Protocol I5F-MC-JSCB(d)

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

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Approval Date: 10-Nov-2016

1. Protocol I5F-MC-JSCB(d)

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

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.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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Approval Date: 10-Nov-2016 GMT

2. Synopsis

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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4. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase (also known as alanine transaminase)
AP	alkaline phosphatase
ASCO	American Society of Clinical Oncology
assent	Agreement from a minor or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some institutional review boards [IRBs]/ethical review boards [ERBs]).
AST	aspartate aminotransferase (also known as aspartate transaminase)
$AUC_{(0\text{-}168hr)}$	area under the plasma concentration-time curve from time zero to 168 hours
$AUC_{0\text{-}\infty}$	area under the plasma concentration-time curve from time zero to infinity
audit	A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BLQ	below the quantifiable lower limit of the assay
C*n*W*n*	Cycle and Week numbers
C_{168hr}	concentration at 168 hours
C_{trough}	trough concentration (predose concentration)
CA 15-3	cancer antigen 15-3
CBC	complete blood count
CEA	carcinoembryonic antigen
CK	creatine kinase (also known as creatine phosphokinase)

CL	total body clearance
C_{max}	maximum plasma concentration
CNS	central nervous system
collection database	A computer database where clinical trial data are entered and validated.
companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product.
complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
continued access period	The period between study completion and end of trial during which patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met.
CR	complete response
CRF/eCRF	case report form/electronic case report form: Sometimes referred to as clinical report form, a printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician
CRPC	castrate-resistant prostate cancer
CRS	clinical research scientist
CS7	A recombinant rat IgG1 antibody specific for murine CSF-1R, used as a surrogate antibody to evaluate the effects of targeting CSF-1R on macrophages in murine models of cancer.
CSF	colony-stimulating factor
CSF-1	colony-stimulating factor-1
CSF-1R	colony-stimulating factor-1 receptor
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

DCR	disease control rate
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least one dose of study treatment.
enter	Patients who are entered in the trial are those who have signed the informed consent form directly or through their legally acceptable representatives.
ERB/IRB	ethical review board/institutional review board: A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
FACS	fluorescence-activated cell sorting (a type of flow cytometry)
FOIA	United States Freedom of Information Act
GCP	good clinical practice
GERD	gastroesophageal reflux disease
GnRH	gonadotropin-releasing hormone
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG1	immunoglobulin G, subclass 1
IL	interleukin
IMC-CS4	sponsor code name for recombinant human immunoglobulin G, subclass 1 (IgG1) monoclonal antibody targeted to the colony-stimulating factor-1 receptor (CSF-1R); also known as LY3022855
INF	interferon

informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form (ICF).
interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for data lock.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
irAE	immune-related adverse event
irRECIST	immune-related RECIST (Response Evaluation Criteria in Solid Tumors)
I.V.	intravenous(ly)
K_d	dissociation constant
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
LDH	lactate dehydrogenase
LY3022855	Lilly code name for recombinant human immunoglobulin G, subclass 1 (IgG1) monoclonal antibody targeted to the colony-stimulating factor-1 receptor (CSF-1R); also known as IMC-CS4
LVEF	left ventricular ejection fraction
monitor	A person responsible for ensuring the investigator site complies with the monitoring plan, applicable local standard operating procedures (SOPs), if any, and global Medical SOPs. Monitors are trained on the investigational product(s), the protocol, informed consent form (ICF), any other written information provided to subjects, relevant SOPs, International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP), and all applicable laws (for example, privacy and data protection) and regulations.
MRI	magnetic resonance imaging
MSD	Meso Scale Discovery
NCI	National Cancer Institute
NK	natural killer (cells)
NOAEL	no-observed-adverse-effect level

NYHA	New York Heart Association
open-label	A study in which there are no restrictions on knowledge of treatment allocation; therefore, the investigator and the study participants are aware of the drug therapy received during the study.
ORR	overall response rate
OS	overall survival
patient	A subject with a defined disease.
PCWG2	Prostate Cancer Clinical Trials Working Group
PD	pharmacodynamic or progressive disease Note - "Pharmacodynamic" and "progressive disease" are spelled out throughout this protocol, except as follows: The abbreviation "PD" appears only in the study design figure and in tables in the protocol attachments. In these locations, the abbreviation is clearly defined.
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
Q2W	once every 2 weeks
QW	once weekly
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	To screen a patient who was previously declared a screen failure for the same study
RP2D	recommended Phase 2 dose
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	A patient who does not meet one or more criteria required for participation in a trial.
sponsor	The party who takes responsibility for the initiation, management and/or financing of a clinical study.

study completion	This study will be considered complete when 16 evaluable patients are attained.
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TK	toxicokinetic
TNF	tumor necrosis factor
TPO	third-party organization
ULN	upper limit of normal
V_{ss}	volume of distribution at steady state
WOCBP	women of childbearing potential

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

5. Introduction

5.1. Rationale and Justification for the Study

Colony-stimulating factor-1 receptor (CSF-1R) is a tyrosine kinase receptor expressed selectively on macrophage and granulocyte cell lineages in normal individuals and on some tumor cells in cancer (Kacinski 1995; Sasmono et al. 2003). Upon colony-stimulating factor-1 (CSF-1) or interleukin-34 (IL-34) binding to CSF-1R, CSF-1R and downstream signaling molecules are phosphorylated and activated, resulting in the regulation of proliferation, differentiation, survival, and migration of monocytes/macrophages (Bourette and Rohrschneider 2000; Pixley and Stanley 2004; Lin et al. 2008). In cancer, increased infiltration of macrophages within and surrounding the tumor mass correlates with increased tumor invasiveness and growth (Nowicki et al. 1996; Lewis and Pollard 2006), and depleting these tumor-associated macrophages results in decreased growth of experimental tumors in mice (Lin et al. 2001, 2006). While CSF-1R levels are infrequently increased in tumors compared with analogous normal tissues, increased CSF-1 in sera of cancer patients is more frequently observed and is associated with poor prognosis and severity of disease in multiple cancers, in particular prostate and breast cancers (Lawicki et al. 2006; Mroczko et al. 2007; Ide et al. 2008; Zhu et al. 2008). These data suggest that targeting CSF-1R has potential to limit cancer progression.

LY3022855 (also known as IMC-CS4) is a recombinant human monoclonal antibody of the immunoglobulin G, subclass 1 (IgG1) targeting CSF-1R. LY3022855prevents the ligands CSF-1 and IL-34 from binding to CSF-1R CCI [redacted], and in this way inhibits CSF-1R activation. CSF-1R activation is required for proper functioning and survival of tumor-associated macrophages. Thus, by blocking CSF-1R activation, CCI [redacted]

Interactions between the innate and adaptive immune systems are critical for normal immune function and also in the tumor microenvironment. For example, high numbers of tumor-associated macrophages inversely correlate with infiltration by CD8+ T cells.

Anti-CSF-1R treatment that limits tumor-associated macrophages enhances CD8+ T-cell infiltration, leading to decreases in tumor burden (DeNardo et al. 2011). Moreover, in a syngeneic breast cancer model, depletion of CD8+ T cells rendered treatment with CS7 less efficacious, indicating interplay between macrophage activity and T-cell infiltration. Thus, knowledge not only of the macrophage subpopulation but also of the T-cell subset may affect the efficacy of LY3022855 treatment in patients.

CCI [redacted] In addition, pharmacodynamic results from the ongoing Phase 1 dose-escalation study of LY3022855, Study I5F-IE-JSCA (also known as IMCL CP24-1001; hereafter referred to as JSCA), have suggested target engagement and biologic activity at a dosage of 1.25 mg/kg once weekly. CCI [redacted]

The sponsor, monitor, and investigators will perform this study in compliance with the protocol, good clinical practice (GCP) and International Conference on Harmonisation (ICH) guidelines, and applicable regulatory requirements.

5.2. Objectives

5.2.1. 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).

5.2.2. 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) (Nishino et al. 2013) (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

5.2.3. Exploratory Objectives

The exploratory objectives of this study are:

- To explore serum biomarkers that may be relevant to the mechanism of action of LY3022855, CCI [redacted]
- To explore the pharmacodynamic effects of LY3022855 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

5.3. General Introduction to LY3022855

LY3022855 is a recombinant human monoclonal antibody of IgG1 that targets CSF-1R, a tyrosine kinase receptor expressed selectively on macrophage and granulocyte cell lineages in normal individuals and on tumor cells in cancer (Kacinski 1995; Sasmono et al. 2003).

CCI [redacted]

The present trial will look specifically at the immunomodulatory activity of LY3022855 in patients with advanced breast or prostate cancer refractory or intolerant to at least one prior therapy for their cancer.

Refer to Section 5.1 for a review of the literature relevant to this study. Refer to Section 5.4.5 for a summary of prior clinical findings relevant to the present trial.

5.3.1. Definition of Immunomodulatory Change

Immunomodulatory change is the capacity to modify, regulate, or potentiate one or more immune functions by changes in immune cell activity or ratios or changes in immune or inflammatory cytokine levels. Data from the sponsor's preclinical animal studies and the literature (DeNardo et al. 2011) highlight the importance of T cells in anti-CSF-1R responses, illustrating the necessity of studying this interaction further.

The present study will evaluate changes in immune function in patients with advanced, refractory breast or prostate cancer by assessing changes in subset distribution and activation marker phenotypes in CD4, CD8, regulatory T cells, and myeloid cells in the peripheral blood. In addition, immune function will be evaluated through assessments of specific immune cytokines in peripheral blood, such as IL-2 and TNF-α, which modulate immune function.

5.4. LY3022855 – Nonclinical and Clinical Experience

5.4.1. Nonclinical Pharmacokinetics

The pharmacokinetics of LY3022855 were evaluated in mice administered 20 mg/kg and in cynomolgus monkeys at dose levels that ranged from 10 to 180 mg/kg. The PK of LY3022855 in cynomolgus monkeys was characterized by a relatively long serum half-life ($t_{1/2}$) after single (183-275 hours) or multiple doses (158-470 hours); these half-lives were substantially longer than that observed in CD-1 mice (110 hours). Accumulation (approximately 2-fold) of LY3022855 was evident after repeated once-weekly dosing in monkeys, suggesting that accumulation may similarly occur in humans, depending on the frequency of dosing. The estimated volume of distribution of LY3022855 in monkeys (approximately 29-64 mL/kg) indicated that LY3022855 was not substantially distributed beyond the vasculature. In the cynomolgus monkey studies, LY3022855 serum exposures were generally proportional to the increases in dose from 10 to 180 mg/kg and no sex differences were observed.

The concentration of serum CSF-1 increased in cynomolgus monkeys that were treated with LY3022855, suggesting that CSF-1 is a pharmacodynamic marker of LY3022855 exposure. However, in contrast to the LY3022855 levels, CSF-1 levels did not increase proportionally with the increase in LY3022855 dose. The concentration of CSF-1 reached apparent maximal level in all dose groups after the first dose, typically between 24 and 168 hours following administration of LY3022855. This observation suggests that the pharmacodynamic effect of LY3022855 on circulating CSF-1 reached saturation at the lowest dose levels (10 or 20 mg/kg). CSF-1 levels were generally sustained throughout the sampling period. However, in the repeat-dose cynomolgus monkey study, the concentration of CSF-1 began to decrease in some animals from the low- (20 mg/kg) and middle- (60 mg/kg) dose groups during the recovery period.

Formal studies to characterize the metabolism and disposition of LY3022855 have not been conducted. As a monoclonal antibody, LY3022855 will be largely confined to the extracellular space, which is supported by data from numerous investigations and is consistent with the PK evaluation of LY3022855. No formal metabolism studies of LY3022855 have been performed

because the catabolism of antibodies by mammalian systems is largely understood and formal studies of the metabolic degradation of these molecules are not warranted.

For details on the nonclinical PK of LY3022855, refer to Section 5 of the current Investigator's Brochure (IB).

5.4.2. Nonclinical Pharmacokinetic/Pharmacodynamic Model

One of the main pharmacological effects of LY3022855 proposed to underlie the inhibition of cancer progression is the depletion of tumor-associated macrophages. To model this effect and estimate the minimum effective blood level required to achieve significant antitumor effects, cancer models established in mice were utilized. However, since LY3022855 does not bind to murine CSF-1R, a surrogate antibody, CS7, was developed and utilized in order to examine PK/pharmacodynamic relationships. The binding affinity of CS7 to murine CSF-1R (dissociation constant [K_d] = 0.13nM) is 6-fold greater than that of LY3022855 to human CSF-1R (K_d = 0.8nM). However, comparable potencies of the antibodies were observed in cell-based assays of inhibition of CSF-1-induced phosphorylation (IC_{50} = 0.3nM for both antibodies), monocyte differentiation (IC_{50} = 0.3nM vs 0.25nM for CS7 and LY3022855, respectively), and inhibition of monocyte proliferation (IC_{50} = 0.13nM or 0.1nM for CS7 and LY3022855, respectively). Therefore, CS7 and LY3022855 were anticipated to have similar pharmacological effects in vivo at similar concentrations. Hence, CS7 was utilized in animal models to directly predict the trough serum LY3022855 levels necessary to achieve relevant efficacy in human subjects.

Based on these assumptions, to estimate target serum concentrations for efficacy in initial clinical investigations, trough concentrations associated with efficacy were determined in human breast cancer HCC-1954 and human leukemia NKM-1 models established in mice. LY3022855 was evaluated in the leukemia model established following intravenous (I.V.) injection of CSF-1R-expressing NKM-1 cells. The rat surrogate, CS7, was used in the breast cancer model established following subcutaneous injection of CSF-1R-negative HCC-1954 cells. The results from the 2 studies identified markedly different efficacious concentrations for the antibodies in the different models. The human NKM-1 model appeared very sensitive to the antitumor effect of LY3022855, as efficacy was achieved at mean trough concentrations down to 0.2 µg/mL. For CS7, notably higher doses and concentrations were required to inhibit human HCC-1954 breast cancer tumor growth, as a mean trough concentration of 425 µg/mL was associated with efficacy.

5.4.3. Clinical Pharmacokinetics

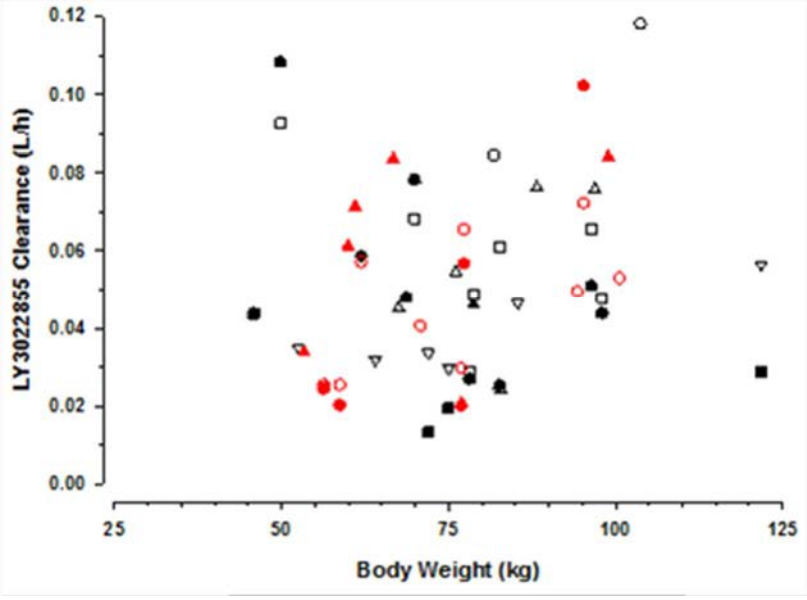
As of 28 January 2016, the clinical experience of LY3022855 PK comprised 27 patients enrolled in Study JSCA (0.3 mg/kg once weekly [QW] [n=4], 0.6 mg/kg QW [n=3], 1.25 mg/kg QW [n=5], 1.25 mg/kg once every 2 weeks [Q2W] [n=9], and 2.5 mg/kg QW [n=6]), and 14 patients enrolled in Study JSCB (1.25 mg/kg Q2W [n=9] and 1 mg/kg on Weeks 1, 2, 4, and 5 of every 6-week cycle [n=5]).

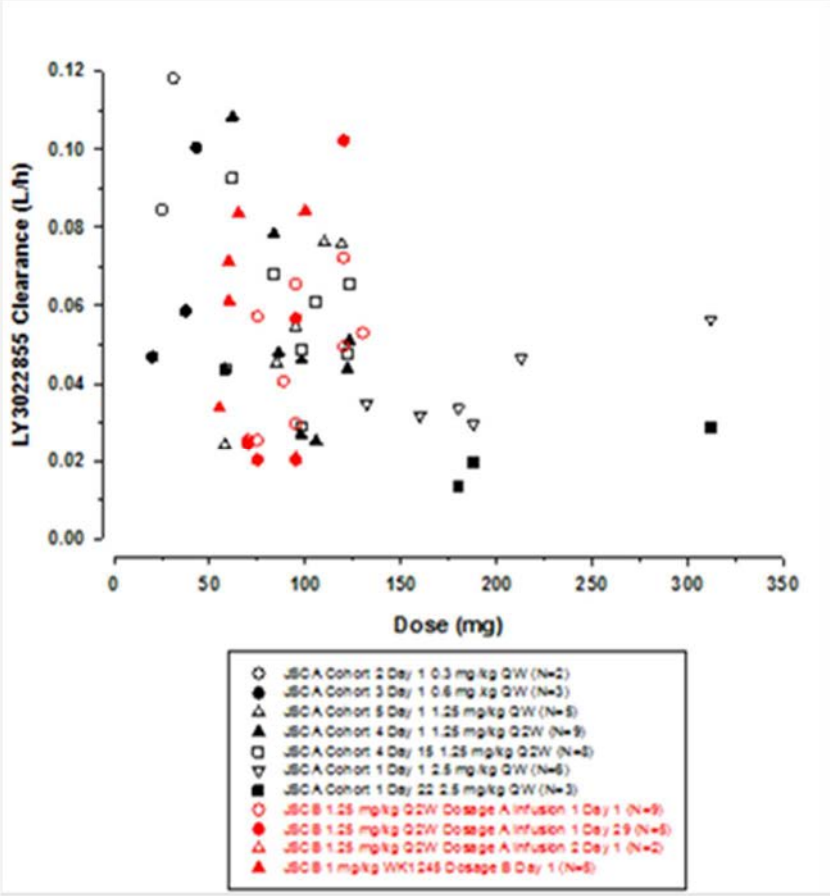
LY3022855 in cancer patients exhibited moderate total body clearance (CL) (mean values on Day 1 ranged from 0.0378 to 0.0651 L/h), low volume of distribution at steady state (V_{ss}) (mean values on Day 1 ranged from 2.85 to 4.93 L), and moderate $t_{1/2}$ (mean values on Day 1 ranged from 30.8 to 92.2 hours).

LY3022855 CL appeared to be nonlinear with respect to LY3022855 concentration, where higher doses of LY3022855 tended to exhibit lower CL values. However, this apparent nonlinearity was confounded by the high incidence of concentrations reported as below the quantifiable lower limit of the assay (BLQ), which could artificially inflate the calculated CL at lower doses.

An apparent lack of relationship between patient body weight and LY3022855 CL (Figure JSCB.1, upper panel) resulted in an amended dose-escalation plan for Study JSCA, to evaluate the safety, PK, and immunogenicity of LY3022855 using a fixed-dosing approach (that is, mg as opposed to mg/kg).

The clinical PK of LY3022855 are described in greater detail in Section 6.1 of the IB.





Abbreviations: N = number of patients treated; QW = once weekly; Q2W = once every 2 weeks.

Figure JSCB.1. Individual observed clearance versus patient body weight (upper panel) and LY3022855 dose (lower panel) for Studies JSCA and JSCB.

5.4.4. Nonclinical Toxicology

A standard nonclinical toxicology program for advancement of a monoclonal antibody into clinical trials in oncology indications was conducted to assess the safety and toxicity of LY3022855. The nonclinical safety assessment of LY3022855 was conducted in cynomolgus monkeys. This species was considered a relevant model for the nonclinical safety evaluation of LY3022855, based on a preliminary cross-species evaluation of tissue/receptor binding and/or functional in vitro pharmacological activity in human and cynomolgus monkey test systems and in a subsequent comprehensive tissue cross-reactivity study using full panels of monkey and human tissues. The toxicology studies conducted with LY3022855 included an exploratory single-dose toxicity and toxicokinetic (TK) dose range-finding study and a pivotal 4-week repeat-dose good laboratory practice toxicity, TK, and immunogenicity study with a 6-week recovery period. Animals were administered LY3022855 by I.V. infusion, the intended clinical method of administration, using the dosing schedule (once weekly) in the planned initial clinical investigations of LY3022855. The pivotal study included evaluations of relevant safety

pharmacology parameters. Because of an anticipated effect of LY3022855 on circulating levels of the target ligand, CSF-1, the levels of CSF-1 were also measured in the study animals as a potential marker of the pharmacodynamic activity of the antibody. A thorough assessment of peripheral blood and spleen mononuclear cell subsets and an immunohistochemical analysis of CD68+ cells (cellular marker of monocytes/macrophages) in liver and spleen were also included to determine the effects that blockade of the CSF-1 receptor might have on these endpoints.

