunoassay technology or enzyme-linked immunosorbent assay (ELISA), and that may include, but not be limited to, the following: CSF-1, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-34, and tumor necrosis factor alpha (TNF-α).

4.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and toxicity profile of LY3022855, as assessed by the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0)
- To assess the pharmacokinetic (PK) serum concentrations of LY3022855
- To document antitumor activity, per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) (Eisenhauer et al. 2009) and immune-related RECIST (irRECIST) (Wolchok et al. 2009) (Note: If a patient has confirmed progressive disease per RECIST 1.1 but not per irRECIST, the patient will be considered to have not progressed.)
- To assess the development of antibodies against LY3022855 (immunogenicity), as assessed by a validated immunogenicity assay

4.3. Exploratory Objectives

The exploratory objectives of this study are:

- To explore serum biomarkers that may be relevant to the mechanism of action of IMC-CS4, CCI [redacted]
- To explore the pharmacodynamic effects of IMC-CS4 on tissue biomarkers, using flash-frozen baseline and posttreatment tumor biopsies
- To assess antitumor activity in bone, per the Prostate Cancer Clinical Trials Working Group (PCWG2) (Scher et al. 2008) criteria

5. Study Design

5.1. Summary of Study Design

Study I5F-MC-JSCB (JSCB) is a single-center, open-label, nonrandomized, noncontrolled Phase 1 study of intravenous (IV) LY3022855 in patients with advanced, refractory breast or prostate cancer. Eligible patients will receive LY3022855 as an infusion. Study JSCB is intended to explore clinical response and immunological activity of single-agent LY3022855 in approximately 40 patients (enrolled, of whom 36 will be evaluable), by assessment of biomarkers, cytokines, and immune cells. The study schema is shown in Figure JSCB.5.1.

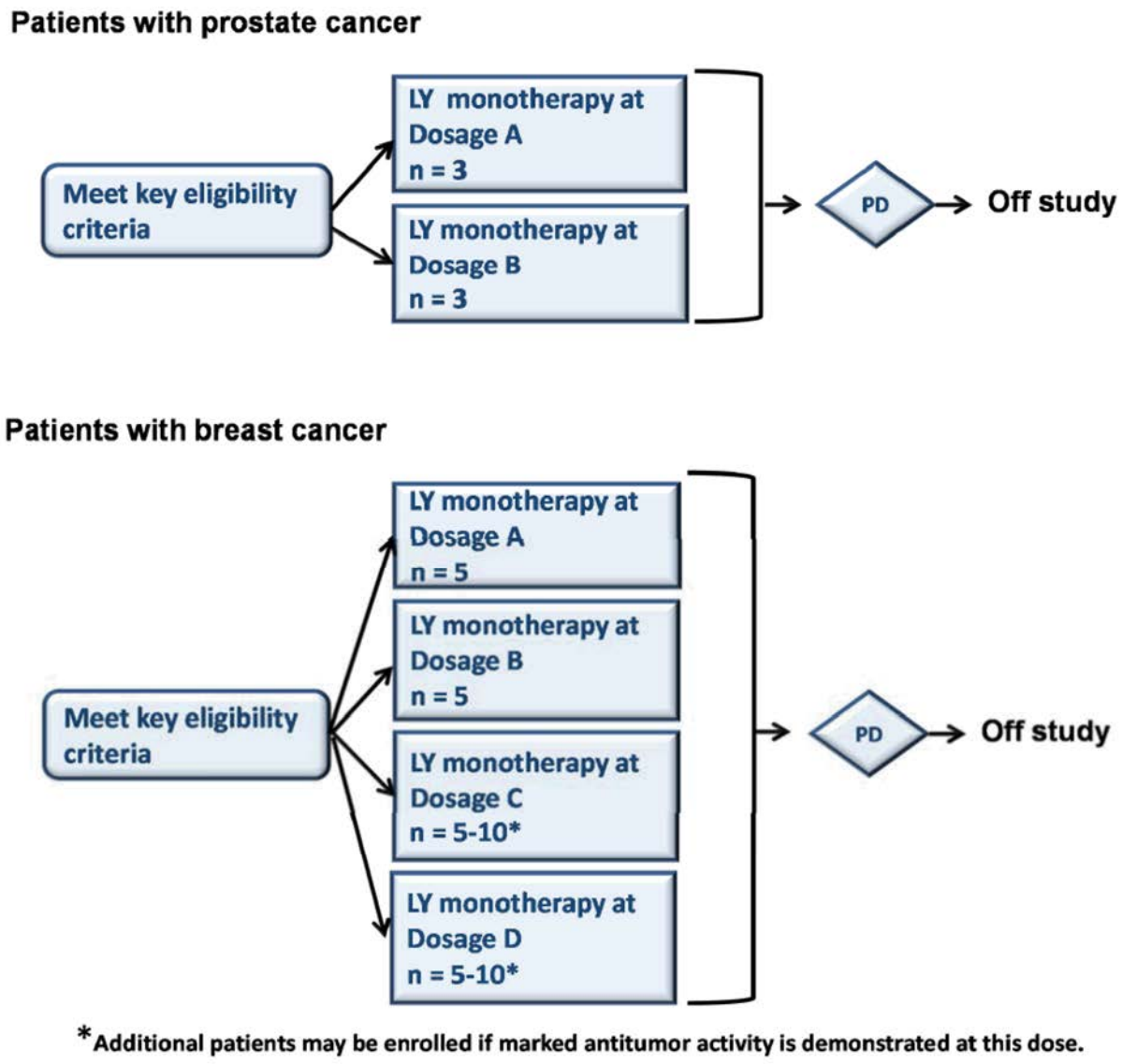

Figure JSCB.5.1. Study design for I5F-MC-JSCB.

5.2. Determination of Sample Size

For this study, approximately 40 patients will be enrolled. Patients with prostate cancer will be treated at 1 of 2 dosages of LY3022855, and patients with breast cancer will be treated at 1 of 4 dosages of LY3022855. Of those enrolled patients, approximately 36 patients will be evaluable: 30 patients with advanced, refractory breast cancer and 6 patients with advanced, refractory prostate cancer.

CSF-1 is the primary pharmacodynamic biomarker documented in Study JSCA. Serum CSF-1 was quantified for 17 patients over time; that is, at baseline and 8 hours after the first infusion. All those patients had increased levels of CSF-1 at 8 hours, compared with the baseline level.

The effect size (or Cohen's d) is 5.81. Consequently, the power of observing any change between the eighth hour and baseline is close to 1 as long as the number of samples is ≥3. However, when the effect size is as small as 1 for the pharmacodynamic markers other than CSF-1, the power is approximately 0.159 if only 3 patients are sampled.

For Dosages C and D (patients with breast cancer), the sample size of 10 for each dosage provides a reasonable power to explore preliminary signals of efficacy. Assuming that a true best overall response rate (ORR) less than 20% indicates inadequate antitumor activity, then at a one-sided type 1 error rate of 5%, the total sample size of 10 will provide 80% power if the true best ORR is 60% or higher, using a 2-stage design method as follows during the first stage, 5 patients will be enrolled and treated on each of Dosages C and D. If 2 or more of the 5 patients on either dosage (C or D) are observed to be responders by the end of the first stage, an additional 5 patients will be enrolled at the applicable dosage. Then, if 5 or more of the total of 10 patients at that dosage are observed to be responders by the end of the second stage, further exploration of drug efficacy is warranted for that dosage.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of the sponsor. The analyses for this study will be descriptive, except for exploratory analyses of biomarker data, as deemed appropriate. Analyses of the biomarker data will be described in a separate biomarker SAP.

Data analyses will be provided by cancer type, dose group, and for all study patients combined, wherever 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, frequency, and percentages.

The following data handling conventions will be used in the analysis (see Table 6.1).

Table 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 document directly.
Enrolled population	Patients who have been assigned to study treatment and have received at least 1 dose of any study treatment.
Screen Failures	Patients who have signed informed consent, do not meet eligibility criteria and are not enrolled.
Evaluable population	Patients who complete 1 cycle of LY3022855 treatment, undergo 1 baseline and 1 posttreatment tumor biopsy procedure, and complete immune blood studies for 1 cycle
Safety Population	Patients who have received at least 1 dose of study drug.

6.2. Handling of Dropouts or Missing Data

Missing data will not be imputed.

6.3. 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, reasons for discontinuation from study treatment, and reasons for discontinuation from study. Reason for

discontinuation from both study treatment and the study will be listed by the pre-determined categories. All patients entered in the study will be included in the summary.

All clinically relevant protocol deviations will be listed by pre-determined categories (for example, inclusion/exclusion criteria, noncompliance with protocol procedures, drug dosage/intervention, use of excluded treatments, informed consent/assent process, continuing after meeting withdrawal criteria, or other).

6.4. Patient Characteristics

6.4.1. Demographics and Baseline Disease Characteristics

Patient demographics and baseline disease characteristics will be listed for all patients on therapy and summarized by cancer type, dose group, and overall.

Patient demographics will include sex, race, age, height, weight, and body mass index (BMI). Baseline disease characteristics will include initial pathological diagnosis and Eastern Cooperative Oncology Group (ECOG) performance status.

6.4.2. Historical Illnesses

Historical illnesses are clinically relevant events in the past that ended before the screening visit. Historical illnesses (using Preferred Term(s) [PTs] from the most current version of the Medical Dictionary for Regulatory Activities [MedDRA]) will be listed for all patients on therapy.

6.4.3. Prior and Post Discontinuation Therapies

Prior systemic therapy, radiotherapy, and surgeries will be listed and summarized for all patients on therapy. Any posttreatment therapies occurring during the study follow up period will also be listed.

6.5. 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 for all patients on therapy by cohort. If concomitant medication use is due to an AE, the associated National Cancer Institute's (NCI) CTCAE v4.0 (NCI 2009) term will be listed.