Assessment of the genotoxicity potential of monoclonal antibodies is not relevant and was, therefore, not studied. Based on the early stage of clinical development and the oncology indication, reproductive toxicity studies of LY3022855 have not been conducted.

5.4.4.1. Single-Dose Toxicity

Single-dose administration of LY3022855 at dose levels of 10, 40, and 140 mg/kg administered by I.V. infusion over a 15-minute period was well tolerated in cynomolgus monkeys (2 monkeys/sex/group) during the 14-day observation period. Sustained dose-proportional exposure to LY3022855 was generally observed throughout the 14-day observation period at all dose levels following administration, with no apparent sex differences. CCI [redacted]

CCI [redacted] Similar elevations in serum enzyme levels have also been observed when treating with other pharmacological agents targeting CSF-1R (Wang et al. 2011) or CSF-1 (Radi et al. 2011).

No other adverse clinical signs or effects on food consumption, body weight, hematology, and organ weights were associated with administration of LY3022855.

CSF-1 serum levels increased relatively quickly after LY3022855 administration and remained sustained throughout the 14-day observation period. CSF-1 was not detected in any control animals at any time. The maximum levels of CSF-1 reached were comparable across dose groups, suggesting that a maximal pharmacodynamic effect of LY3022855 on this parameter was achieved at even the lowest dose level in the study.

The no-observed-adverse-effect level (NOAEL) in this study was considered to be CCI [redacted] This dose corresponded to a dosing Day 1 CCI [redacted]

5.4.4.2. Repeat-Dose Toxicity

In the pivotal repeat-dose toxicity, TK, and immunogenicity study of LY3022855, doses of 0, 20, 60, and 180 mg/kg/dose LY3022855 were administered by I.V. infusion once weekly to cynomolgus monkeys (5/sex/group) for 4 weeks, followed by a 6-week recovery period. Standard toxicological and relevant safety pharmacology (cardiovascular, central nervous [CNS], and respiratory systems) endpoints were assessed. As in the single-dose study, circulating levels of CSF-1 were measured. A thorough assessment of peripheral blood and spleen mononuclear cell subsets and an immunohistochemical analysis of CD68+ mononuclear cells in liver and spleen were also conducted.

Intravenous infusion of LY3022855 was generally well tolerated at all dose levels. Sustained dose-proportional to slightly-greater-than-dose-proportional increases in exposure to LY3022855 were generally observed, and no sex differences in exposure were apparent. Moderate accumulation (approximately 2-fold) of LY3022855 occurred after repeated administration. Anti-drug antibodies (ADA) CCI

As noted in the single-dose exploratory study, circulating concentrations of CSF-1 increased shortly after LY3022855 administration. CSF-1 was not detected in any control animals. In contrast to LY3022855, the concentration of CSF-1 did not vary with dose, as comparable maximum levels were reached in all 3 dose groups. Towards the end of the recovery period, CSF-1 levels generally decreased in the 20- and 60-mg/kg dose groups, but remained elevated in the 180-mg/kg dose group.

The key toxicological findings attributed to LY3022855 administration in this study were periorbital swelling, increases in serum transaminases as noted in the exploratory study, changes in leukocyte populations (monocytes, neutrophils, CD68+ mononuclear cells, natural killer [NK] cells), and target organ effects in liver (Kupffer cell hypertrophy/hyperplasia), spleen (follicular hypertrophy/dendritic cell hyperplasia), and bone marrow (hypercellularity). The immunomodulatory effects on leukocytes, Kupffer cells, spleen, and bone marrow likely reflect an exaggerated pharmacological response to LY3022855, possibly associated with elevations in circulating CSF-1 levels noted during the study.

Elevations in ALT after the last dosing of LY3022855 were generally minimal in the lowest dose group (20 mg/kg) and minimal to moderate at the 60- and 180-mg/kg dose levels. AST levels were minimally to moderately increased at all dose levels. ALT and AST returned to baseline in the 20-mg/kg group and trended towards baseline in the 60- and 180-mg/kg groups during the recovery period, but remained increased in some individual animals compared with baseline. No histological changes in the liver were noted to correlate with the transaminase increases, nor were any changes noted in liver functional parameters (that is, AP, bilirubin, and coagulation). Therefore, based on the small magnitude of the elevations and the absence of histological or functional changes, the increases in ALT and AST were not considered adverse.

Increases in circulating white blood cells due to increases in neutrophils and monocytes were observed in both sexes at 60 and 180 mg/kg. Flow cytometry analysis of spleen and peripheral blood revealed increases in monocytes in spleen and blood at 60 and 180 mg/kg and reductions in splenic NK cells in all LY3022855-treated groups. Variability in NK cell numbers in the peripheral blood of animals in all dose groups (including control) precluded assigning a definitive relationship with LY3022855 treatment. These changes in white blood cell counts, in conjunction with minimal reversible increases in serum globulin concentrations with a corresponding decrease in albumin to globulin ratio, are consistent with the presence of an inflammatory response. However, no histopathologic evidence of inflammation was observed. The monocyte, neutrophil, and globulin changes were reversible by the end of the recovery period, while the splenic NK cell reductions were still apparent in some animals. These changes were not considered adverse because of their small magnitude.

Anatomic pathology changes attributed to the administration of LY3022855 at the end of the dosing period included increased spleen weights in females (all dose groups), which generally correlated with splenic follicular hypertrophy (males at 60 and 180 mg/kg; females at 20 and 180 mg/kg), bone marrow hypercellularity (all female dose groups, one male at 60 mg/kg), bone marrow lymphoid aggregates (one male, one female at 180 mg/kg), and Kupffer cell hypertrophy/hyperplasia (primarily minimal, all male dose groups, one female at 60 mg/kg). Immunohistochemical analyses confirmed the presence of increased size or number of CD68+ Kupffer cells in the liver and increased numbers of CD68+ mononuclear cells in the spleen at all dose levels. The CD68+ cells in the spleen were likely follicular dendritic cells. The immunohistochemical findings in liver and spleen generally correlated with the histopathologic diagnoses of Kupffer cell hypertrophy/hyperplasia and splenic follicular hypertrophy. Similar anatomic pathology findings in spleen, liver, and bone marrow were observed after the recovery period. These changes were not considered adverse because of their small magnitude.

Slight to moderate periorbital swelling was observed primarily during the recovery phase in all LY3022855-treated groups (20, 60, and 180 mg/kg/dose). This clinical sign has been reported to occur in humans with another antibody to CSF-1 (Sadis et al. 2009) and may thus represent a delayed response to LY3022855 in the treated monkeys. Watery feces was observed only in the 60-mg/kg/dose animals, but is considered possibly related to the administration of LY3022855. These clinical signs were not considered adverse based on their limited impact to the overall health of the animal. No adverse effects were noted in assessments of the central nervous (neurological behavioral examination), respiratory (rate), or cardiovascular (heart rate, blood pressure, electrocardiogram [ECG]) systems. In addition, no evidence of an adverse reaction or intolerance attributable to LY3022855 was apparent at the injection sites after I.V. infusion in the cynomolgus monkey repeat-dose toxicity studies.

Based on the absence of any definitive LY3022855-related adverse findings, the NOAEL for LY3022855 administered via 15-minute I.V. infusion weekly on 4 occasions was considered to be 180 mg/kg/dose. The dose corresponded to a dosing Day 22 mean C_{max} of 7985 µg/mL, C_{168hr} of 2945 µg/mL, and mean $AUC_{(0\text{-}168hr)}$ of 711340 µg· hr/mL.

5.4.5. Clinical Experience

Clinical experience with LY3022855 comprises 43 patients (as of 28 January 2016) who received the following doses I.V. in 2 ongoing Lilly-sponsored Phase 1 studies (I5F-IE-JSCA [JSCA] and I5F-MC-JSCB [JSCB]): 2.5 mg/kg QW (n=6), 0.3 mg/kg QW (n=4), 0.6 mg/kg QW (n=3), 1.25 mg/kg Q2W (n=20), 1.25 mg/kg QW (n=5), and 1 mg/kg on Weeks 1, 2, 4, and 5 of every 6-week cycle (n=5). At the first human dose studied, 2.5 mg/kg QW (Study JSCA), which was also the highest dose administered, laboratory abnormalities, including Grade 2-3 creatine kinase (CK) and Grade 2-3 AST elevations, were noted in 5 patients but were not classified as dose-limiting toxicities (DLTs) due to the lack of clinical signs or symptoms of organ toxicity. Because of these laboratory abnormalities, the protocol for Study JSCA was amended and dose escalation was restarted at a lower dose, 0.3 mg/kg QW.

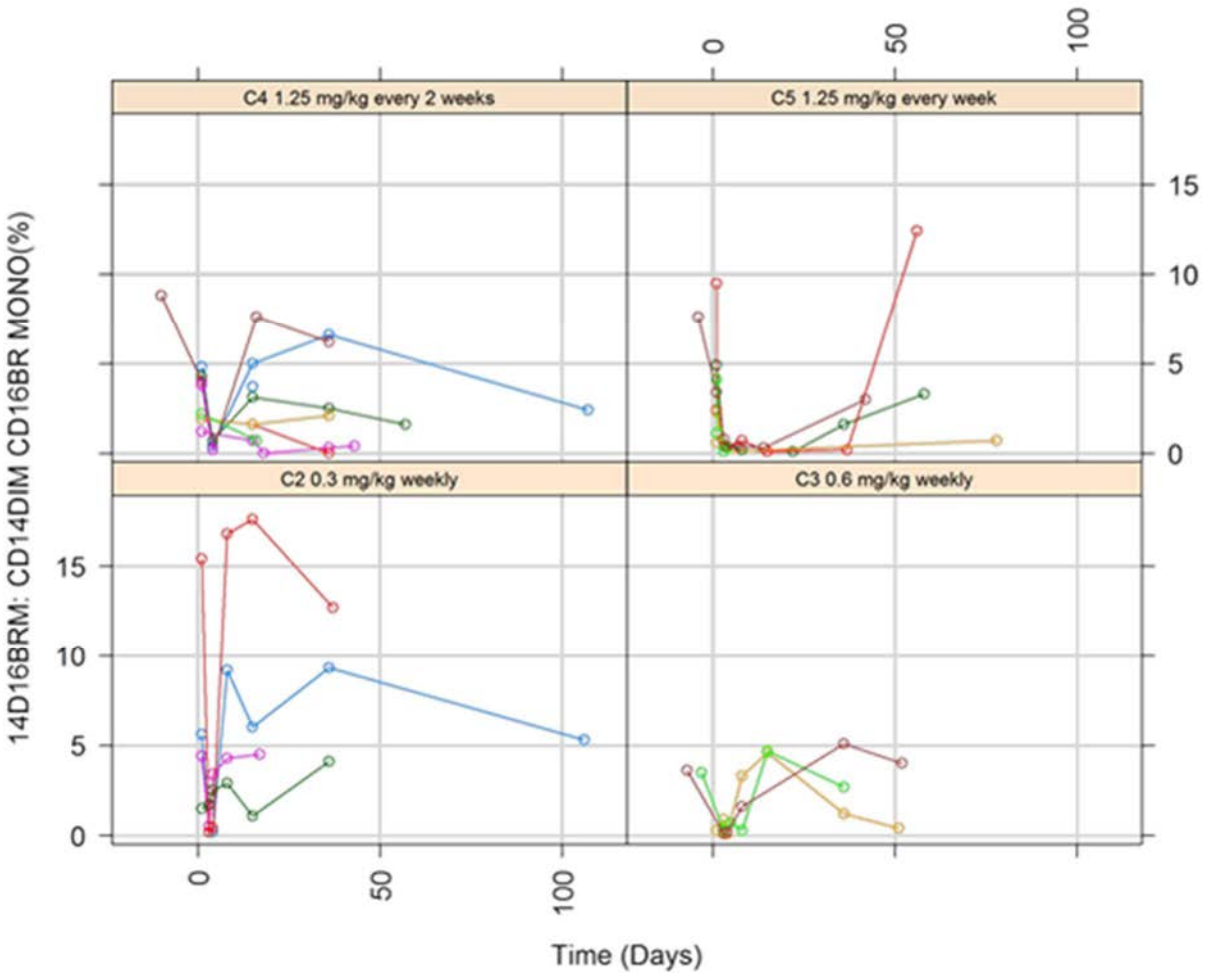
Elevated levels of CK and AST, in the absence of clinical signs or symptoms or other laboratory abnormalities suggestive of end-organ damage are, in retrospect, believed to be pharmacodynamic indicators of target engagement, rather than markers of drug-related toxicity. This belief is strengthened by findings of Radi et al. (2011), in which preclinical models support the hypothesis that increases in the levels of serum enzymes can be the result of decreases in Kupffer cells, in the apparent absence of hepatic or skeletal muscle injury. In all cases where elevated enzymes were observed following LY3022855 administration in Study JSCA, the levels decreased to Grade <2 upon discontinuation of LY3022855, indicating that these effects were reversible.

As of 12 October 2016, four DLTs have been observed in Study JSCA: an event of left ventricular dysfunction (Cohort 4, 1.25 mg/kg Q2W), an event of pancreatitis (a patient in Cohort 5, 1.25 mg/kg QW), an event of rhabdomyolysis (another patient in Cohort 5), and an event of Grade 3 CK elevation (Cohort 7a, 150 mg QW). The patient with the DLT of left ventricular dysfunction had a baseline left ventricular ejection fraction (LVEF) of 35%, which obfuscated the relationship between LY3022855 and the DLT event; therefore, the patient was considered to be a suboptimal candidate for study participation. The patient in Cohort 5 who experienced pancreatitis had a medical history significant for irritable bowel syndrome and gastroesophageal reflux disease (GERD), rendering the patient prone to nausea and abdominal pain. During the course of treatment in Study JSCA, this patient's serum levels of lipase gradually increased, from 21 U/L (baseline) to 138 U/L (Cycle 1, Week 6 [C1W6]) (C1W2 = 79 U/L, C1W3 = 90 U/L, C1W4 = 121 U/L, C1W5 = 149 U/L). Following the C1W3 administration of LY3022855, the patient's treatment with study drug was held due to rising lipase levels. Steroids were not initiated until the patient presented for medical attention with complaints of nausea, vomiting, and abdominal pain on C1W6, at which time the patient was diagnosed with Grade 3 pancreatitis. The symptoms improved with hospitalization, supportive therapy, and systemic steroids. Although this particular case resulted in a DLT, the relationship between elevated lipase and gastrointestinal symptoms is not clear, given the patient's history of irritable bowel syndrome and GERD.

Following the occurrence of the 2 DLTs in Cohort 5 of Study JSCA, dose escalation was temporarily halted. Subsequent PK and pharmacodynamic analyses revealed the following:

- A lack of correlation between body weight and LY3022855 clearance (Figure JSCB.1)
- Intermittent inhibition of CSF-1R signaling with Q2W dosing of LY3022855, as evidenced by levels of both circulating CSF-1 and peripheral $CD14^{dim}CD16^{bright}$ cells by fluorescence-activated cell sorting (FACS) (Figure JSCB.2)
- Sustained inhibition of CSF-1R signaling with 2.5 mg/kg QW and 1.25 mg/kg QW dosing (Study JSCA Cohorts 1 and 5, respectively) of LY3022855, as evidenced by levels of both circulating CSF-1 and peripheral $CD14^{dim}CD16^{bright}$ cells by FACS (Figure JSCB.2)

Based on these observations, the protocol for Study JSCA was amended to: (1) examine fixed (non-weight-based) dosing of LY3022855 on weekly administration schedules to optimize the biological effects of LY3022855 on CSF-1R inhibition, (2) redefine a DLT as any LY3022855-related AE that occurs during Cycle 1 and does not improve to Grade ≤2, unless stated otherwise, despite medical management, including steroids (if applicable) within 7 days of documented occurrence, and (3) incorporate management guidelines for immune-related AEs. Dosing in Study JSCA resumed at a fixed dose of 100 mg QW, which is comparable to 1.33 mg/kg in a 75-kg person and within the coefficient of variation in exposure (34% to 49%). As of 12 October 2016, 3 patients in Study JSCA have received 100 mg QW for 6 weeks (Cycle 1, DLT assessment period) without experiencing a DLT. Of the 3 patients treated at the next higher dose level of 150 mg QW, 1 patient experienced a DLT of Grade 3 CK elevation associated with elevated serum and urine myoglobin.



Abbreviation: C = cohort.

Figure JSCB.2. $CD14^{dim}CD16^{bright}$ (relative percentage of $CD45^{+}$ $HLA\text{-}DR^{+}$ $CD14^{+}$) in the blood of patients from Study JSCA.

More information about the known and expected benefits, risks, and reasonably anticipated AEs may be found in the IB. Information on AEs expected to be related to the investigational product may be found in Section 7 (Development Core Safety Information) of the IB. Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

5.5. Rationale for Selection of Dose

The optimal dose and schedule of LY3022855 in humans are not known. The protocol will utilize 4 dosages of LY3022855,where Dosages A and B are weight based, while Dosages C and D are non-weight based (that is, fixed), as prior data suggest that weight-based dosing does not affect exposure (Section 5.4.3). Refer to Table JSCB.1 for a summary of the LY3022855 dosages to be used in this study.

Table JSCB.1. Summary of LY3022855 Dosages in Study JSCB

Dosage	Dose	Schedule (based on a 6-week cycle)
Dosage A (weight based dose)	1.25 mg/kg	Q2W
Dosage B (weight based dose)	1 mg/kg	Weeks 1, 2, 4, and 5 of a 6-week cycle
Dosage C (non-weight based/fixed dose)	100 mg	QW
Dosage D (non-weight based/fixed dose)	100 mg	Q2W

Abbreviations: QW = weekly; Q2W = every 2 weeks (Weeks 1, 3, and 5).

The rationale for each dosage is presented as follows.

Dosage A is based on the following observations from Study JSCA:

- A dosage of 1.25 mg/kg every 2 weeks was the lowest dosage tested in Study JSCA that demonstrated a significant increase in the 2 ligands of CSF-1R (CSF-1, IL-34).
- Results demonstrated an acceptable clinical safety profile of LY3022855 at a dose of 1.25 mg/kg every 2 weeks.

Dosage B rationale:

- PK parameters from Study JSCA revealed a 34% to 49% coefficient of variation in exposure ($AUC_{0-\infty}$) for patients administered LY3022855 at 1.25 mg/kg every 2 weeks or 1.25 mg/kg weekly. Dosage B at 1 mg/kg on Weeks 1, 2, 4, and 5 of a 6-week cycle will result in a cumulative dose of 4 mg/kg every 6 weeks, which is 0.25 mg/kg (6.7%) greater than the cumulative dose per (6-week) cycle of Dosage A (1.25 mg/kg every 2 weeks). However, a 6.7% increase in exposure is within the variation of exposure documented in Cohorts 4 and 5. Thus, Dosage B is a reasonable dose and schedule in terms of safety. Additionally, dosing 2 consecutive weeks is expected to enhance inhibition of CSF-1R, based upon preliminary pharmacodynamic data (CSF-1 and IL-34) from Cohorts 4 and 5. Furthermore, interruption of dosing every 3 weeks provides an opportunity for LY3022855-associated laboratory abnormalities to normalize prior to resumption of dosing, as has been observed in the Phase 1 dose-escalation Study JSCA.

Dosage C rationale:

- Pharmacodynamic data (Section 5.4.5) suggest that weekly administration of LY3022855 results in enhanced target engagement. Thus, Dosage C will be implemented to examine weekly administration of LY3022855.

Dosage D rationale:

- It has been observed that all patients who were treated with LY3022855 and experienced antitumor activity (as evidenced by tumor shrinkage or stability) as of 24 August 2016 were treated on a Q2W schedule. Thus, Dosage D will be implemented to continue exploring Q2W dosing, but at a fixed (non-weight-based) dose. Furthermore, the Q2W schedule may be preferable for quality of life, because the patient will require fewer clinic visits.

6. Investigational Plan

6.1. Study Population

Individuals with advanced, refractory breast or prostate cancer are eligible. Specifically, to be enrolled in the trial, patients must have a biopsy-proven breast or prostate cancer diagnosis with clinical evidence of advanced-stage disease and must be willing to undergo 2 separate core needle or surgical biopsy procedures (1 at baseline [predose] and 1 prior to Cycle 2), optimally from the same lesion. Patients are considered evaluable if they complete 1 cycle of treatment (at least Cycle 1, Day 43, based on a 6-week cycle), undergo 1 baseline and 1 posttreatment tumor biopsy procedure (ie, attempted, whether the biopsy is successful or not), and complete immune blood studies for 1 cycle.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened if agreed upon by the sponsor. If a patient discontinues prior to the second biopsy, the patient will be replaced.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1.1. Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria during screening prior to first dose of study drug.

[1] Have a confirmed diagnosis of advanced, refractory breast or prostate cancer that is evaluable by radiologic testing. Patients must have experienced tumor progression on or treatment intolerance to at least one prior therapy for their cancer and have declined or are ineligible for a standard treatment.

[2a] For patients with metastatic castrate-resistant prostate cancer (CRPC) only:

a) must continue ongoing androgen deprivation therapy (gonadotropin-releasing hormone [GnRH] agonist or antagonist) with castrate levels of serum testosterone <50 ng/dL determined within 4 weeks prior to starting treatment;

b) if receiving an antiandrogen as part of first-line hormonal therapy, must have shown progression of disease off the antiandrogen prior to enrollment;

c) must be willing to continue androgen deprivation therapy while on study, if no prior orchiectomy;

d) must meet at least 1 of the following 3 criteria for progressive metastatic disease, according to PCWG2 criteria:

i. a rise in prostate-specific antigen (minimal value 2 ng/mL; ≥3 consecutive rising values), or

ii. ≥2 new metastases on transaxial imaging or radionuclide bone scan, or

iii. soft tissue progression;

e) replacement hormone therapy (including prednisone or equivalent up to 10 mg/day) initiated before study entry is permitted per Section 7.5.

[2b] For patients with breast cancer only:

a) may continue ongoing antiestrogen therapy (for example, an aromatase inhibitor),

b) replacement hormone therapy initiated before study entry is permitted per Section 7.5, and

c) may continue ongoing trastuzumab therapy.

[3] Are ≥18 years of age.

[4] Have given written informed consent prior to any study-specific procedures.

[5] Have adequate organ and hematologic function, including:

- Hepatic: Bilirubin ≤1.5 × the upper limit of normal (ULN), and ALT and AST ≤3.0 × ULN. For patients with tumor involvement of the liver, AST and ALT ≤5.0 × ULN are acceptable. For patients with tumor involvement of the bone, alkaline phosphatase ≤5.0 × ULN is acceptable.
- Renal: Serum creatinine ≤2.0 × ULN.
- Absolute neutrophil count (ANC) ≥1.0 × 10^9/L.
- Hemoglobin ≥9 g/dL (5.58 mmol/L).
- Platelets ≥90 × 10^9/L.

[6] Have a performance status of ≤2 on the Eastern Cooperative Oncology Group (ECOG) scale. See Attachment 8.

[7] Except as addressed in Inclusion Criterion [2], have discontinued all disease-modifying therapy for the primary cancer >28 days prior to initiation of study treatment. In addition, clinically significant toxicities associated with any prior therapy for the primary cancer, including investigational treatments, have resolved or stabilized to Grade ≤1 toxicity >28 days prior to initiation of study treatment with the exception of neuropathy, which must have resolved to Grade ≤2. Continuation of a stable dose (minimum of 28 days prior to study entry) of denosumab or bisphosphonate is permitted on study.

[8] Are reliable and willing to make themselves available for the duration of the study and are willing and able to comply with study procedures (includes 1 baseline and 1 posttreatment tumor biopsy procedure) and instructions. Patients enrolled in this trial must receive the study treatment at the study center.

[9a] Male patients:

agree to use a reliable method of birth control and to not donate sperm during the study and for at least 12 weeks following last dose of study drug or country requirements, whichever is longer.

[9b] Female patients:

are women of childbearing potential who test negative for pregnancy within 7 days prior to enrollment based on a urine or serum pregnancy test and agree to use a reliable method of birth control during the study and for 12 weeks following the last dose of the study drug and also must not be breastfeeding,

OR

are postmenopausal women. Postmenopausal women include women with:

1) at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by medical history

or

2) spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea that induced the amenorrhea (for example, oral contraceptives, hormones, gonadotropin releasing hormone, antiestrogens, selective estrogen receptor modulators, or chemotherapy)

or

3) spontaneous amenorrhea 6 to 12 months and a follicle-stimulating hormone level greater than 40 mIU/mL.

[10] Have an estimated life expectancy that, in the judgment of the investigator, will permit the patient to complete 1 cycle of treatment.

[11] May have received treatment with an investigational product or non-approved use of a drug (other than the study drug used in this study) or device for non-cancer indications; however, not within 28 days prior to the initial dose of study drug (see also Exclusion Criterion [12]).

Refer to Section 7.5 for additional details regarding concomitant therapy.

6.1.2. Exclusion Criteria

Potential study patients may not be included in the study if any of the following apply during screening.

[12] Have received treatment within 28 days prior to the initial dose of study drug with an investigational product or non-approved use of a drug or device (other than the study drug/device used in this study) for non-cancer indications or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study (see also Inclusion Criterion [11]).

[13] Have serious preexisting medical conditions (left to the discretion of the investigator).

[14] Have symptomatic CNS malignancy or metastasis (screening not required).

Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids (to control CNS edema), and their disease is asymptomatic for at least 28 days prior to enrollment. Magnetic resonance imaging (MRI) documenting disease stability within 60 days prior to enrollment is also required.

[15] Have an active fungal, bacterial, and/or known viral infection, including human immunodeficiency virus (HIV) or viral (B or C) hepatitis (screening required for HIV and viral hepatitis B and C within 60 days prior to enrollment).

[16] Have any of the following cardiovascular conditions:

a) symptomatic coronary artery disease currently or within the past 6 months,

b) confirmed left ventricular ejection fraction ≤50% or any cardiac insufficiency > New York Heart Association (NYHA) class II* currently or within the past 6 months,

c) uncontrolled hypertension (>170/100 mm Hg) currently or within the past 7 days, or

d) serious cardiac arrhythmia (well-controlled atrial fibrillation is permitted) currently or within the past 6 months.

[17] Have a second active primary malignancy that, in the judgment of the investigator or sponsor, may affect the interpretation of the results.

[18] Are unwilling or unable to participate in tumor biopsies.

[19] Have corrected QT interval of >500 msec on screening ECG.

[20] Have received treatment with agents specifically targeting CSF-1 or CSF-1R, including imatinib, nilotinib, and sunitinib.

*NYHA Congestive Heart Failure Classification (NYHA 1994):

Class I – Patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II – Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

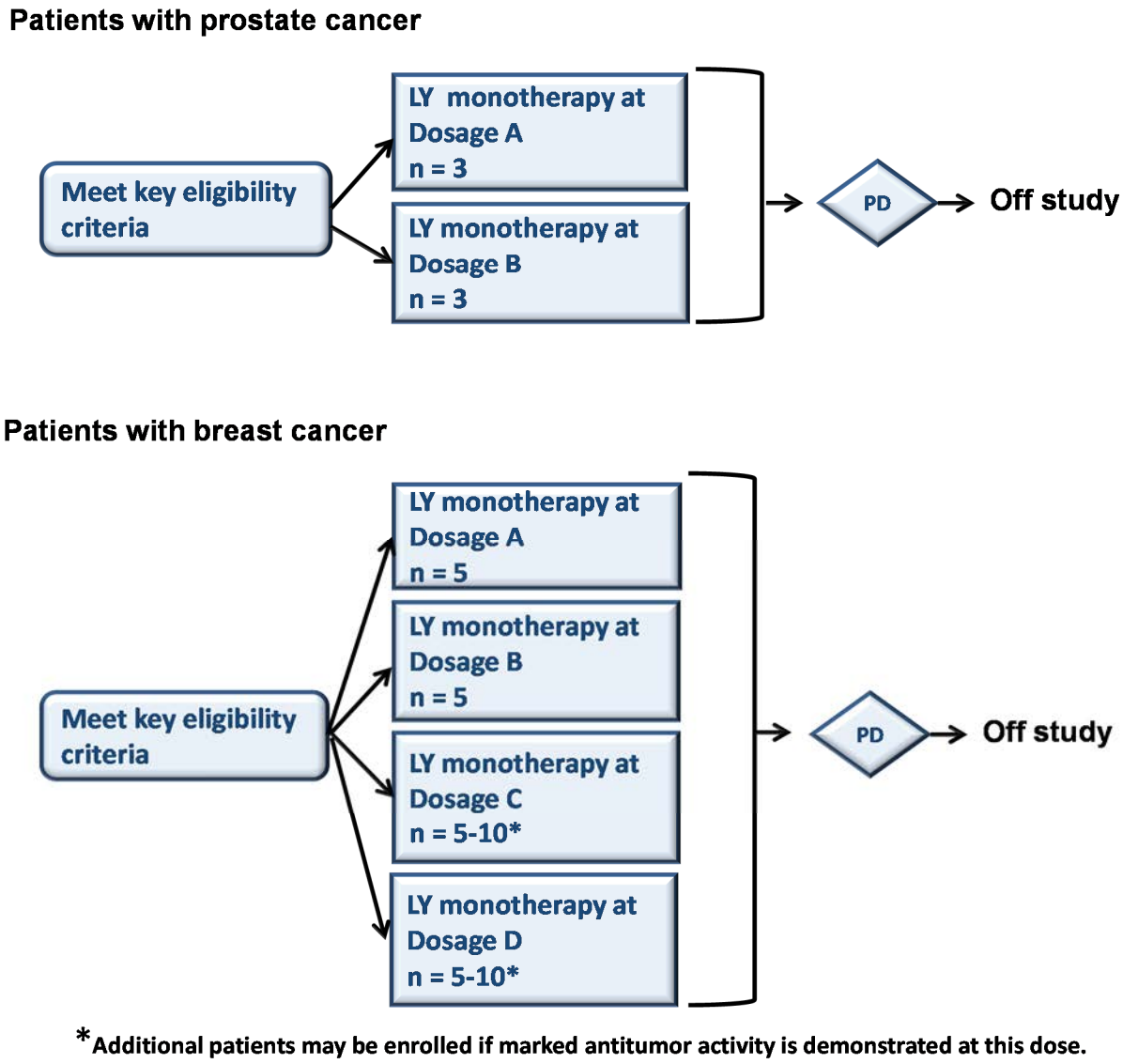
Class III – Patients with marked limitation of activity; they are comfortable only at rest.

Class IV – Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Refer to Section 7.5 for additional details regarding concomitant therapy.

6.2. Summary of Study Design

Study I5F-MC-JSCB (JSCB) is a single-center, open-label, nonrandomized, noncontrolled Phase 1 study of I.V. LY3022855 in patients with advanced, refractory breast or prostate cancer. Eligible patients will receive LY3022855 as an infusion, suggested to be administered over approximately 90 minutes for the first infusion, decreasing by 30 minutes for subsequent infusions, until administered over 30 minutes (refer to Section 7.2 for further details of study drug administration). 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.3.



Abbreviations: LY = LY3022855 (IMC-CS4); PD = progressive disease.

Figure JSCB.3. Study JSCB study design.

Enrollment will be sequential, starting with the assignment of patients to Dosage A (LY3022855, 1.25 mg/kg every 2 weeks [Q2W] of a 6-week cycle), then the assignment of patients to Dosage B (LY3022855, 1.0 mg/kg on Weeks 1, 2, 4, and 5 of a 6-week cycle) once the Dosage A cohort is fully enrolled. Once the Dosage B breast cancer cohort is fully enrolled, patients with breast cancer will be assigned by the sponsor to Dosage C (LY3022855, 100 mg QW of a 6-week cycle) or D (LY3022855, 100 mg Q2W of a 6-week cycle) on an alternating basis until 5 patients are enrolled to each of Dosages C and D. Once 5 patients are enrolled to each of Dosages C and D, the sponsor and the investigators will review clinical data to determine if enrollment of an additional 5 patients to each of Dosages C and D is warranted (refer to Section 10 for details regarding sample size).

Patients will receive Dosage A, B, C, or D for one 6-week cycle or until the patient meets one or more criteria for study discontinuation. After 1 cycle, patients who are benefitting from study treatment (that is, no disease progression or unacceptable toxicity) may continue to receive study treatment at the same dose and schedule until there is clear (confirmed) evidence of disease progression or other withdrawal criteria are met. At the time of study completion, if a patient continues to benefit from study treatment, that patient may enter the continued access period.

Immune studies will include evaluations of changes in baseline over time in: (1) 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, as well as (2) serum cytokines, as determined by MSD multiplex cytokine immunoassay technology or ELISA, and that may include but not be limited to CSF-1, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-34, and TNF-α. Blood samples for the immunomodulatory studies will be taken as described in Attachment 4, Attachment 5, and Attachment 6.

In addition, for all patients, 2 separate tumor biopsy procedures will be performed (attempted): the first will be performed at baseline (predose), within 14 days prior to dosing on Cycle 1, Day 1, and the second will be performed within 14 days prior to dosing on Cycle 2, Day 1. Biopsy samples will be flash frozen, for exploratory biomarker research, to be used in understanding the pharmacodynamic effects of LY3022855. To ensure adequate enrollment for the immune studies, additional patients will be enrolled as needed to replace a patient who either: (1) discontinues from the study prior to the second biopsy procedure, or (2) does not have sufficient tumor tissue for the second biopsy procedure and in the opinion of the investigator is benefitting from study treatment (in which case, the patient will be allowed to remain on study treatment). In addition to the required blood and tumor samples previously noted, optional tumor biopsies and/or blood samples for biomarker research may be obtained at the investigator's discretion in discussion with the patient, such as at the time of radiographic response or treatment progression.

For patients with measurable disease per RECIST, clinical endpoints for response will be standard tumor response as determined by RECIST 1.1 and irRECIST criteria. For the prostate cancer cohort only, progression in bone will be determined by using the PCWG2 criteria, which defines progression as the point at which at least 2 new lesions are observed on bone scan (compared with baseline), and are then confirmed on a follow-up bone scan performed at least 6 weeks later. However, if the point when the new lesions are observed is the first interval bone scan (that is, Week 6), then the confirmatory bone scan must demonstrate at least 2 additional new lesions (that is, a total of at least 4 new lesions from baseline). Further details of the PCWG2 criteria are provided in Section 8.3.

To document the immunomodulatory activity of LY3022855 treatment in patients with advanced, refractory breast or prostate cancers, an adequate sample size is required (refer to Section 10).

The planned duration of treatment is not fixed; patients will remain on study until they fulfill one of the criteria for study discontinuation (Section 6.3).

Refer to Attachment 1 for the Study Schedule.

6.2.1. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) when 36 evaluable patients* are attained. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient.

* Patients are considered evaluable if they complete 1 cycle of treatment (at least Cycle 1, Day 43, based on a 6-week cycle), undergo 1 baseline and 1 posttreatment tumor biopsy procedure (ie, attempted, whether the biopsy is successful or not), and complete immune blood studies for 1 cycle.

6.2.2. Continued Access Period

All patients remaining on study treatment without disease progression following the final analysis of the primary and secondary endpoints will be able to enter the continued access period of the study. The continued access period begins after study completion and ends at the end of trial. During the continued access period, patients on study treatment who continue to experience clinical benefit may continue to receive study treatment until disease progression, death, unacceptable toxicity, or start of new anticancer treatment. The continued access period includes a follow-up visit. The follow-up visit begins after the last dose of study drug and lasts approximately 30 days. If it is deemed to be in the best interest of the patient to start a new anticancer treatment prior to the scheduled end of the follow-up visit, the follow-up visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

Lilly will notify investigators when the continued access period begins.

During the continued access period, all AEs, SAEs, study drug dosing, and dose reduction of treatment will be collected on the electronic case report form (eCRF).

Serious adverse events will also be reported to Lilly Global Patient Safety and collected in the pharmacovigilance system. In the event that an SAE occurs, additional information (such as local laboratory results, concomitant medications, and hospitalizations) may be requested by Lilly in order to evaluate the reported SAE.

Investigators may perform other standard procedures and tests needed to treat and evaluate patients; however, Lilly will not routinely collect the results of these assessments.

6.3. Discontinuations

6.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor clinical research physician (CRP) and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the Lilly CRP agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without investigational product if the Lilly CRP does not agree with the investigator's determination that it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

In addition, patients will be discontinued from the study drug in the following circumstances:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator/Physician Decision
    - the investigator/physician decides that the patient should be discontinued from the study or study drug(s)
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug(s) occurs prior to introduction of the other agent
- Patient Decision
    - the patient or the patient's designee (for example, parents or legal guardian) requests to be discontinued from the study or study drug
- Sponsor Decision
    - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP

- The patient has confirmed evidence of progressive disease.
    - Exceptions for continuing with study treatment beyond confirmed radiographic progression may be made on a case-by-case basis for patients who are believed to be clinically benefiting from protocol therapy and both the investigator and sponsor (the CRP/clinical research scientist [CRS]) agree that continuing protocol therapy is in the patient's best interest.
- The patient experiences unacceptable toxicity.
- The patient experiences a Grade 3 or 4 infusion-related reaction (IRR) to LY3022855.
- The patient experiences Grade ≥2 AST or ALT elevation and Grade ≥2 bilirubin elevation (cases confirmed by Hy's Law).
- The patient is noncompliant with study procedures and/or treatment (Section 7.6).

The reason for and date of discontinuation will be collected for all patients. The Date of Discontinuation (for any of the above reasons) from study treatment is to be reported on the eCRF. Patients who discontinue will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

6.3.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges it necessary for any scientific, medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

6.3.3. Discontinuation of the Study

The study will be discontinued if Lilly, while considering the rights, safety, and well-being of the patient(s), judges it necessary for any scientific, medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7. Treatment

7.1. Materials and Supplies

LY3022855 for Injection is supplied at 5 mg/mL strength as a solution dosage, packaged in glass vials with an elastomeric closure. Each vial of LY3022855 for Injection contains 20 mL of the drug product (100 mg/20-mL vial). Vials of LY3022855 for Injection should be stored refrigerated at 2°C to 8°C. The drug product is formulated to contain the active LY3022855 in 10mM histidine, 100mM glycine, 100mM arginine, and 0.01% polysorbate 80 at pH 6.0. LY3022855 is a clear or slightly opalescent and colorless or slightly yellow liquid without visible particles.

LY3022855 will be administered as an I.V. infusion. The dose is prepared and infused at room temperature (23°C-27°C). LY3022855 will be diluted in normal saline to a final volume of 250 mL. Lilly instructions regarding dilution requirements should be followed.

Clinical study materials will be labeled according to the country's regulatory requirements.

7.2. Study Drug Administration

Four dosages of LY3022855 will be administered in this study. Refer to Table JSCB.1 for a summary of the LY3022855 dosages to be used. Eligible patients will receive LY3022855 as an I.V. infusion administered over a minimum duration of 30 minutes and a maximum duration of 4 hours, based on the known safety and stability of the prepared drug. The infusion rate should not exceed 25 mg/minute.

Suggested infusion times are as follows:

- 90 minutes for the first infusion; if no IRR is observed, decrease the infusion time to 60 minutes
- 60 minutes for the second infusion; if no IRR is observed, decrease the infusion time to 30 minutes
- 30 minutes for the third and subsequent infusions

If, at any time, a patient experiences an IRR, the infusion time should not be decreased.

For Dosages A and B, the first dose of LY3022855 is dependent upon the patient's baseline body weight in kilograms. Subsequent doses of LY3022855 must be recalculated if there is a ≥10% change (increase or decrease) in body weight from baseline; subsequent doses may be recalculated if there is a <10% change (increase or decrease) in body weight from baseline.

For patients with fluid retention, the estimated dry weight, instead of the actual body weight, should be used for dose calculation or recalculation (in the setting of substantial fluid retention, the Lilly CRP or designee should be consulted regarding optimal assessment of dry weight).

Dosages C and D are to be non-weight based (fixed dosing).

The investigator or designee is responsible for:

- explaining the correct use of the investigational agent(s) to the site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of study drug dispensation, destruction, and collection, and
- returning or destroying all unused medication to Lilly or its designee at the end of the study.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug(s) so that the situation can be assessed.

7.2.1. Dose Adjustments and Delays

Dose reductions are not permitted within a cycle, only between cycles.