6.6. Efficacy Analyses

One of the secondary objectives of the study is to measure any antitumor activity. Thus, tumor response data will be reported using listings and descriptive statistics. The ORR is estimated by the proportion of enrolled patients who have a best overall response of complete response (CR) or partial response (PR). The disease control rate (DCR) is estimated by the proportion of enrolled patients who have a best overall response of CR, PR, or stable disease. A 95% exact confidence interval will be constructed to determine the level of precision of the ORR and DCR, if appropriate. Time-to-event variables such as progression-free survival (PFS), duration of response, and overall survival (OS) will be tabulated, if appropriate. The Kaplan-Meier method

(Kaplan and Meier 1958) will be used to estimate the survival curves, medians, and survival rates at specified time points, if applicable.

6.7. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of the study drug and have had samples collected, and PK serum concentrations of IMC-CS4 will be determined.

The parameters for PK analysis will include, but not be limited to, maximum concentration (C_{max}) and trough concentration of LY3022855. Additional 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.

Pharmacodynamic data from all patients undergoing pharmacodynamic assessments will be analyzed.

A separate statistical analysis plan will be prepared for analyses of PK and pharmacodynamics data.

6.8. Biomarker Analyses

Biomarker analyses related to the exploratory objectives of this study will be described in a separate SAP, if deemed necessary.

6.9. Safety Analyses

6.9.1. Extent of Exposure

The number of cycles of treatment received, dose delays, and dose intensity will be summarized. Dose intensity will be defined as the percentage of the planned cumulative dose (based on treatment assignment) administered during the cycle. Dose adjustments including the reasons for dose adjustment will also be listed and summarized.

6.9.2. Adverse Events

All patients who receive at least 1 dose of any study drug will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE, v4.0. In addition, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within MedDRA. 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 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 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 drug or any preexisting condition that increases in CTCAE grade on or after the day of the first dose of study drug. Comparisons of preexisting conditions to on-treatment events at the LLT level will be used in the treatment-emergent 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 dosage and overall for all patients on therapy if deemed appropriate.

6.9.3. Deaths

All deaths on study will be listed along with the reason for death, if known. A summary of deaths will also be produced.

6.9.4. Clinical Laboratory Evaluation

Laboratory data will be listed for all patients on therapy. Abnormal results will be listed separately for all patients on therapy. In addition to the investigator-reported AEs, all relevant hematology and chemistry laboratory values will be graded according to CTCAE v4.0. These calculated grades will be included on the listing and summarized by maximum postbaseline grade over the entire study.

6.9.5. Vital Signs and Other Physical Findings

Temperature, blood pressure, pulse rate, respiration rate, weight, and ECOG performance status will be listed and summarized for all patients on therapy.

6.9.6. Electrocardiograms

All electrocardiogram (ECG) data will be listed.

6.10. Protocol Violations

Protocol violations that can be derived from the data and are related to inclusion/exclusion criteria or treatment will be listed. These violations will include those defined by:

- inclusion/exclusion criteria
- treatment compliance/prohibited medications

6.11. Interim Analyses and Data Monitoring

This is a Phase 1 study designed to document the immunomodulatory activity, and to evaluate safety, toxicity profile, and antitumor activities of LY3022855 treatment in patients with advanced, refractory breast, or prostate cancers, data will be analyzed on an ongoing basis.

For Dosages C and D (patients with breast cancer), interim analyses will be conducted in each dosage to review available safety, efficacy, PK, and pharmacodynamic data after 5 patients in that particular dosage cohort have either completed approximately 3 cycles of therapy or discontinued from the treatment. If 2 or more responders are observed, an additional 5 patients will be enrolled. Further interim analysis may be considered if deemed appropriate by the sponsor.

If it is deemed that enough data are obtained to assess the primary objective and the secondary objectives, a clinical study report might be created before the last patient visit. In this case, all data observed until the data cutoff date will be used for the analysis of safety, efficacy, PK, and pharmacodynamic biomarkers. All data defined in the protocol will continue to be collected from patients on treatment after the data cutoff date. These data may be reported separately, or the analyses on all patients including these data may not be performed.

6.12. Development Safety Update Report Analyses

The following reports will be produced for the Development Safety Update Report (DSUR):

- Summary of patient demographics by age and gender
- Summary of patient demographics by racial groups
- Summary of cumulative patient exposure information
- Listing of Discontinuations Due to Adverse Event During the Reporting Period
- Listing of Subjects Who Died During the Reporting Period.

6.13. 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 treatment group and PT.
- 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 for 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 clinical study report (CSR), manuscripts, and so forth.

A participant flow will be created that will describe how many enrolled patients completed the study, and, for those who did not, the frequency of each reason for not completing. This analysis will be based on study discontinuation, not treatment discontinuation. A patient will be identified as having completed the study on the study discontinuation electronic case report form (eCRF) only after completing the follow up visit.

7. References

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