If benefitting from treatment (that is, no disease progression or other withdrawal criteria), a patient who experiences a toxicity may continue to receive LY3022855 upon agreement of the sponsor and according to the dose reduction guidelines for this study (Table JSCB.2). For any given patient in the study, their dose may be reduced up to a maximum of 3 times.

Table JSCB.2. General Dose Reduction Guidelines

Dosage	Starting Dose and Schedule	First Reduction	Second Reduction	Third Reduction
A	1.0 mg/kg (Weeks 1, 2, 4, and 5)	0.6 mg/kg (QW)	0.3 mg/kg (QW)	0.3 mg/kg (Q2W)
B	1.25 mg/kg (Q2W)	0.6 mg/kg (QW)	0.3 mg/kg (QW)	0.3 mg/kg (Q2W)
C	100 mg (QW)	75 mg (QW)	50 mg (QW)	40 mg (QW)
D	100 mg (Q2W)	75 mg (Q2W)	50 mg (Q2W)	40 mg (Q2W)

Abbreviations: QW = weekly; Q2W = every 2 weeks (Weeks 1, 3, and 5).

In the case of the toxicities listed in Table JSCB.3, study treatment may be held (if appropriate, in the opinion of the investigator and upon agreement with the sponsor) for a maximum of 4 weeks, until resolution to baseline or improvement to Grade <2. Upon resolution to baseline or improvement to Grade <2, study treatment may be administered at a reduced dose (according to Table JSCB.2), beginning with the next cycle, if appropriate, in the opinion of the investigator and upon agreement with the sponsor. If toxicity does not resolve to baseline or improve to Grade <2 within 4 weeks following the last administered dose, study treatment should be permanently discontinued and the patient should be discontinued from the trial.

Once a patient has had a dose reduction (has started a new cycle at the reduced dose), all subsequent infusions will be at the reduced dose level; there will be no resumption to prior dose level(s). Any patient experiencing toxicity that would necessitate more than 3 dose reductions must discontinue treatment. Dose reductions must be confirmed by the sponsor.

Table JSCB.3. Toxicities for Which Dose Adjustments and Delays Apply

- Grade 4 hematologic toxicity
- Grade 3 hematologic toxicity lasting >7 days
- Grade 3 or 4 nonhematologic toxicity. Exceptions maybe be made for the following, if agreed upon by the sponsor AND the investigator:
  - Grade ≥3 liver function test (LFT) abnormality, such as alkaline phosphatase, gamma glutamyl transferase (GGT), AST, and ALT, not suspected to be drug related
  - Transient Grade ≥2 bilirubin elevation in the presence of known liver metastases lasting ≤7 days
  - Laboratory abnormalities that improve to Grade <2 or baseline levels within 7 days after initial documentation
  - Laboratory abnormalities ≥Grade 3 that are deemed not clinically significant
  - Grade ≥3 asymptomatic elevation of CK **WITHOUT** elevation in serum and urine myoglobin

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; CRP = clinical research physician.

Refer to Section 7.2.1.1 (Infusion-Related Reactions) regarding dose adjustment, delay, and discontinuation of study treatment due to LY3022855 IRRs.

7.2.1.1. Infusion-Related Reactions

If a patient experiences **Grade 1** IRR/allergic reaction, the infusion rate should be decreased by 50% for the duration of the infusion. In case of a **Grade 2** IRR/allergic reaction, the infusion must be stopped until resolution to Grade ≤1; the infusion may then be resumed at 50% of the prior infusion rate (the duration of the infusion should not exceed 3 hours). Once the infusion rate has been reduced for a Grade 1 or 2 IRR, it is recommended to maintain the lower infusion rate for all subsequent infusions (premedication must be provided prior to any subsequent doses of LY3022855 if the patient has experienced a Grade 1 or 2 IRR). Occurrence of a **Grade 3 or 4** IRR requires immediate and permanent discontinuation of LY3022855.

During Cycles 1 and 2 only, patients are to be observed closely for any potential AEs, from the start of the infusion until at least 1 hour after the end of the infusion of LY3022855. This observation is to be done in an area with resuscitation equipment and medications necessary for advanced life support and cardiopulmonary resuscitation, such as bronchodilators, vasopressor agents (for example, epinephrine), oxygen, glucocorticoids, antihistamines, and I.V. fluids, etc.

CAUTION: Infusion-related reactions may occur during or following LY3022855 administration.

Premedication is not recommended to be administered prior to the first infusion of LY3022855. However, if the patient experiences a Grade 1 or 2 IRR, premedication must be provided prior to any subsequent doses of LY3022855. The choice of premedication is to be made after discussion and agreement between the investigator and the Lilly CRP. In such cases (Grade 1 or 2 IRRs), administration of steroids should be avoided, if possible. Any premedication administered should be documented in the eCRF, including dose and route of administration.

If at any time a patient experiences an IRR to LY3022855, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of IRRs.

For further details regarding IRRs, including characterization according to CTCAE v4.0 and treatment guidelines, refer to the LY3022855 IB.

7.2.1.2. Other Adverse Events

Based on observations in nonclinical toxicological studies with LY3022855 and/or observations in one clinical trial with another monoclonal antibody targeting CSF-1 (Sadis et al. 2009), patients receiving LY3022855 should be closely monitored for signs indicative of hepatic function impairment (for example, increases in transaminases, LDH, bilirubin, coagulation disorders), inflammation (for example, leukocyte alterations, C-reactive protein), CK increases, and periorbital swelling. For details, refer to the LY3022855 IB.

7.2.1.2.1. Immune-Related Adverse Events (irAEs)

Symptoms occurring during or following infusion of investigational therapy will be defined according to the NCI-CTCAE, Version 4.0.

In the setting of symptoms consistent with irAEs occurring following infusion of investigational therapy, investigators are encouraged to refer to Attachment 10 as a guideline for the management of potential toxicities encountered with immuno-oncology agents. Due to the potential of rapid and serious sequelae associated with irAEs, early intervention with immunomodulatory agents as indicated is encouraged, concurrent with further diagnostic medical evaluations for possible non-immune-related causes of AEs. Attachment 10 is a guideline for the management of irAEs; local standards may supersede recommendations when deemed appropriate by the investigator.

7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive LY3022855 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 for each patient.

7.4. Blinding

This is an open-label study.

7.5. Concomitant Therapy

No other chemotherapy, immunotherapy, or experimental drugs will be permitted while the patients are on this study (refer to Sections 6.1.1 and 6.1.2 for entry criteria). Exceptions will be made for:

- Prostate cancer patients continuing GnRH agonist/antagonist therapy (refer to Inclusion Criterion [2] in Section 6.1.1)
- Prostate cancer patients receiving prednisone up to 10 mg/day (or an equivalent dose of another glucocorticoid agent)
- Breast cancer patients continuing antiestrogen therapy (for example, an aromatase inhibitor) or trastuzumab

Palliative radiotherapy will be allowed provided patients do not have overt signs of progression. Any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study. Appropriate documentation for all forms of premedication, supportive care, and concomitant medication must be captured on the eCRF. Replacement hormonal therapy initiated before study entry will be allowed.

Patients should receive full supportive care with the exception that the routine use of granulocyte colony-stimulating factors is not permitted during this study. Should the use of hematopoietic colony-stimulating factors (CSFs) be necessary, the American Society of Clinical Oncology (ASCO) recommendations for the use of CSFs (Smith et al. 2006) should be followed. If clinically indicated at any time during the study, erythropoietin and packed red blood cell transfusions may be used according to ASCO guidelines (Rizzo et al. 2010).

All concomitant medications should be recorded throughout the patient's participation in the study.

7.6. Treatment Compliance

LY3022855 will be administered I.V. 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 eCRF.

7.6.1. Evaluable Patients

Patients who withdraw from the study before receiving study drug(s) will be replaced and will not be included in the safety or efficacy assessments. Safety analyses will be conducted on all patients who have received at least one dose of study drug, regardless of whether they are deemed evaluable for the assessment of a dose level.

Any patient who does not complete 1 cycle of LY3022855 treatment, undergo 1 baseline and 1 posttreatment tumor biopsy procedure (ie, attempted, whether the biopsy is successful or not), and complete immune blood studies for 1 cycle will be deemed nonevaluable for assessment of a dose level.

Patients who complete 1 cycle of LY3022855 treatment, undergo 1 baseline and 1 posttreatment tumor biopsy procedure (ie, attempted, whether the biopsy is successful or not), and complete immune blood studies for 1 cycle will be considered evaluable for the assessment of a dose level. Nonevaluable patients may be replaced to ensure that 36 evaluable patients are attained.

Patients who complete 1 cycle of therapy but, for whatever reason, are not evaluable for PK may be replaced upon consultation with the investigator(s) and the Lilly CRP or CRS to ensure adequate PK data.

8. Safety, Pharmacokinetic, Pharmacodynamic, and Efficacy Data Collection

8.1. Safety Evaluations

The safety and tolerability of LY3022855 have been assessed in nonclinical toxicology studies and the results from these studies are detailed in the IB. This Phase 1 study contains detailed safety monitoring that will permit further characterization of the safety profile of LY3022855 in patients, beyond that initially characterized in Phase 1 study JSCA. Study procedures and their timing, including collection of blood and urine samples, are described in the Study Schedule (Attachment 1).

Standard laboratory tests, including chemistry, hematology, coagulation, and urinalysis panels, will be performed. A urine or serum pregnancy test (based on institutional standards) will be administered if applicable. Other clinical laboratory tests will also be collected. Attachment 2 lists the specific tests that will be performed for this study.

8.1.1. Safety Data Collection and Review

Investigators are responsible for monitoring the safety of patients who have entered into this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of the patient during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JSCB.4 presents a summary of AE and SAE reporting guidelines. Table JSCB.4 also shows which database or system is used to store AE and SAE data.

8.1.2. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any clinically significant findings from labs, vital sign measurements, and so on that occur should also be reported to Lilly

or its designee as an AE. Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

The investigator, monitor, and sponsor will review the collected data regularly for evidence of AEs. All patients will be assessed routinely for AEs as outlined in the study schedule. All AEs observed will be graded using CTCAE v4.0.

The National Cancer Institute (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. All AEs observed will be graded using CTCAE v4.0. Any minor version of CTCAE v4.0 (for example, version 4.0X) may be used for this study. Minor CTCAE v4.0 updates from the NCI will not necessitate a protocol amendment. For AEs without matching terminology within the CTCAE v4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the eCRF. This collection is in addition to verbatim text used to describe the AE.

In addition to collecting the AE verbatim, the CTCAE term, and the CTCAE severity grade, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within the Medical Dictionary for Regulatory Activities dictionary.

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Data on fetal outcome and breastfeeding should be collected, if feasible, for regulatory reporting and drug safety evaluation.

Upon documentation of pregnancy, the patient must be removed from the study and treatment with study drug(s) must be stopped immediately.

For all enrolled patients, study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. While the patient is on study, site personnel will record any change in these preexisting condition(s) and the occurrence and nature of any AEs. In addition, all AEs related to protocol procedures are reported to Lilly or designee.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure or study drug via eCRF.

The investigator decides whether he or she interprets the observed AEs as either related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terminologies are defined:

- **Related**: A direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly related**: A cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Unrelated**: Without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures, all "related" and "possibly related" AEs and SAEs will be defined as related to study drug.

8.1.2.1. Serious Adverse Events

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalizations or elective procedures for underlying preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

An SAE is any adverse event during this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization (except for study drug administration)
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study drug.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they

are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

If an investigator becomes aware of SAEs occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure or study drug, the investigator should report the SAEs to the sponsor, and the SAEs will be entered in the Lilly Safety System.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

8.1.2.2. Adverse Event and Serious Adverse Event Reporting

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System (see Attachment 7 for reporting recommendations).

8.1.2.2.1. Prior to Administration of Study Drug(s)

During screening, all AEs and SAEs (regardless of relatedness to protocol procedures) are collected after the patient has signed the informed consent form (ICF). For patients who do not enroll in the trial (that is, have not received at least one dose of LY3022855), only AEs and SAEs related to protocol procedures are required to be collected.

8.1.2.2.2. On Therapy

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring while the patient is receiving study drug must be reported to Lilly or its designee. A patient is considered to be receiving study drug from the time he/she receives the first dose of study drug until the time he/she receives the last dose of study drug.

8.1.2.2.3. 30-Day Follow-Up Visit

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring during the 30-Day Follow-up visit must be reported to Lilly or its designee. The 30-Day Follow-up visit starts following the last dose of study drug and lasts approximately 30 days. At the end of the 30-Day Follow-up visit, the patient will be required to have specific safety assessments (Attachment 1). The timing of these safety assessments is to occur 30 days ±7 days after the last dose of study drug.

Following the safety assessments that mark the end of the 30-Day Follow-up visit, the patient will be discontinued from the study, unless there is an ongoing AE or SAE that is at least possibly related to study drug. In this instance, the patient should be followed in subsequent follow-up visits (every 30 days) until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up.

If it is deemed to be in the best interest of the patient to start a new anticancer treatment prior to the scheduled end of the 30-Day Follow-up visit, the duration for this visit may be shortened. In

this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

After the 30-Day Follow-up visit, AEs are not required to be reported unless the investigator feels the AEs were related to either study drug, drug delivery system, or a protocol procedure. If an investigator becomes aware of an SAE believed to be related to protocol procedures or study drug, the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

8.1.2.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious adverse events that are not listed in the Development Core Safety Information in the IB and that the investigator identifies as related to study drug or procedure. The United States 21 CFR 312.32, the European Union Clinical Trial Directive 2001/20/EC, and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulatory regulations and the associated detailed guidances.

8.1.2.4. Summary of AE/SAE Reporting Guidelines

The AE and SAE reporting guidelines are summarized in Table JSCB.4.

Table JSCB.4. Adverse Event and Serious Adverse Reporting Guidelines for Study JSCB

Timing	Types of AEs/SAEs Reported	Collection Database	Lilly Safety System
Prestudy (baseline assessments) (starts at the signing of informed consent and ends immediately before the first dose of study drug)	Preexisting conditions All AEs All SAEs, regardless of relatedness	x x x	 x
On therapy (starts at first dose of study drug and ends at last dose of study drug)	All AEs All SAEs, regardless of relatedness	x x	 x
30-Day Follow-up visit (starts just after the last dose of study drug and ends when end-of-study safety assessments are completed [30 days ± 7 days after last dose of study drug])	All AEs All SAEs, regardless of relatedness	x x	 x
Subsequent follow-up visits, if necessary for patient monitoring	Ongoing AEs possibly related to study drug(s) or protocol procedures All SAEs related to protocol procedures or study drug	x x	 x
Continued access period (starts after study completion and ends at the end of the trial)	All AEs All SAEs, regardless of relatedness	x x	 x
Continued access period follow-up (starts just after the last dose of study drug and ends when end-of-study safety assessments are completed [30 days ± 7 days after last dose of study drug])	All AEs All SAEs, regardless of relatedness	x x	 x
Patient no longer on study	All SAEs related to protocol procedures or study drug that the investigator becomes aware of		x

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

8.1.3. Other Safety Measures

8.1.3.1. Electrocardiograms

For each patient, a local 12-lead digital ECG will be collected (normal vs clinically significantly abnormal) according to the Study Schedule (Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed to ensure high-quality records.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) to determine whether the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation from at least one of the replicate ECGs from each time point.

8.1.4. Safety Monitoring

The Lilly CRP or CRS will monitor safety data throughout the course of the study.

Representatives from Lilly Global Patient Safety will specifically monitor SAEs. Lilly will review SAEs within time frames mandated by company standard operating procedures. The Lilly CRP/CRS will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist, and periodically review:

- Trends in safety data.
- Laboratory analytes, including AP, ALT, AST, CK, LDH, and C-reactive protein.
- Adverse events, including monitoring of hepatotoxicity and muscle damage.
- If a study patient experiences elevated ALT ≥5 × ULN and elevated total bilirubin ≥2 × ULN, clinical and laboratory monitoring should be initiated by the investigator.
- For patients entering the study with ALT ≥3 × ULN, monitoring should be triggered at ALT ≥2 × baseline.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and to comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3).

8.1.5. Complaint Handling

Lilly collects complaints on study drugs used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

Complaints related to concomitant drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the complaint process in accordance with the instructions provided for this study:

- recording a complete description of the complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

8.2. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific clinical laboratory tests that will be performed for this study.

Attachment 4, Attachment 5, and Attachment 6 list the detailed schedules for sample collections specifically for PK, pharmacodynamics, and immunogenicity in this study.

8.2.1. Samples for Study Qualification and Health Monitoring

Blood, urine, and tissue samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health.

C-reactive protein will be assessed as a serum marker of inflammation. Total CK will be monitored via the chemistry panel, and serum and urine myoglobin will be measured in the event that serum CK $\geq 2.5 \times$ ULN. Coagulation parameters will be assessed prior to biopsy procedures. Refer to Attachment 1 for details about the timing of all assessments.

Tissue biopsy will be taken by core needle or surgical biopsy. For each core needle biopsy, an attempt should be made to collect 6 core needle samples; however, if it is not medically feasible to collect 6 samples, the investigator or designee should attempt to collect as much tumor tissue as is deemed medically feasible. Fine-needle aspiration should not be used as a method of tissue acquisition, unless first discussed with and agreed upon by the Lilly CRP. Due diligence should be used to ensure that tumor specimen (not normal adjacent or tumor margins) is provided.

Investigators must document their review of each laboratory safety report. Investigators must also document their determination of clinical significance of all abnormal laboratory values.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.2.2. Samples for Drug Concentration Measurements Pharmacokinetics/Pharmacodynamics

Pharmacokinetic and pharmacodynamic samples will be collected as specified in Attachment 1.

8.2.2.1. Pharmacokinetic Samples

At the visits and times specified in the sampling schedule (Attachment 4, Attachment 5, and Attachment 6), venous blood samples of approximately 3 to 6 mL each will be collected to determine the serum concentrations of LY3022855. If a patient remains on study until Cycle 3, additional samples will be drawn at that time. Additional samples may be drawn at additional time points during the study, if warranted and agreed upon by the investigator, Lilly, and the patient. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time of each sampling must be clearly and accurately recorded.

These samples will be analyzed at a laboratory designated by the sponsor. Serum concentrations of LY3022855 will be assayed using a validated ELISA method.

The PK samples will be stored at a facility (in the United States) designated by the sponsor.

The remaining serum from the samples collected for PK may be pooled and used for exploratory metabolism work as deemed appropriate.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last patient visit for the study.

8.2.2.2. Pharmacodynamic Samples

The following pharmacodynamic assessments are based on the primary study objective and are, therefore, required assessments. Samples will be tested for changes from baseline over time in peripheral blood immune cell subsets and in serum cytokines to document the immunomodulatory activity of LY3022855 treatment in patients with advanced, refractory breast or prostate cancers. Flow cytometric analysis using an antibody panel that may include, but not be limited to markers Live-Dead, CD3, CD4, CD8, CD14, CD16, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS will be used to evaluate T-cell and monocyte subsets from peripheral blood. In addition, serum cytokine levels will be determined by MSD multiplex cytokine immunoassay technology or ELISA, and may include, but not be limited to CSF-1, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-34, and TNF-α.

Collection of samples for other biomarker research is also part of this study.

Required samples for biomarker research to be collected from all patients in this study are the following:

- blood (for exploratory analysis of serum biomarkers that may be relevant to the mechanism of action of LY3022855,[redacted]
- tumor tissue (for exploratory analysis of the immunomodulatory effects of LY3022855 administration, including the understanding of the pharmacodynamic effects of LY3022855)

Tissue biopsy will be taken by core needle biopsy or surgical biopsy. Fine-needle aspiration should not be used as a method of tissue acquisition, unless first discussed with the Lilly CRP. Due diligence should be used to ensure that tumor specimen (not normal adjacent or tumor margins) is provided. Pathology notes accompanying the tissue may also be requested. Tissue and blood samples will be kept with the intention to perform tests as new techniques, research tools, and biomarkers become available.

Optional tissue (core needle or surgical biopsy) and/or blood samples (in addition to the required samples previously described) for biomarker research may be obtained at the investigator's discretion in discussion with the patient, such as at the time of radiographic response or treatment progression.

The samples will be coded with the patient number and stored at a facility selected by the sponsor for up to a maximum of 15 years after the last patient visit for the study. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Samples will be destroyed according to a process consistent with local regulation. Patients may request to have their samples destroyed at any time.

8.2.3. Samples for Tailoring Biomarkers

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY3022855. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The samples will be coded with the patient number and stored for up to a maximum of 15 years after the last patient visit for the study, at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Samples will be destroyed according to a process consistent with local regulation.

Refer to Section 8.2.2.2, Pharmacodynamic Samples, for details of samples collected for other biomarker research that is part of this study. These other samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to CSF-1, CSF-1R, and/or the mechanism of action of study drugs (LY3022855).

8.2.4. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against LY3022855. Immunogenicity will be assessed by a validated assay designed to detect ADA in the presence of LY3022855. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY3022855.

In addition to planned sampling for immunogenicity testing, if at any time a patient experiences an IRR to LY3022855, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of IRRs.

Samples may be stored for a maximum of 15 years following last patient visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to LY3022855. The duration allows the sponsor to respond to regulatory requests related to LY3022855.

8.3. Efficacy Evaluation

One of the secondary objectives of the study is to measure any antitumor activity. Refer to Attachment 1 for details regarding the timing of specific efficacy measures.

Each patient will be assessed by one or more of the following radiologic tests for tumor measurement:

- Computed tomography (CT) scan
- Magnetic resonance imaging (MRI)
- Chest x-ray, as clinically indicated

Each patient's full extent of disease will also be assessed as follows:

- For patients with measurable disease defined by RECIST, tumor measurements are to be assessed by RECIST 1.1 (Eisenhauer et al. 2009; Attachment 9) and irRECIST (Nishino et al. 2013).
- For patients with prostate cancer, bone metastatic disease is to be evaluated by PCWG2 criteria (Scher et al. 2008). A CRPC patient will be considered to have progressed by bone scan when at least 2 new lesions are observed on bone scan (compared with baseline), and are then confirmed on a follow-up bone scan performed at least 6 weeks later. However, if the point when the new lesions are observed is the first interval scan (Week 6), then the confirmatory bone scan must demonstrate at least 2 additional new lesions (that is, a total of at least 4 new lesions, compared with baseline). This confirmatory bone scan is required, given the prevalence of pseudoprogression, often referred to as "bone scan flare." For this trial, bone scans will be performed at baseline, Week 6 (first interval), and every 6 weeks thereafter, or as clinically indicated.
  The following are further details of the PCWG2 criteria for progression in bone:
  - For the first interval assessment bone scan performed following Cycle 1, Day 1, at least 2 new lesions, compared with baseline, must be visualized, and a confirmatory bone scan at least 6 weeks later should be performed and demonstrate at least 2 new lesions (that is, a total of at least 4 new lesions from baseline).
  - For all other interval assessment bone scans (that is, after the first posttreatment scan), at least 2 new lesions, compared with baseline, must be visualized, and a confirmatory bone scan should be performed and demonstrate confirmation of these 2 (or more) new lesions (that is, a total of at least 2 new lesions from baseline) to be considered progression.
  - The date of progression is considered the date of the first scan that demonstrates at least 2 new lesions.
  - Changes in intensity of bone lesions or the extent of existing bone lesions on bone scintigraphy are not considered in the assessment of bone disease progression per PCWG2 criteria.
  - Ambiguous results on bone scintigraphy may be clarified with other imaging modalities (CT/MRI), per investigator discretion.

Within 4 weeks prior to first dose of study drug (that is, baseline), each patient will be assessed by a radiologic imaging study for tumor measurement. Ultrasound will not be permitted as a method of tumor measurement.

Tumor assessment should be repeated every 6 weeks, using the same radiologic method that was used at baseline.

8.4. Procedure/Sampling Compliance

Every attempt will be made to enroll patients who have the ability to understand and comply with instructions. Noncompliant patients may be discontinued from the study.

The collection times of safety assessments, PK samples, pharmacodynamic samples, and efficacy measurements are given as targets, to be achieved within reasonable limits. The scheduled time points may be subject to minor alterations; however, the actual collection time must be correctly recorded on the eCRF or lab requisition form.

The scheduled collection times may be modified by the sponsor based on analysis of the safety and PK information obtained during the study. Any major modifications that might affect the conduct of the study, patient safety, and/or data integrity will be detailed in a protocol amendment.

9. Data Management Methods

9.1. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by e-mail, telephone, and/or fax.
- Review and evaluate eCRF data and/or use standard system edit checks and manual listing reviews to detect errors in data collection.
- Conduct a quality review of the eCRF database.

In addition, Lilly or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable IRBs/ERBs with direct access to the original source documents.

9.2. Data Capture Systems

9.2.1. Case Report Form

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

For data handled by a data management third-party organization (TPO), eCRF data and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to the Lilly data warehouse, using standard Lilly file transfer processes.

For data handled by the sponsor internally, eCRF data and some or all data that are related will be managed by the sponsor and stored electronically in the sponsor's system.

9.2.2. Ancillary Data

Data managed by a central vendor will be stored electronically in the central laboratory's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to the Lilly generic labs system.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

10. Data Analyses

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. Refer to Section 6.1 for the definition of an evaluable patient.

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.

All data collected will be summarized using descriptive statistics or graphics, if appropriate, and will also be listed.

10.1. 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, pharmacokineticist, and statistician. The CRP 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.

10.2. Patient Disposition

All patient discontinuations will be documented, and the extent of each patient's participation in the study will be reported. If known, a reason for their discontinuation will be given.

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 discontinuing (overall and by reason for discontinuation), will be provided.

A summary of all important protocol deviations will be provided.

10.3. Patient Characteristics

Patient characteristics will include the following:

- Patient demographics
- Baseline disease characteristics
- ECOG performance status
- Preexisting conditions
- Historical illnesses
- Prior disease-related therapies (including information on best response and time to progressive disease)
- Concomitant medications

Other patient characteristics will be summarized as deemed appropriate.

10.4. Safety Analyses

All patients who receive at least one dose of LY3022855 will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE v4.0.

All safety summaries and analyses will be based upon the Safety Population, defined as all enrolled patients who have received at least one dose of study drug.

Overall exposure to study drug, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics.

An overall summary 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.

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

Reasons for death will be summarized separately for on-therapy and within 30 days after last dose of study drug.

Laboratory results will be classified according to CTCAE v4.0. Laboratory results not corresponding to a CTCAE v4.0 grade will not be graded.

10.5. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on patients who have received at least one dose of the study drug and have had samples collected, and PK serum concentrations of LY3022855 will be determined.

The parameters for analysis will include but not be limited to maximum concentration (C_{max}) and trough concentration (C_{trough}) 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. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

10.6. Pharmacodynamic Analyses

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

To study the impact of the study drug and the dose levels on the patients, the changes from baseline over time in peripheral blood immune cell subsets will be documented. The immunomodulatory activity of LY3022855 will be documented by examining markers that include, but are not limited to: Live-Dead, CD3, CD4, CD8, CD14, CD16, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS. The expression of those markers will be quantified by flow cytometric analysis with an antibody panel.

In addition, changes from baseline over time in serum cytokines will be determined by MSD multiplex cytokine immunoassay or ELISA. The markers to be measured using these technologies include, but are not limited to: CSF-1, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-34, and TNF-α.

Biomarker measures of protein expression, based on flow cytometry, MSD, and ELISA, will be summarized by tumor type and/or dosage, based on enrolled patients. Summary statistics may include means, medians, corresponding standard errors, quartiles, and ranges. Graphics, including profile plots of markers over time, will be generated to explore potential patterns between patients. Correlation analyses between biomarkers and relative laboratory tests may be performed to further explore the activity of LY3022855.

10.7. Pharmacokinetic/Pharmacodynamic Analyses

An exploratory correlative analysis of LY3022855 PK and pharmacodynamics may be conducted.

10.8. Efficacy Analyses

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.

10.9. Interim Analyses

Since this is a Phase 1 study, safety data will be reviewed 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 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 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, and the analyses on all patients including these data may not be performed.

11. Informed Consent, Ethical Review, and Regulatory Considerations

11.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have in regard to the study procedures and patient requirements throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study in a timely manner.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study and to document that the patient is satisfied with his or her understanding of the potential risks and benefits of participating in the study and desires to participate in the study.

The investigator is ultimately responsible for ensuring that informed consent is given by each patient or legal representative before the study is started. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol screening procedures and prior to the administration of study drug.

In this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

11.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites(s). All ICFs must be compliant with the ICH guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

The study site's ERB(s) should be provided with the following prior to any study activities and during the course of the trial for any amendments/addendums or administrative notifications:

- the current IB
- ICF
- relevant curricula vitae

11.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines

2) ICH GCP Guideline [E6]

3) applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of the sponsor will be assigned to a TPO.

An identification code assigned by the sponsor to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other study-related data.

11.3.1. Investigator Information

Site-specific contact information may be provided in a separate document.

11.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative along with the IB acknowledgement form.

11.3.3. Final Report Signature

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The sponsor's responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

12. References

Bourette RP, Rohrschneider LR. Early events in M-CSF receptor signaling. *Growth Factors.* 2000;17(3):155-166.

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0, DCTD, NCI, NIH, DHHS. 2009. Publish date: 29 May 2009.

DeNardo DG, Brennan DJ, Rexhepaj E, Ruffell B, Shiao SL, Madden SF, Gallagher WM, Wadhwani N, Keil SD, Junaid SA, Rugo HS, Hwang ES, Jirström K, West BL, Coussens LM. Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy. *Cancer Discov*. 2011;1(1):54-67.

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.

Ide H, Hatake K, Terado Y, Tsukino H, Okegawa T, Nutahara K, Higashihara E, Horie S. Serum level of macrophage colony-stimulating factor is increased in prostate cancer patients with bone metastasis. *Hum Cell.* 2008;21(1):1-6.

Kacinski BM. CSF-1 and its receptor in ovarian, endometrial and breast cancer. *Ann Med.* 1995;27(1):79-85.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Amer Stat Assoc*. 1958;53(282):457-481.

Lawicki S, Szmitkowski M, Wojtukiewicz M. The pretreatment plasma level and diagnostic utility of M-CSF in benign breast tumor and breast cancer patients. *Clin Chim Acta.* 2006;371(1-2):112-116.

Lewis CE, Pollard JW. Distinct role of macrophages in different tumor microenvironments. *Cancer Res*. 2006;66(2):605-612.

Lin H, Lee E, Hestir K, Leo C, Huang M, Bosch E, Halenbeck R, Wu G, Zhou A, Behrens D, Hollenbaugh D, Linnemann T, Qin M, Wong J, Chu K, Doberstein SK, Williams LT. Discovery of a cytokine and its receptor by functional screening of the extracellular proteome. *Science.* 2008;320(5877):807-811.

Lin EY, Li JF, Gnatovskiy L, Deng Y, Zhu L, Grzesik DA, Qian H, Xue XN, Pollard JW. Macrophages regulate the angiogenic switch in a mouse model of breast cancer. *Cancer Res.* 2006;66(23):11238-11246.

Lin EY, Nguyen AV, Russell RG, Pollard JW. Colony-stimulating factor 1 promotes progression of mammary tumors to malignancy. *J Exp Med.* 2001;193(6):727-740.

Mroczko B, Groblewska M, Wereszczynska-Siemiatkowska U, Okulczyk B, Kedra B, Laszewicz W, Dabrowski A, Szmitkowski M. Serum macrophage-colony stimulating factor levels in colorectal cancer patients correlate with lymph node metastasis and poor prognosis. *Clin Chim Acta.* 2007;380(1-2):208-212.

Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. *Clin Cancer Res*. 2013;19(14):3936-3943.

Nowicki A, Szenajch J, Ostrowska G, Wojtowicz A, Wojtowicz K, Kruszewski AA, Maruszynski M, Aukerman SL, Wiktor-Jedrzejczak W. Impaired tumor growth in colony-stimulating factor 1 (CSF-1)-deficient, macrophage-deficient op/op mouse: evidence for a role of CSF-1-dependent macrophages in formation of tumor stroma. *Int J Cancer*. 1996;65(1):112-119.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655.

Pixley FJ, Stanley ER. CSF-1 regulation of the wandering macrophage: complexity in action. *Trends Cell Biol.* 2004;14(11):628-638.

Radi ZA, Koza-Taylor PH, Bell RR, Obert LA, Runnels HA, Beebe JS, Lawton MP, Sadis S. Increased serum enzyme levels associated with kupffer cell reduction with no signs of hepatic or skeletal muscle injury. *Am J Pathol*. 2011;179(1):240-247.

Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spivak JL, Bennett CL, Bohlius J, Evanchuk D, Goode MJ, Jakubowski AA, Regan DH, Somerfield MR; American Society of Clinical Oncology; American Society of Hematology. American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *J Clin Oncol.* 2010;28(33):4996-5010.

Sadis S, Mukherjee A, Olson S, Dokmanovich M, Maher R, Cai C-H, Le V. Safety, pharmacokinetics, and pharmacodynamics of PD-0360324, a human monoclonal antibody to monocyte/macrophage colony stimulating factor, in healthy volunteers. ACR/ARHP Annual Meeting Abstract (Poster 408), Philadelphia PA, 2009.

Sasmono RT, Oceandy D, Pollard JW, Tong W, Pavli P, Wainwright BJ, Ostrowski MC, Himes SR, Hume DA. A macrophage colony-stimulating factor receptor-green fluorescent protein transgene is expressed throughout the mononuclear phagocyte system of the mouse. *Blood.* 2003;101(3):1155-1163.

Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, Eisenberger MA, Higano C, Bubley GJ, Dreicer R, Petrylak D, Kantoff P, Basch E, Kelly WK, Figg WD, Small EJ, Beer TM, Wilding G, Martin A, Hussain M; Prostate Cancer Clinical Trials Working Group. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol*. 2008;26(7):1148-1159.

Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Bennett CL, Cantor SB, Crawford J, Cross SJ, Demetri G, Desch CE, Pizzo PA, Schiffer CA, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Wolff AC. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol.* 2006;24(19):3187-3205.

Wang T, Papoutsi M, Wiesmann M, DeCristofaro M, Keselica MC, Skuba E, Spaet R, Markovits J, Wolf A, Moulin P, Pognan F, Vancutsem P, Petryk L, Sutton J, Chibout SD, Kluwe W. Investigation of correlation among safety biomarkers in serum, histopathological examination, and toxicogenomics. *Int J Toxicol*. 2011;30(3):300-312.

Zhu XD, Zhang JB, Zhuang PY, Zhu HG, Zhang W, Xiong YQ, Wu WZ, Wang L, Tang ZY, Sun HC. High expression of macrophage colony-stimulating factor in peritumoral liver tissue is associated with poor survival after curative resection of hepatocellular carcinoma. *J Clin Oncol.* 2008;26(16):2707-2716.

Attachment 1. Protocol JSCB Study Schedules

Baseline and Cycle 1 Assessments (for All Dosing Schedules)

Procedure	Baseline Relative Day Prior to Day 1 of Cycle 1			Treatment Cycle 1 only						Comments
	≤28	≤14	≤7	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Eligibility Assessments										
Informed consent		X								ICF must be signed prior to performance of any protocol-specific tests/procedures.
Medical history		X								
β-hCG Pregnancy test			X							At baseline, a urine or serum pregnancy test is required for WOCBP. Thereafter, every 12 weeks after the first dose or according to local regulations, whichever is more frequent.
ECG		X				X			X	Note that in cases where ECG and blood sample collection are scheduled at the same time, all blood sampling should be performed prior to ECG assessment.
ECOG PS assessment		X		X	X	X	X	X	X	
Safety Assessments										
Physical examination		X		X		X		X		Includes height (at baseline only), and thoracic, abdominal, and symptom-directed examination.
Vital signs and weight measurement		X		X	X	X	X	X	X	Vital signs include temperature, pulse rate, respiration rate, and blood pressure. Vital signs will be checked and recorded prior to each infusion of LY3022855, midway through each infusion, at the end of each infusion, and every 15 minutes for the first hour following each infusion, including Cycle 1, Day 1 (also to be checked and recorded at nontreatment visits during Cycle 1).
Toxicity/AE assessment		X		X	X	X	X	X	X	Any preexisting toxicity should be documented, recorded, and graded (CTCAE v4.0 grade) as a part of the baseline medical history. AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator. Data on SAEs that occur before the end of the trial will be stored in the collection database and the Lilly Safety System.
Concomitant medication assessment		X		X	X	X	X	X	X	Including those medications taken within 28 days prior to the first dose of study therapy.

Procedure	Baseline Relative Day Prior to Day 1 of Cycle 1			Treatment Cycle 1 only						Comments
	≤28	≤14	≤7	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Laboratory Tests										
HIV and viral hepatitis B and C screening	X*									Includes HIV and hepatitis B and C, per institutional standards. If done within 28 days prior to Cycle 1, Day 1 as part of standard of care, does not need to be repeated. * Should be done within 60 days prior to enrollment.
Hematology		X		X	X	X	X	X	X	Every week for the first 12 weeks on therapy.
Coagulation		X					X*			Evaluations performed as part of the baseline assessment do not need to be repeated on Cycle 1, Day 1, unless required in the opinion of the investigator. * Required within 14 days of planned posttreatment tumor biopsy.
Serum chemistry		X		X	X	X	X	X	X	Every week for the first 12 weeks on therapy.
CEA and CA 15-3	X									Applies only to breast cancer cohorts and if clinically applicable.
C-reactive protein assessment		X		X	X	X	X	X	X	Every week for the first 12 weeks on therapy, and every 2 weeks thereafter.
Urinalysis		X								Evaluations performed as part of the baseline assessment do not need to be repeated on Cycle 1, Day 1, unless required in the opinion of the investigator. Urinalysis evaluations will be performed at the beginning of each cycle (that is, approximately every 6 weeks following the first dose of study therapy). If urine dipstick >1+ for protein, obtain 24-hour urine collection for protein analysis.
Serum and urine myoglobin		X*		X*	X*	X*	X*	X*	X*	*As clinically indicated, if serum CK ≥2.5 × ULN.
Tailoring biomarkers	X									10 mL of blood to be drawn for future pharmacogenetic biomarker testing.
Blood sampling for PK, PD, IG	Refer to Attachment 4, Attachment 5, and Attachment 6.									All sampling indicated in Attachment 4, Attachment 5, and Attachment 6 is to be done only after study eligibility is met.
Efficacy Assessments										
Imaging studies (CT/MRI)	X*								X	Radiographic assessment of tumor response should be performed prior to the start of a cycle so that results are available before the patient receives a new cycle of treatment. If done within 28 days prior to Cycle 1, Day 1, as part of standard of care, does not need to be repeated prior to the start of Cycle 1. * For patients with treated CNS metastases that are eligible for this study, a baseline MRI documenting disease stability within 60 days prior to enrollment is required.

Procedure	Baseline Relative Day Prior to Day 1 of Cycle 1			Treatment Cycle 1 only						Comments
	≤28	≤14	≤7	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Bone scan	X								X*	**Breast cancer cohort**: A baseline bone scan is required, except in the event that a PET scan is performed within 28 days prior to the first dose of study therapy that is negative for bone disease. Routine bone scans during treatment are not required, except in the setting of bone-only disease (no lymph node, visceral, skin, or subcutaneous metastases), or as deemed appropriate by the investigator. ***Prostate cancer cohort**: Bone scans are required at baseline and (follow-up [posttreatment]) every 6 weeks thereafter, or as clinically indicated. If done within 28 days prior to Cycle 1, Day 1, as part of standard of care, does not need to be repeated prior to the start of Cycle 1.
Tumor assessments	X								X	Radiographic assessment of tumor response should be performed prior to the start of a cycle so that results are available before the patient receives a new cycle of treatment. If done within 28 days prior to Cycle 1, Day 1, as part of standard of care, does not need to be repeated prior to the start of Cycle 1.
Tumor core needle or surgical biopsy		X						X		**Required**: The first tumor biopsy will be taken (attempted) at baseline (predose), within 14 days prior to dosing on Cycle 1, Day 1, and the second tumor biopsy will be taken (attempted) within 14 days prior to dosing on Cycle 2, Day 1. **Optional**: In cases of disease progression, if the patient's condition allows it, an optional tumor biopsy will be performed, as clinically indicated (refer to Section 8.2.2.2).
Ad hoc tumor tissue and blood sampling				X						**Optional**: Additional tumor tissue and/or blood samples for biomarker research may be obtained at the investigator's discretion in discussion with the patient, such as at the time of radiographic response or treatment progression. If, at any time during the study, tumor tissue is obtained through a core biopsy, surgical biopsy, or resection as routine clinical care, the sponsor requests a tissue block or unstained slides for analysis of potentially relevant surrogate biomarkers.
Study Therapy Administration										
Administer LY3022855 Weekly (on Days 1, 8, 15, 22, 29, and 36)				X	X	X	X	X	X	
Administer LY3022855 Every 2 Weeks (on Days 1, 15, and 29)				X		X		X		
Administer LY3022855 on Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29)				X	X		X	X		

Abbreviations: β-hCG = beta human chorionic gonadotropin; AE = adverse event; CA 15-3 = cancer antigen 15-3; CEA = carcinoembryonic antigen; CK = creatine kinase; CNS = central nervous system; CT = computed tomography; CTCAE v4.0 = Common Terminology Criteria for Adverse Events, version 4.0; ECG = electrocardiogram; ECOG PS= Eastern Cooperative Oncology Group performance status; HIV = human immunodeficiency virus; ICF = informed consent form; IG = immunogenicity; MRI = magnetic resonance imaging; PET = positron emission tomography; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event; ULN = upper limit of normal; WOCBP = women of childbearing potential.

Cycle 2 Assessments (for All Dosing Schedules)

Procedure	Treatment Cycle 2 only						Comments
	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Safety Assessments							
β-hCG Pregnancy test							Urine or serum pregnancy test is required for WOCBP every 12 weeks after the first dose or according to local regulations, whichever is more frequent.
ECG							Note that in cases where ECG and blood sample collection are scheduled at the same time, all blood sampling should be performed prior to ECG assessment.
ECOG PS assessment				X			To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29).
Physical examination	X						Includes thoracic, abdominal, and symptom-directed examination.
Vital signs and weight measurement				X			To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29). Vital signs include temperature, pulse rate, respiration rate, and blood pressure. Vital signs will be checked and recorded prior to each infusion of LY3022855, midway through each infusion, at the end of each infusion, and every 15 minutes for the first hour following each infusion.
Toxicity/AE assessment				X			To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29). AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator. Data on SAEs that occur before the end of the trial will be stored in the collection database and the Lilly Safety System.
Concomitant medication assessment				X			To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29).
Laboratory Tests							
Hematology	X	X	X	X	X	X	Every week for the first 12 weeks on therapy.
Serum chemistry	X	X	X	X	X	X	Every week for the first 12 weeks on therapy.
CEA and CA 15-3	X						Applies only to breast cancer cohorts and if clinically applicable.
C-reactive protein assessment	X	X	X	X	X	X	Every week for the first 12 weeks on therapy, and every 2 weeks thereafter.

Procedure	Treatment Cycle 2 only						Comments
	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Urinalysis	X						Urinalysis evaluations will be performed at the beginning of each cycle (that is, approximately every 6 weeks following the first dose of study therapy). If urine dipstick >1+ for protein, obtain 24-hour urine collection for protein analysis.
Serum and urine myoglobin	X*	X*	X*	X*	X*	X*	*As clinically indicated, if serum CK ≥2.5 × ULN.
Blood sampling for PK, PD, IG	Refer to Attachment 4, Attachment 5, and Attachment 6.						
Efficacy Assessments							
Imaging studies (CT/MRI)						X	Radiographic assessment of tumor response should be performed prior to the start of a cycle so that results are available before the patient receives a new cycle of treatment.
Bone scan						X*	**Breast cancer cohort**: Routine bone scans during treatment are not required, except in the setting of bone-only disease (no lymph node, visceral, skin, or subcutaneous metastases), or as deemed appropriate by the investigator. ***Prostate cancer cohort**: Follow-up (posttreatment) bone scans are required every 6 weeks, or as clinically indicated.
Tumor assessments						X	Radiographic assessment of tumor response should be performed prior to the start of a cycle so that results are available before the patient receives a new cycle of treatment.
Ad hoc tumor tissue and blood sampling	X						**Optional**: Additional tumor tissue and/or blood samples for biomarker research may be obtained at the investigator's discretion in discussion with the patient, such as at the time of radiographic response or treatment progression. If, at any time during the study, tumor tissue is obtained through a core biopsy, surgical biopsy, or resection as routine clinical care, the sponsor requests a tissue block or unstained slides for analysis of potentially relevant surrogate biomarkers.
Study Therapy Administration							
Administer LY3022855 Weekly (on Days 1, 8, 15, 22, 29, and 36),	X	X	X	X	X	X	
Administer LY3022855 Every 2 Weeks (on Days 1, 15, and 29	X		X		X		
Administer LY3022855 Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29	X	X		X	X		

Abbreviations: β-hCG = beta human chorionic gonadotropin; AE = adverse event; CA 15-3 = cancer antigen 15-3; CEA = carcinoembryonic antigen; CK = creatine kinase; CT = computed tomography; ECG = electrocardiogram; ECOG PS= Eastern Cooperative Oncology Group performance status; IG = immunogenicity; MRI = magnetic resonance imaging; PET = positron emission tomography; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event; ULN = upper limit of normal; WOCBP = women of childbearing potential.

Cycle 3+ Assessments (for All Dosing Schedules)

Procedure	Treatment Cycle 3 and beyond						Comments
	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Safety Assessments							
β-hCG Pregnancy test	X						Urine or serum pregnancy test is required for WOCBP 12 weeks after the first dose and every 12 weeks thereafter, or according to local regulations, whichever is more frequent.
ECG					X*	X*	Note that in cases where ECG and blood sample collection are scheduled at the same time, all blood sampling should be performed prior to ECG assessment. * As clinically indicated, prior to last infusion of treatment cycle.
ECOG PS assessment	X						To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29).
Physical examination	X						Includes thoracic, abdominal, and symptom-directed examination.
Vital signs and weight measurement	X						To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29). Vital signs include temperature, pulse rate, respiration rate, and blood pressure. Vital signs will be checked and recorded prior to each infusion of LY3022855, midway through each infusion, at the end of each infusion, and every 15 minutes for the first hour following each infusion.
Toxicity/AE assessment	X						To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29). AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator. Data on SAEs that occur before the end of the trial will be stored in the collection database and the Lilly Safety System.
Concomitant medication assessment	X						To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29).

Procedure	Treatment Cycle 3 and beyond						Comments
	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Laboratory Tests							
Hematology:							
For Weekly and Every-2-Week schedules	X		X		X		Cycle 3 and beyond: Every 2 weeks for patients receiving treatment on the Weekly or Every-2-Week dosing schedule (on Days 1, 15, and 29).
For Weeks 1, 2, 4, and 5 schedule	X			X			Cycle 3 and beyond: Every 3 weeks for patients receiving treatment Weeks 1, 2, 4, and 5 (on Weeks 1 and 4 [that is, Days 1 and 22]).
Serum chemistry:							
For Weekly and Every-2-Week schedules	X		X		X		Cycle 3 and beyond: Every 2 weeks for patients receiving treatment on the Weekly or Every-2-Week dosing schedule (on Days 1, 15, and 29).
For Weeks 1, 2, 4, and 5 schedule	X			X			Cycle 3 and beyond: Every 3 weeks for patients receiving treatment Weeks 1, 2, 4, and 5 (that is, on Weeks 1 and 4 [that is, Days 1 and 22]).
CEA and CA 15-3	X						Applies only to breast cancer cohorts and if clinically applicable.
C-reactive protein assessment	X		X		X		Cycle 3 and beyond: Every 2 weeks.
Urinalysis	X						Urinalysis evaluations will be performed at the beginning of each cycle (that is, approximately every 6 weeks following the first dose of study therapy). If urine dipstick >1+ for protein, obtain 24-hour urine collection for protein analysis.
Serum and urine myoglobin	X*	X*	X*	X*	X*	X*	*As clinically indicated, if serum CK ≥2.5 × ULN.
Blood sampling for PK, PD, IG	Refer to Attachment 4, Attachment 5, and Attachment 6.						
Efficacy Assessments							
Imaging studies (CT/MRI)						X	Radiographic assessment of tumor response should be performed prior to the start of a cycle so that results are available before the patient receives a new cycle of treatment.
Bone scan	X*						**Breast cancer cohort**: Routine bone scans during treatment are not required, except in the setting of bone-only disease (no lymph node, visceral, skin, or subcutaneous metastases), or as deemed appropriate by the investigator. ***Prostate cancer cohort**: Follow-up (posttreatment) bone scans are required every 6 weeks, or as clinically indicated.
Tumor assessments						X	Radiographic assessment of tumor response should be performed prior to the start of a cycle so that results are available before the patient receives a new cycle of treatment.

Procedure	Treatment Cycle 3 and beyond						Comments
	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Ad hoc tumor tissue and blood sampling	X						**Optional**: Additional tumor tissue and/or blood samples for biomarker research may be obtained at the investigator's discretion in discussion with the patient, such as at the time of radiographic response or treatment progression. If, at any time during the study, tumor tissue is obtained through a core biopsy, surgical biopsy, or resection as routine clinical care, the sponsor requests a tissue block or unstained slides for analysis of potentially relevant surrogate biomarkers.
Study Therapy Administration							
Administer LY3022855 Weekly (on Days 1, 8, 15, 22, 29, and 36)	X	X	X	X	X	X	For patients being treated on Dosage C and who are clinically benefitting, after the completion of Cycle 3, the dosing interval may be changed to once-every-2-week dosing after discussion with the sponsor. If a patient's dosage is changed from that of Dosage C (that is, weekly) to every-2-week dosing and then the patient develops progressive disease, the patient's dosage may then be changed back to weekly dosing if agreed upon by the investigator and sponsor.
Administer LY3022855 Every 2 Weeks (on Days 1, 15, and 29)	X		X		X		
Administer LY3022855 on Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29)	X	X		X	X		

Abbreviations: β-hCG = beta human chorionic gonadotropin; AE = adverse event; CA 15-3 = cancer antigen 15-3; CEA = carcinoembryonic antigen; CK = creatine kinase; CT = computed tomography; ECG = electrocardiogram; ECOG PS= Eastern Cooperative Oncology Group performance status; IG = immunogenicity; MRI = magnetic resonance imaging; PET = positron emission tomography; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event; ULN = upper limit of normal; WOCBP = women of childbearing potential.

Follow-up Assessments (for All Dosing Schedules)

Procedure	30-Day Follow-up	Comments Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Safety Assessments		
β-hCG Pregnancy test	X	Urine or serum pregnancy test is required for WOCBP.
ECG	X	In cases where ECG and blood sample collection are scheduled at the same time, all blood sampling should be performed prior to ECG assessment.
ECOG PS assessment	X	
Physical examination	X	Includes thoracic, abdominal, and symptom-directed examination.
Vital signs and weight measurement	X	Vital signs include temperature, pulse rate, respiration rate, and blood pressure.
Toxicity/AE assessment	X	All SAEs and LY3022855-related AEs will be followed until the event is resolved, stabilized, returned to baseline, deemed irreversible, or otherwise explained (frequency of follow-up evaluations is left to the discretion of the investigator). Data on SAEs that occur before the end of the trial will be stored in the collection database and the Lilly Safety System.
Concomitant medication assessment	X	
Laboratory Tests		
Hematology	X	
Serum chemistry	X	
C-reactive protein assessment	X	
Urinalysis	X	If urine dipstick > 1+ for protein, obtain 24-hour urine collection for protein analysis.
Serum and urine myoglobin	X*	*As clinically indicated, if serum CK ≥2.5 × ULN.
Blood sampling for PK, PD, IG	Refer to Attachment 4, Attachment 5, and Attachment 6.	
Efficacy Assessments		
Tumor core needle or surgical biopsy	X	**Optional**: In cases of disease progression, if the patient's condition allows it, an optional tumor biopsy will be performed, as clinically indicated (refer to Section 8.2.2.2).

Abbreviations: β-hCG = beta human chorionic gonadotropin; AE = adverse event; CK = creatine kinase; CRP = clinical research physician; ECG = electrocardiogram; ECOG PS= Eastern Cooperative Oncology Group performance status; IG = immunogenicity; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event; ULN = upper limit of normal; WOCBP = women of childbearing potential.

Attachment 2. Protocol JSCB Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]
- Hemoglobin
- Hematocrit
- Platelets
- Leukocytes (WBC), including differential
- Neutrophils – absolute and percentage
- Lymphocytes – absolute and percentage
- Monocytes – absolute and percentage
- Eosinophils – absolute and percentage
- Basophils – absolute and percentage

Coagulation[a]
- Partial thromboplastin time (PTT)
- Prothrombin time (PT)/INR

Urinalysis[a]
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Blood
- Leukocyte esterase

Clinical Chemistry[a] **(Serum Concentrations)**
- Sodium
- Potassium
- Chloride
- Bicarbonate
- Magnesium
- Calcium
- Phosphorus
- Total bilirubin
- Direct bilirubin
- Alkaline phosphatase
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Gamma glutamyl transpeptidase
- Albumin
- Total protein
- Creatinine
- Blood urea nitrogen (BUN)
- Uric acid
- Glucose (random)
- Lipase
- Amylase
- Creatine kinase (CK)

Serum or Urine Pregnancy Test[a]

Cardiac[a]
- Troponin I or T

Serologies[a]
- HIV screening
- Viral hepatitis B and C screening

Isoenzymes[b]
- Lactate dehydrogenase (LDH)
- Creatine kinase (CK)
- Alkaline phosphatase

Serum Markers of Bone Metabolism[b]
- CTX-I

Serum Markers of Inflammation[a]
- C-reactive protein

Additional tests to be performed, as clinically indicated, at a routine follow-up visit[a]
- Serum myoglobin – if CK ≥2.5 × ULN
- Urine myoglobin – if CK ≥2.5 × ULN

Serum Tumor Markers - as clinically indicated[a]
- CEA
- CA 15-3

Abbreviations: CA 15-3 = cancer antigen 15-3; CEA = carcinoembryonic antigen; CK = creatine kinase; HIV = human immunodeficiency virus; PT/INR = International Normalized Ratio of prothrombin time; ULN = upper limit of normal; WBC = white blood cells.

[a] Local or investigator-designated laboratory.

[b] Assayed by Lilly-designated laboratory.

Attachment 3. Protocol JSCB Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly clinical research physician (CRP).

Hepatic Monitoring Tests (local laboratory)

Hepatic Hematology	**Haptoglobin**[a]
Hemoglobin	
Hematocrit	**Hepatic Coagulation**
RBC	Prothrombin time, INR
WBC	
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies**[a]
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody**
AST	
GGT	**Anti-smooth muscle antibody**
CK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; GGT = gamma glutamyl transferase; Ig = immunoglobulin; INR = International Normalized Ratio; RBC = red blood cells; WBC = white blood cells.

a As clinically indicated.

Attachment 4. Protocol JSCB Pharmacokinetic, Pharmacodynamic, and Immunogenicity Sampling Schedule for Dosages A and B Only

Note: **All sampling indicated in Attachment 4 is to be done only after study eligibility is met.**

Pharmacokinetic, Pharmacodynamic, and Immunogenicity Blood Sampling Schedule for Weekly Dosing

	Prior to the first infusion	***Dosing Day*** **Cycle 1, Day 1 (C1D1)**		**C1D2**	***Dosing Day*** **C1D8**	***Dosing Day*** **C1D15**	***Dosing Day*** **C1D22**	***Dosing Day*** **C1D29**	***Dosing Day*** **C1D36**	
Analyses	(≤14 days of C1D1)	**1 hr** (±6 min) **EOI**	**4 hr** (±24 min) **EOI**	**24 hr** (±2 hr 24 min) **EOI**	**Predose** (±25 hr)	**Predose** (±25 hr)	**Predose** (±25 hr)	**Predose** (±25 hr)	**Predose** (±25 hr)	**Comments**
Pharmacokinetics	X	X	X	X	X		X		X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X				X		X			See Note at end of table.
Pharmacodynamics										
PD #1 - Central lab	X			X	X		X		X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab			X	X						PD #2=CBC with differential
PD #3 - MSKCC lab				X						PD #3=ALT, AST
PD #4 - MSKCC lab	X				X		X		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry										
FC #1 - Central lab	X			X	X		X			FC #1=CD14, CD16
FC #2 - MSKCC lab	X				X	X	X	X	X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X			X	X	X	X	X	X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab	X				X		X			CTX-I
Troponin I or T - MSKCC lab	X				X	X				

Weekly Schedule (continued)								
	Dosing Day **C2D1**	***Dosing Day*** **C3D1**			**C3D2**	***Dosing Day*** **C3D8**	***Dosing Day*** **C3D22**	
Analyses	**Predose** (±25 hr)	**Predose** (±25 hr)	**1 hr** (±6 min) **EOI**	**4 hr** (±24 min) **EOI**	**24 hr** (±2 hr 24 min) **EOI**	**Predose** (±25 hr)	**Predose** (±25 hr)	**Comments**
Pharmacokinetics	X	X	X	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X						See Note at end of table.
Pharmacodynamics								
PD #1 - Central lab		X			X	X	X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab				X	X			PD #2=CBC with differential
PD #3 - MSKCC lab					X			PD #3=ALT, AST
PD #4 - MSKCC lab		X				X	X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry								
FC #1 - Central lab		X			X	X	X	FC #1=CD14, CD16
FC #2 - MSKCC lab		X						FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X				X			AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab						X		CTX-I

Weekly Schedule (continued)			
Analyses	***Dosing Day*** **C5D1** **Predose** (±25 hr)	**30-Day Follow-up** (±7 days)	**Comments**
Pharmacokinetics	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X*	X	*To be done at this time point and every 12 weeks thereafter, until last dose. See Note at end of table.
Pharmacodynamics			
PD #1 - Central lab		X	PD #1=CSF-1, IL-34
PD #4 - MSKCC lab		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry			
FC #1 - Central lab		X	FC #1=CD14, CD16
FC #2 - MSKCC lab		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab		X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab		X	CTX-I
Troponin I or T - MSKCC lab		X*	*Only obtain for patients with cardiac symptoms.

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; C = cycle; CBC = complete blood count; CK = creatine kinase; CSF-1 = colony-stimulating factor-1; D = day; EOI = post end of infusion; FC = flow cytometry; IFN = interferon; IL = interleukin; LDH = lactate dehydrogenase; MSD = Meso Scale Discovery; MSKCC = Memorial Sloan Kettering Cancer Center; PD = pharmacodynamic(s); PK = pharmacokinetic(s); TNF = tumor necrosis factor.

Note: If at any time a patient experiences an infusion-related reaction to LY3022855, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of infusion-related reactions.

Pharmacokinetic, Pharmacodynamic, and Immunogenicity Blood Sampling Schedule for Every-2-Week Dosing

Analyses	**Prior to the first infusion** (≤14 days of C1D1)	***Dosing Day*** **Cycle 1, Day1 (C1D1)** **1 hr** (±6 min) **EOI**	**4 hr** (±24 min) **EOI**	**C1D2** **24 hr** (±2 hr 24 min) **EOI**	**C1D8** **168 hr** (±25 hr) **EOI**	**Comments**
Pharmacokinetics	X	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X					See Note at end of table.
Pharmacodynamics						
PD #1 - Central lab	X			X	X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab			X	X		PD #2=CBC with differential
PD #3 - MSKCC lab				X		PD #3=ALT, AST
PD #4 - MSKCC lab	X				X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry						
FC #1 - Central lab	X			X	X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X				X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X			X	X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab	X					CTX-I
Troponin I or T - MSKCC lab	X					

Every-2-Week Schedule (continued)					
Analyses	***Dosing Day*** **C1D15** **Predose** (±50 hr)	***Dosing Day*** **C1D29** **Predose** (±50 hr)	**C1D30** **24 hr** (±2 hr 24 min) **EOI**	**C1D36** **168 hr** (±25 hr) **EOI**	**Comments**
Pharmacokinetics	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X	X			See Note at end of table.
Pharmacodynamics					
PD #1 - Central lab	X		X	X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab			X		PD #2=CBC with differential
PD #3 - MSKCC lab		X*	X		PD #3=ALT, AST * For this time point, a separate sample should not be collected for PD #3 assessment. Use the serum chemistry sample (Attachment 1) taken at this time point for the PD #3 assessment.
PD #4 - MSKCC lab	X			X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry					
FC #1 - Central lab	X		X	X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X	X		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X	X	X	X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab	X				CTX-I
Troponin I or T - MSKCC lab	X				

Every-2-Week Schedule (continued)							
	Dosing Day C2D1	*Dosing Day* C3D1			C3D2	C3D8	
Analyses	**Predose**	**Predose**	**1 hr** (±6 min) **EOI**	**4 hr** (±24 min) **EOI**	**24 hr** (±2 hr 24 min) **EOI**	**168 hr** (±25 hr) **EOI**	**Comments**
Pharmacokinetics	X	X	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X					See Note at end of table.
Pharmacodynamics							
PD #1 - Central lab	X	X			X	X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab				X	X		PD #2=CBC with differential
PD #3 - MSKCC lab						X	PD #3=ALT, AST
PD #4 - MSKCC lab	X	X				X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry							
FC #1 - Central lab	X	X				X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X	X				X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X	X			X	X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Troponin I or T - MSKCC lab	X						

Every-2-Week Schedule (continued)				
Analyses	***Dosing Day*** **C3D15** **Predose** (±50 hr)	***Dosing Day*** **C5D1** **Predose** (±50 hr)	**30-Day Follow-up** (±7 days)	**Comments**
Pharmacokinetics	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X*	X	*To be done at this time point and every 12 weeks thereafter, until last dose. See Note at end of table.
Pharmacodynamics				
PD #1 - Central lab	X		X	PD #1=CSF-1, IL-34
PD #4 - MSKCC lab	X		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry				
FC #1 - Central lab	X		X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab			X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab			X	CTX-I
Troponin I or T - MSKCC lab			X*	*Only obtain for patients with cardiac symptoms.

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; C = cycle; CBC = complete blood count; CK = creatine kinase; CSF-1 = colony-stimulating factor-1; D = day; EOI = post end of infusion; FC = flow cytometry; IFN = interferon; IL = interleukin; LDH = lactate dehydrogenase; MSD = Meso Scale Discovery; MSKCC = Memorial Sloan Kettering Cancer Center; PD = pharmacodynamic(s); PK = pharmacokinetic(s); TNF = tumor necrosis factor.

Note: If at any time a patient experiences an infusion-related reaction to LY3022855, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of infusion-related reactions.

Pharmacokinetic, Pharmacodynamic, and Immunogenicity Blood Sampling Schedule for Weeks 1, 2, 4, and 5 Dosing

Analyses	Prior to the first infusion	*Dosing Day* Cycle 1, Day1 (C1D1)		C1D2	*Dosing Day* C1D8		C1D15	Comments
	(≤14 days of C1D1)	**1 hr** (±6 min) **EOI**	**4 hr** (±24 min) **EOI**	**24 hr** (±2 hr 24 min) **EOI**	**Predose** (±25 hr)	**1 hr** (±6 min) **EOI**	**168 hr** (±25 hr) **EOI**	
Pharmacokinetics	X	X	X	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X				X			See Note at end of table.
Pharmacodynamics								
PD #1 - Central lab	X			X	X			PD #1=CSF-1, IL-34
PD #2 - MSKCC lab			X					PD #2=CBC with differential
PD #3 - MSKCC lab							X*	PD #3=ALT, AST * For this time point, a separate sample should not be collected for PD #3 assessment. Use the serum chemistry sample (Attachment 1) taken at this time point for the PD #3 assessment.
PD #4 - MSKCC lab	X				X		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry								
FC #1 - Central lab	X			X	X			FC #1=CD14, CD16
FC #2 - MSKCC lab	X				X		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X			X	X		X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab	X				X			CTX-I
Troponin I or T - MSKCC lab	X							

Weeks 1, 2, 4, and 5 Schedule (continued)							
	Dosing Day **C1D22**	***Dosing Day*** **C1D29**	***Dosing Day*** **C2D1**	***Dosing Day*** **C3D1**			
Analyses	**Predose** (±50 hr)	**Predose** (±25 hr)	**Predose** (±50 hr)	**Predose** (±50 hr)	**1 hr** (±6 min) **EOI**	**4 hr** (±24 min) **EOI**	**Comments**
Pharmacokinetics	X	X	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X		X			See Note at end of table.
Pharmacodynamics							
PD #1 - Central lab	X	X	X	X			PD #1=CSF-1, IL-34
PD #2 - MSKCC lab						X	PD #2=CBC with differential
PD #4 - MSKCC lab	X	X	X	X			PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry							
FC #1 - Central lab	X	X	X	X			FC #1=CD14, CD16
FC #2 - MSKCC lab	X	X		X			FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X	X	X	X			AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab		X					CTX-I
Troponin I or T - MSKCC lab	X						

Weeks 1, 2, 4, and 5 Schedule (continued)							
	Dosing Day C3D8		C3D15	*Dosing Day* C3D22	*Dosing Day* C5D1	*Dosing Day* C5D29	
Analyses	**Predose** (±25 hr)	**1 hr** (±6 min) **EOI**	**168 hr** (±25 hr) **EOI**	**Predose** (±50 hr)	**Predose** (±50 hr)	**Predose** (±25 hr)	**Comments**
Pharmacokinetics	X	X	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity					X*		*To be done at this time point and every 12 weeks thereafter, until last dose. See Note at end of table.
Pharmacodynamics							
PD #1 - Central lab	X			X		X	PD #1=CSF-1, IL-34
PD #4 - MSKCC lab	X			X		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry							
FC #1 - Central lab	X						FC #1=CD14, CD16
FC #2 - MSKCC lab	X		X	X			FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab				X			AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab	X						CTX-I

Weeks 1, 2, 4, and 5 Schedule (continued)			
Analyses	***Dosing Day*** **C6D29** **Predose** (±25 hr)	**30-Day Follow-up** (±7 days)	**Comments**
Pharmacokinetics	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X	See Note at end of table.
Pharmacodynamics			
PD #1 - Central lab	X	X	PD #1=CSF-1, IL-34
PD #4 - MSKCC lab	X	X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry			
FC #1 - Central lab		X	FC #1=CD14, CD16
FC #2 - MSKCC lab		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab		X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab		X	CTX-I
Troponin I or T - MSKCC lab		X*	*Only obtain for patients with cardiac symptoms.

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; C = cycle; CBC = complete blood count; CK = creatine kinase; CSF-1 = colony-stimulating factor-1; D = day; EOI = post end of infusion; FC = flow cytometry; IFN = interferon; IL = interleukin; LDH = lactate dehydrogenase; MSD = Meso Scale Discovery; MSKCC = Memorial Sloan Kettering Cancer Center; PD = pharmacodynamic(s); PK = pharmacokinetic(s); TNF = tumor necrosis factor.

Note: If at any time a patient experiences an infusion-related reaction to LY3022855, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of infusion-related reactions.

Attachment 5. Protocol JSCB Pharmacokinetic, Pharmacodynamic, and Immunogenicity Sampling Schedule for Dosage C Only

Note: All sampling indicated in Attachment 5 is to be done only after study eligibility is met.

Pharmacokinetic, Pharmacodynamic, and Immunogenicity Blood Sampling Schedule for Weekly Dosing

Analyses	Prior to the first infusion (≤14 days of C1D1)	*Dosing Day* Cycle 1, Day 1 (C1D1) 1 hr (±6 min) EOI	4 hr (±24 min) EOI	C1D2 24 hr (±2 hr 24 min) EOI	*Dosing Day* C1D8 Predose (±25 hr)	*Dosing Day* C1D15 Predose (±25 hr)	*Dosing Day* C1D22 Predose (±25 hr)	*Dosing Day* C1D29 Predose (±25 hr)	*Dosing Day* C1D36 Predose (±25 hr)	Comments
Pharmacokinetics	X	X	X	X	X	X	X		X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X				X		X			See Note at end of table.
Pharmacodynamics										
PD #1 - Central lab	X			X	X		X		X	PD #1=CSF-1, IL-34
PD #3 - MSKCC lab				X						PD #3=ALT, AST
PD #4 - MSKCC lab	X				X		X		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry										
FC #1 - Central lab	X			X	X		X			FC #1=CD14, CD16
FC #2 - MSKCC lab	X				X	X	X	X	X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X			X	X	X	X	X	X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab	X									CTX-I
Troponin I or T - MSKCC lab	X					X				

Weekly Schedule (continued)								
	Dosing Day **C2D1**	***Dosing Day*** **C3D1**			**C3D2**	***Dosing Day*** **C3D8**	***Dosing Day*** **C3D22**	
Analyses	**Predose** (±25 hr)	**Predose** (±25 hr)	**1 hr** (±6 min) **EOI**	**4 hr** (±24 min) **EOI**	**24 hr** (±2 hr 24 min) **EOI**	**Predose** (±25 hr)	**Predose** (±25 hr)	**Comments**
Pharmacokinetics	X	X	X	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X						See Note at end of table.
Pharmacodynamics								
PD #1 - Central lab		X			X	X	X	PD #1=CSF-1, IL-34
PD #3 - MSKCC lab					X			PD #3=ALT, AST
PD #4 - MSKCC lab		X				X	X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry								
FC #1 - Central lab		X			X	X	X	FC #1=CD14, CD16
FC #2 - MSKCC lab		X						FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X				X			AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes

Weekly Schedule (continued)			
Analyses	***Dosing Day*** **C5D1** **Predose** (±25 hr)	**30-Day Follow-up** (±7 days)	**Comments**
Pharmacokinetics	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X*	X	*To be done at this time point and every 12 weeks thereafter, until last dose. See Note at end of table.
Pharmacodynamics			
PD #1 - Central lab		X	PD #1=CSF-1, IL-34
PD #4 - MSKCC lab		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry			
FC #1 - Central lab		X	FC #1=CD14, CD16
FC #2 - MSKCC lab		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab		X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab		X	CTX-I
Troponin I or T - MSKCC lab		X*	*Only obtain for patients with cardiac symptoms.

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; C = cycle; CBC = complete blood count; CK = creatine kinase; CSF-1 = colony-stimulating factor-1; D = day; EOI = post end of infusion; FC = flow cytometry; IFN = interferon; IL = interleukin; LDH = lactate dehydrogenase; MSD = Meso Scale Discovery; MSKCC = Memorial Sloan Kettering Cancer Center; PD = pharmacodynamic(s); PK = pharmacokinetic(s); TNF = tumor necrosis factor.

Note: If at any time a patient experiences an infusion-related reaction to LY3022855, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of infusion-related reactions.

Attachment 6. Protocol JSCB Pharmacokinetic, Pharmacodynamic, and Immunogenicity Sampling Schedule for Dosage D Only

Note: All sampling indicated in Attachment 6 is to be done only after study eligibility is met.

Pharmacokinetic, Pharmacodynamic, and Immunogenicity Blood Sampling Schedule for Every-2-Week Dosing

Analyses	Prior to the first infusion (≤14 days of C1D1)	*Dosing Day* Cycle 1, Day1 (C1D1) 1 hr (±6 min) EOI	*Dosing Day* Cycle 1, Day1 (C1D1) 4 hr (±24 min) EOI	C1D2 24 hr (±2 hr 24 min) EOI	C1D8 168 hr (±25 hr) EOI	Comments
Pharmacokinetics	X	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X					See Note at end of table.
Pharmacodynamics						
PD #1 - Central lab	X			X	X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab			X	X		PD #2=CBC with differential
PD #3 - MSKCC lab				X		PD #3=ALT, AST
PD #4 - MSKCC lab	X				X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry						
FC #1 - Central lab	X			X	X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X				X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X			X	X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab	X					CTX-I
Troponin I or T - MSKCC lab	X					

Every-2-Week Schedule (continued)					
	Dosing Day **C1D15**	***Dosing Day*** **C1D29**	**C1D30**	**C1D36**	
Analyses	**Predose** (±50 hr)	**Predose** (±50 hr)	**24 hr** (±2 hr 24 min) **EOI**	**168 hr** (±25 hr) **EOI**	**Comments**
Pharmacokinetics	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X	X			See Note at end of table.
Pharmacodynamics					
PD #1 - Central lab	X		X	X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab			X		PD #2=CBC with differential
PD #3 - MSKCC lab		X*	X		PD #3=ALT, AST * For this time point, a separate sample should not be collected for PD #3 assessment. Use the serum chemistry sample (Attachment 1) taken at this time point for the PD #3 assessment.
PD #4 - MSKCC lab	X			X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry					
FC #1 - Central lab	X		X	X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X	X		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X	X	X	X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Troponin I or T - MSKCC lab	X				

Every-2-Week Schedule (continued)							
	Dosing Day C2D1	*Dosing Day* C3D1			C3D2	C3D8	
Analyses	**Predose**	**Predose**	**1 hr** (±6 min) **EOI**	**4 hr** (±24 min) **EOI**	**24 hr** (±2 hr 24 min) **EOI**	**168 hr** (±25 hr) **EOI**	**Comments**
Pharmacokinetics	X	X	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X					See Note at end of table.
Pharmacodynamics							
PD #1 - Central lab	X	X			X	X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab				X	X		PD #2=CBC with differential
PD #3 - MSKCC lab						X	PD #3=ALT, AST
PD #4 - MSKCC lab	X	X				X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry							
FC #1 - Central lab	X	X				X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X	X				X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X	X			X	X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Troponin I or T - MSKCC lab	X						

Every-2-Week Schedule (continued)				
Analyses	***Dosing Day*** **C3D15** **Predose** (±50 hr)	***Dosing Day*** **C5D1** **Predose** (±50 hr)	**30-Day Follow-up** (±7 days)	**Comments**
Pharmacokinetics	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X*	X	*To be done at this time point and every 12 weeks thereafter, until last dose. See Note at end of table.
Pharmacodynamics				
PD #1 - Central lab	X		X	PD #1=CSF-1, IL-34
PD #4 - MSKCC lab	X		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry				
FC #1 - Central lab	X		X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab			X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab			X	CTX-I
Troponin I or T - MSKCC lab			X*	*Only obtain for patients with cardiac symptoms.

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; C = cycle; CBC = complete blood count; CK = creatine kinase; CSF-1 = colony-stimulating factor-1; D = day; EOI = post end of infusion; FC = flow cytometry; IFN = interferon; IL = interleukin; LDH = lactate dehydrogenase; MSD = Meso Scale Discovery; MSKCC = Memorial Sloan Kettering Cancer Center; PD = pharmacodynamic(s); PK = pharmacokinetic(s); TNF = tumor necrosis factor.

Note: If at any time a patient experiences an infusion-related reaction to LY3022855, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of infusion-related reactions.

Attachment 7. Protocol JSCB Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events

When contacting Lilly to report a SAE, please have the following information available:

Patient Demographics

- patient identification (number), sex, date of birth, origin, height, and weight

Study Identification

- full trial protocol number, investigator's name, and investigator's number

Study Drug

- drug code or drug name, unit dose, total daily dose, frequency, route, start dose, cycle details, start date, and last dose date (if applicable)

Adverse Event

- description, date of onset, severity, treatment (including hospitalization), action taken with respect to study drug, clinical significance, and test and procedure results (if applicable)

Relationship to Study Drug and Protocol Procedures

Concomitant Drug Therapy

- indication, total daily dose, duration of treatment, start date, and action taken

In Case of Death

- cause, autopsy finding (if available), date, and relationship to study drug and protocol procedures

Attachment 8. Protocol JSCB ECOG Performance Status

ECOG Performance Status

Activity Status	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655.

Attachment 9. Protocol JSCB RECIST Criteria 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the new Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable).
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the eCRF in millimeters (or decimal fractions of centimeters [cm]).

Nontarget Lesions

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the eCRF (for example, multiple liver metastases recorded as one liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with I.V. contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without I.V. contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in CR. Specific guidelines for both prostate-specific antigen response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cytology, Histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease.

PET Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a CR or PR in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

Partial Response (PR): At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Nontarget Lesions

Complete Response: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10 mm short axis).

Non-CR/ non-progressive disease: Persistence of one or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of one or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The Best Overall Response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table 1. Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 is to be used when patients have *nonmeasurable* disease only.

Table 2. Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease; SD = stable disease.

[a] non-CR/non-PD is preferred over SD for nontarget disease.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6-8 weeks is reasonable. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontarget lesions is not required.

However, in *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from first dose.

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective

progression is observed (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of progressive disease).

Independent Review of Response and Progression

When objective response (CR + PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Attachment 10. Protocol JSCB Guidelines for the Management of Immune-Related Adverse Events

Guidelines for the Management of Potential Toxicities Encountered with Immuno-Oncology Agents

System Organ Class	Adverse Event	CTCAE, Version 4.0 Grade (if applicable) and/or Symptoms[a]		Treatment Plan[b]
		Grade	Symptoms	
Endocrine	Thyroid issues		Asymptomatic, with TSH <0.5 × LLN or >2 × ULN	Continue drug and include free T4 in subsequent cycles.
			Symptomatic	Continue drug. Administer thyroid replacement.
	Hypotension, altered mental status, headache, fatigue		Endocrine issues aside from thyroid (for example, hypophysitis, diabetes mellitus)	Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Resume drug when symptoms resolve and are stable on hormone replacement. In case of adrenal crisis, administer stress-dose steroids. Permanently discontinue for Grade 3 or 4.
Gastrointestinal	Diarrhea, abdominal pain, blood in stool	2		Withhold drug for 1 wk. Administer antidiarrheal medication and check etiology. Resume drug when symptoms resolve to Grade <1. If >5 days' duration despite antidiarrheals, begin steroids (0.5 mg/kg/d prednisone); can resume drug during taper when symptoms resolve to Grade <1.
	Diarrhea, ileus, perforation	≥3		Withhold drug and administer 1-2 mg/kg/day prednisone (no steroids if possible perforation); discontinue drug if Grade 3 persists or Grade 4. If >3 days despite steroids, add nonsteroid immunosuppressive.
	Symptomatic pancreatitis	1 or 2		Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Can resume drug during taper.
		≥3		Permanently discontinue drug. Administer steroids (1-2 mg/kg/d prednisone). Can resume drug during taper.

System Organ Class	Adverse Event	CTCAE, Version 4.0 Grade (if applicable) and/or Symptoms[a]		Treatment Plan[b]
		Grade	Symptoms	
Hepatobiliary	Liver abnormality		AST or ALT >5 × ULN but ≤20 × ULN AND total bilirubin ≤ULN	Discuss with sponsor and consider continuing protocol treatment provided patient remains without other evidence of liver toxicity.
			AST or ALT >20 × ULN AND total bilirubin ≤ULN	Discuss with sponsor and consider holding protocol treatment until AST/ALT becomes ≤20 × ULN.
			AST or ALT >5 × ULN AND total bilirubin >ULN	Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Consider resuming protocol treatment once total bilirubin ≤ULN. Discontinue protocol therapy permanently if bilirubin does not return to below the ULN within 3 wk of holding drug.
		3 or 4	GGT or alkaline phosphatase	Continue protocol treatment provided patient remains without other evidence of liver toxicity.
Musculoskeletal	Muscle abnormality		CK >2.5 × but ≤10 ULN AND Serum and urine myoglobin ≤ULN	Discuss with sponsor and consider continuing protocol treatment provided patient remains without other evidence of muscle or renal toxicity.
			CK ≥2.5 × ULN AND Serum and urine myoglobin >ULN	Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Consider resuming protocol treatment once serum and urine myoglobin ≤ULN. Discontinue protocol therapy permanently if serum and urine myoglobin does not return to below the ULN within 3 wk of holding drug.

System Organ Class	Adverse Event	CTCAE, Version 4.0 Grade (if applicable) and/or Symptoms[a]		Treatment Plan[b]
		Grade	Symptoms	
Nervous	Weakness, paresthesia (for example, Guillain-Barré syndrome, myasthenia gravis)		No impact on activities of daily living (ADL)	Withhold drug. Resume drug when symptoms resolve.
			Impact on ADL	Withhold drug. Administer appropriate medical intervention and steroids (1-2 mg/kg/d prednisone). Can resume drug during taper and after discussion with sponsor.
Respiratory	Dyspnea, hypoxia, pneumonitis	1		Consider to withhold drug. Resume drug when stable.
		2	Mild to moderate symptoms	Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Can resume drug during taper.
		≥3	Severe	Permanently discontinue drug. Administer steroids (1-2 mg/kg/d prednisone). If >2 days despite steroids, add nonsteroid immunosuppressive.
Renal and urinary	Elevated creatinine, decreased urine output, blood in urine, edema	1	<1.5 × baseline	Continue drug.
		2 to 3	>1.5 × ULN but <6 × ULN OR >1.5 × baseline	Withhold drug. Administer steroids (1- 2 mg/kg/d prednisone).If symptoms resolve to Grade ≤1, taper steroids over 1 month. Can resume drug during taper. If elevations persist >7 days or worsen treat with Grade 4 recommendations.
		4	>6 × ULN	Permanently discontinue drug. Administer steroids (1-2 mg/kg/d prednisone).
Skin	Rash, pruritus		≤50% skin affected	Withhold drug. Start supportive medications for pruritus, for example, hydroxyzine/loratadine. If symptoms persist or worsen after 1 wk, administer topical or systemic steroids. Resume drug if rash improves to mild (localized) and steroid dose <7.5 mg.
			Stevens-Johnson syndrome, toxic epidermal necrolysis, necrosis, bullous or hemorrhagic lesions	Permanently discontinue drug. Begin steroids (1-2 mg/kg/d prednisone).

Abbreviations: ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; I.V. = intravenous(ly); LLN = lower limit of normal; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] If definition of grade not specified, use CTCAE, Version 4.0 definition.

[b] Treatment plan should always include a thorough workup of the issue to rule out other potential etiologies.

Note: Other steroid options can be given at equivalent doses. For severe cases, recommend using IV steroids. For adrenal crisis, mineralocorticoid also needs to be added to stress-dose IV steroids. Also, steroids should be tapered over 1 month once symptoms improve to ≤ grade 1, and drug should not be restarted until taper over at least 1 month complete. During steroid use, add prophylactic antibiotics for opportunistic infections. Immunosuppressive refers to infliximab or cyclophosphamide.

Attachment 11. Protocol JSCB Protocol Amendment I5F-MC-JSCB(d) Summary Phase 1 Study to Identify the Immunomodulatory Activity of LY3022855 (IMC-CS4) in Patients with Advanced, Refractory Breast or Prostate Cancer

Overview

Protocol I5F-MC-JSCB Phase 1 Study to Identify the Immunomodulatory Activity of LY3022855 (IMC-CS4) in Patients with Advanced, Refractory Breast or Prostate Cancer has been amended. The new protocol is indicated by Amendment (d) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Revised globally throughout the protocol to refer to the molecule primarily as LY3022855 (Lilly code), rather than as IMC-CS4 (ImClone code).
- Updated the reference for irRECIST from Wolchok et al. 2009 to Nishino et al. 2013.
- Updated LY3022855 content on clinical pharmacokinetics (Section 5.4.3) and clinical experience (Section 5.4.5), based on updated information.
- MAIN REASON FOR AMENDMENT: Revised and/or added content on dose rationale (Section 5.5), study design (Section 6.2), study drug administration (Section 7.2), dose adjustments and delays (Section 7.2.1), data analyses (Section 10), study schedules (Attachment 1), and sampling schedules (Attachments 5 and 6) to account for the addition of 2 new dosages, Dosage C (100 mg QW) and Dosage D (100 mg Q2W), based on the RP2D from Study JSCA. Clinical activity in terms of tumor reduction or disease stability was observed in patients with breast cancer enrolled to Study JSCA. Based upon these results, additional patients will be enrolled to this study for the purpose of collecting additional information to further delineate the immunomodulatory activity of LY3022855 in patients with breast cancer.
- Revised language to permit re-screening of patients, if agreed upon by the sponsor.
- Revised Exclusion Criterion [16] to exclude only those patients with current (but not historical) cardiovascular risks, to permit enrollment of patients with historical cardiovascular risks who have been treated and are now asymptomatic.

- Revised criteria for dose adjustments and delays in Section 7.2.1 for clarity. Extended the time permitted for holding study treatment and increased the number of dose reductions permitted to provide additional opportunity for resolution of any toxicities occurring in patients benefitting from study treatment.
- Added new Section 7.2.1.2.1 on immune-related AEs (irAEs) and a guideline for management of irAEs (Attachment 10), due to the immune modulation potential of LY3022855.
- Added further details in Section 10.8 regarding data analyses for efficacy (tumor response data).
- Added further details in Section 10.9 regarding interim analyses.
- Deleted some assessments in Attachment 1 for physical examinations during Cycle 1, to minimize physician visits.
- Added assessments in Attachment 1 for cancer markers CEA and CA 15-3, which apply to breast cancer cohorts.
- Deleted some assessments in Attachment 1 for ECG to simplify study conduct.
- Deleted some sampling time points in Attachment 4 for PK, pharmacodynamics, flow cytometry, and isoenzymes to simplify study conduct.
- Deleted the sampling summary attachment, because it is not required in the protocol.

Additional minor clarifications/corrections were made, including but not limited to:

- Deleted language in Section 10 stating a SAP will be provided.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

4. Abbreviations and Definitions

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
BLQ	below the quantifiable lower limit of the assay
CnWn	Cycle and Week numbers
CA 15-3	cancer antigen 15-3
CEA	carcinoembryonic antigen
CL	total body clearance
DCR	disease control rate
FACS	fluorescence-activated cell sorting (a type of flow cytometry)
GERD	gastroesophageal reflux disease
IMC-CS4	s~~S~~ponsor code name for recombinant human immunoglobulin G, subclass 1 (IgG1) monoclonal antibody targeted to the colony-stimulating factor-1 receptor (CSF-1R); also known as LY3022855
irAE	immune-related adverse event
LVEF	left ventricular ejection fraction
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic or progressive disease Note - "Pharmacodynamic" and "progressive disease" are spelled out throughout this protocol, except as follows: The abbreviation "PD" appears only in ~~Figure JSCB.1~~the study design figure and in tables in the protocol attachments. In these locations, the abbreviation is clearly defined.
PFS	progression-free survival
Q2W~~q2w~~	once every 2 weeks
QW~~qw~~	once weekly
V_{ss}	volume of distribution at steady state
WOCBP	women of child-bearing potential

5.1. Rationale and Justification for the Study

LY3022855 ~~(hereafter referred to~~also known as IMC-CS4) is a recombinant human monoclonal antibody of the immunoglobulin G, subclass 1 (IgG1) targeting CSF-1R. LY3022855~~IMC-CS4~~ prevents the ligands CSF-1 and IL-34 from binding to CSF-1R CCI [redacted], and in this way inhibits CSF-1R activation. CSF-1R activation is required for proper functioning and survival of tumor-associated macrophages. Thus, by blocking CSF-1R activation, CCI [redacted]

Anti-CSF-1R treatment that limits tumor-associated macrophages enhances CD8+ T-cell infiltration, leading to decreases in tumor burden (DeNardo et al. 2011). Moreover, in a syngeneic breast cancer model, depletion of CD8+ T cells rendered treatment with CS7 less efficacious, indicating interplay between macrophage activity and T-cell infiltration. Thus, knowledge not only of the macrophage subpopulation but also of the T-cell subset may affect the efficacy of LY3022855~~IMC-CS4~~ treatment in patients.

CCI [redacted] In addition, pharmacodynamic results from the ongoing Phase 1 dose-escalation study of LY3022855~~IMC-CS4~~, Study I5F-IE-JSCA (also known as IMCL CP24-1001; hereafter referred to as JSCA), have suggested target engagement and biologic activity at a dosage of 1.25 mg/kg once weekly. CCI [redacted]

5.2.1. Primary Objective

The primary objective of this study is to document the immunomodulatory activity of LY3022855~~IMC-CS4~~ treatment in patients with advanced, refractory breast or prostate cancers, according to the following measures:

5.2.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and toxicity profile of LY3022855~~IMC-CS4~~, 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~~IMC-CS4~~
- 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~~Nishino et al. 2013) (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~~IMC-CS4~~ (immunogenicity), as assessed by a validated immunogenicity assay

5.2.3. Exploratory Objectives

The exploratory objectives of this study are:

- To explore serum biomarkers that may be relevant to the mechanism of action of LY3022855~~IMC-CS4~~, CCI
- To explore the pharmacodynamic effects of LY3022855~~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

5.3. General Introduction to LY3022855~~IMC-CS4~~

LY3022855~~IMC-CS4~~ is a recombinant human monoclonal antibody of IgG1 that targets CSF-1R, a tyrosine kinase receptor expressed selectively on macrophage and granulocyte cell lineages in normal individuals and on tumor cells in cancer (Kacinski 1995; Sasmono et al. 2003).

CCI

The present trial will look specifically at the immunomodulatory activity of LY3022855~~IMC-CS4~~ in patients with advanced breast or prostate cancer refractory or intolerant to at least one prior therapy for their cancer.

5.4. LY3022855 ~~IMC-CS4~~ – Nonclinical and Clinical Experience

5.4.1. Nonclinical Pharmacokinetics ~~of IMC-CS4~~

The pharmacokinetics of LY3022855~~IMC-CS4~~ were evaluated in mice administered 20 mg/kg and in cynomolgus monkeys at dose levels that ranged from 10 to 180 mg/kg. The PK of LY3022855~~IMC-CS4~~ in cynomolgus monkeys was characterized by a relatively long serum half-life ($t_{1/2}$) after single (183-275 hours) or multiple doses (158-470 hours); these half-lives were substantially longer than that observed in CD-1 mice (110 hours). Accumulation (approximately 2-fold) of LY3022855~~IMC-CS4~~ was evident after repeated once-weekly dosing in monkeys, suggesting that accumulation may similarly occur in humans, depending on the frequency of dosing. The estimated volume of distribution of LY3022855~~IMC-CS4~~ in monkeys (approximately 29-64 mL/kg) indicated that LY3022855~~IMC-CS4~~ was not substantially distributed beyond the vasculature. In the cynomolgus monkey studies, LY3022855~~IMC-CS4~~ serum exposures were generally proportional to the increases in dose from 10 to 180 mg/kg and no sex differences were observed.

The concentration of serum CSF-1 increased in cynomolgus monkeys that were treated with LY3022855~~IMC-CS4~~, suggesting that CSF-1 is a pharmacodynamic marker of LY3022855~~IMC-CS4~~ exposure. However, in contrast to the LY3022855~~IMC-CS4~~ levels, CSF-1 levels did not increase proportionally with the increase in LY3022855~~IMC-CS4~~ dose. The concentration of CSF-1 reached apparent maximal level in all dose groups after the first dose, typically between 24 and 168 hours following administration of LY3022855~~IMC-CS4~~. This observation suggests that the pharmacodynamic effect of LY3022855~~IMC-CS4~~ on circulating CSF-1 reached saturation at the lowest dose levels (10 or 20 mg/kg). CSF-1 levels were generally sustained throughout the sampling period. However, in the repeat-dose cynomolgus monkey study, the concentration of CSF-1 began to decrease in some animals from the low- (20 mg/kg) and middle- (60 mg/kg) dose groups during the recovery period.

Formal studies to characterize the metabolism and disposition of LY3022855~~IMC-CS4~~ have not been conducted. As a monoclonal antibody, LY3022855~~IMC-CS4~~ will be largely confined to the extracellular space, which is supported by data from numerous investigations and is consistent with the PK evaluation of LY3022855~~IMC-CS4~~. No formal metabolism studies of LY3022855~~IMC-CS4~~ have been performed because the catabolism of antibodies by mammalian systems is largely understood and formal studies of the metabolic degradation of these molecules are not warranted.

For details on the nonclinical PK of LY3022855~~IMC-CS4~~, refer to Section 5 of the current Investigator's Brochure (IB).

5.4.2. Nonclinical Pharmacokinetic/Pharmacodynamic Model

One of the main pharmacological effects of LY3022855~~IMC-CS4~~ proposed to underlie the inhibition of cancer progression is the depletion of tumor-associated macrophages. To model this effect and estimate the minimum effective blood level required to achieve significant antitumor effects, cancer models established in mice were utilized. However, since

LY3022855~~IMC-CS4~~ does not bind to murine CSF-1R, a surrogate antibody, CS7, was developed and utilized in order to examine PK/pharmacodynamic relationships. The binding affinity of CS7 to murine CSF-1R (dissociation constant [K_d] = 0.13nM) is 6-fold greater than that of LY3022855~~IMC-CS4~~ to human CSF-1R (K_d = 0.8nM). However, comparable potencies of the antibodies were observed in cell-based assays of inhibition of CSF-1-induced phosphorylation (IC_{50} = 0.3nM for both antibodies), monocyte differentiation (IC_{50} = 0.3nM vs 0.25nM for CS7 and LY3022855~~IMC-CS4~~, respectively), and inhibition of monocyte proliferation (IC_{50} = 0.13nM or 0.1nM for CS7 and LY3022855~~IMC-CS4~~, respectively). Therefore, CS7 and LY3022855~~IMC-CS4~~ were anticipated to have similar pharmacological effects in vivo at similar concentrations. Hence, CS7 was utilized in animal models to directly predict the trough serum LY3022855~~IMC-CS4~~ levels necessary to achieve relevant efficacy in human subjects.

Based on these assumptions, to estimate target serum concentrations for efficacy in initial clinical investigations, trough concentrations associated with efficacy were determined in human breast cancer HCC-1954 and human leukemia NKM-1 models established in mice. LY3022855~~IMC-CS4~~ was evaluated in the leukemia model established following intravenous (I.V.) injection of CSF-1R-expressing NKM-1 cells. The rat surrogate, CS7, was used in the breast cancer model established following subcutaneous injection of CSF-1R-negative HCC-1954 cells. The results from the 2 studies identified markedly different efficacious concentrations for the antibodies in the different models. The human NKM-1 model appeared very sensitive to the antitumor effect of LY3022855~~IMC-CS4~~, as efficacy was achieved at mean trough concentrations down to 0.2 µg/mL. For CS7, notably higher doses and concentrations were required to inhibit human HCC-1954 breast cancer tumor growth, as a mean trough concentration of 425 µg/mL was associated with efficacy.

5.4.3. Clinical Pharmacokinetics ~~of IMC-CS4~~

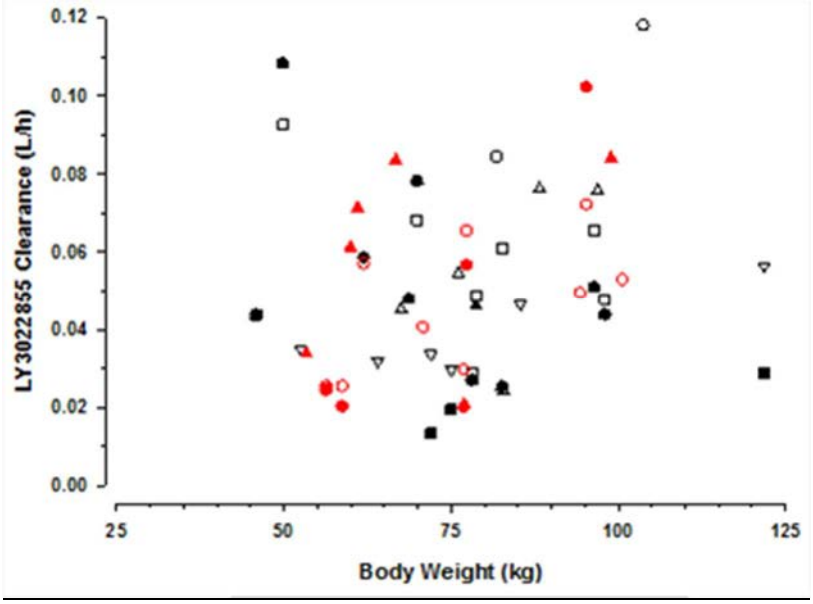
As of 28 January 2016, the clinical experience of LY3022855 PK comprised 27 patients enrolled in Study JSCA (0.3 mg/kg once weekly [QW] [n=4], 0.6 mg/kg QW [n=3], 1.25 mg/kg QW [n=5], 1.25 mg/kg once every 2 weeks [Q2W] [n=9], and 2.5 mg/kg QW [n=6]), and 14 patients enrolled in Study JSCB (1.25 mg/kg Q2W [n=9] and 1 mg/kg on Weeks 1, 2, 4, and 5 of every 6-week cycle [n=5]).

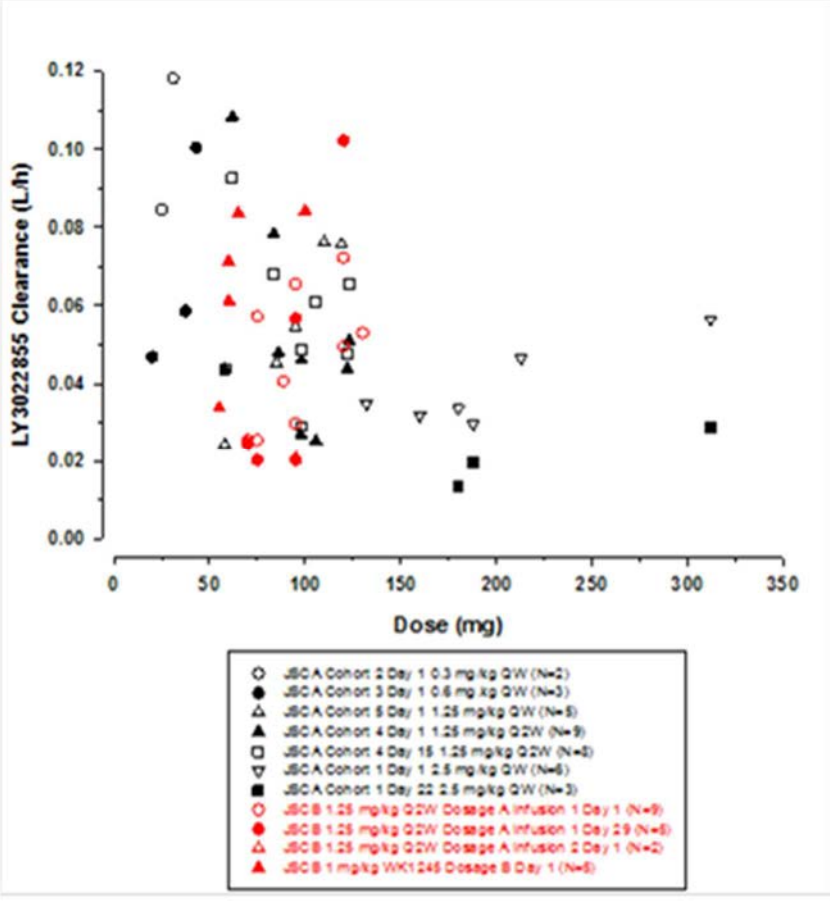
LY3022855 in cancer patients exhibited moderate total body clearance (CL) (mean values on Day 1 ranged from 0.0378 to 0.0651 L/h), low volume of distribution at steady state (V_{ss}) (mean values on Day 1 ranged from 2.85 to 4.93 L), and moderate $t_{1/2}$ (mean values on Day 1 ranged from 30.8 to 92.2 hours).

LY3022855 CL appeared to be nonlinear with respect to LY3022855 concentration, where higher doses of LY3022855 tended to exhibit lower CL values. However, this apparent nonlinearity was confounded by the high incidence of concentrations reported as below the quantifiable lower limit of the assay (BLQ), which could artificially inflate the calculated CL at lower doses.

An apparent lack of relationship between patient body weight and LY3022855 CL (Figure JSCB.1, upper panel) resulted in an amended dose-escalation plan for Study JSCA, to evaluate the safety, PK, and immunogenicity of LY3022855 using a fixed-dosing approach (that is, mg as opposed to mg/kg).

The clinical PK of LY3022855 are described in greater detail in Section 6.1 of the IB.





Abbreviations: N = number of patients treated; QW = once weekly; Q2W = once every 2 weeks.

Figure JSCB.1. Individual observed clearance versus patient body weight (upper panel) and LY3022855 dose (lower panel) for Studies JSCA and JSCB.

~~For the ongoing Phase 1 study of IMC-CS4, Study JSCA, PK data from 5 cohorts have been analyzed, wherein IMC-CS4 was administered in the following order~~:

- ~~Cohort 1 2.5 mg/kg once weekly~~
- ~~Cohort 2 0.3 mg/kg once weekly~~
- ~~Cohort 3 0.6 mg/kg once weekly~~
- ~~Cohort 4 1.25 mg/kg every 2 weeks~~
- ~~Cohort 5 1.25 mg/kg once weekly~~

~~PK samples were collected following the first dose for all 5 cohorts and again following subsequent doses at Cycle 1, Week 4 for Cohort 1, and at Cycle 1, Week 3 for Cohort 4.~~

~~Following single-dose administration of IMC-CS4, the area under the serum concentration-time curve serum exposure ($AUC_{(0-\infty)}$), the maximum serum concentration (C_{max}), and the trough~~

~~concentrations (C_{trough}) increased with increasing dose. For the 1.25-mg/kg every-week dose, the trough concentrations following the first dose ranged from approximately 8 to 12 µg/mL, whereas for the 1.25-mg/kg every-2-week dose, the trough concentrations following the first dose ranged from approximately 3 to 7 µg/mL.~~

~~Following multiple dose (fourth dose [Cycle 1, Week 4]) of IMC-CS4 at the 2.5-mg/kg every-week dosing schedule (the highest dose tested), the geometric mean clearance (at steady state) and exposure ($AUC_{(0-\tau)}$) were 0.0189 L/hr and 11600 hr*µg/mL, respectively. The terminal elimination half-life ranged from 7 to 12 days, and the accumulation ratios ranged from 2.08 to 3.03. The trough concentrations (C_{trough}) ranged from 24.1 to 44.5 µg/mL. However, these results were obtained from only 3 patients from one dose group (2.5 mg/kg every week).~~

5.4.4. Nonclinical Toxicology ~~of IMC-CS4~~

A standard nonclinical toxicology program for advancement of a monoclonal antibody into clinical trials in oncology indications was conducted to assess the safety and toxicity of LY3022855~~IMC-CS4~~. The nonclinical safety assessment of LY3022855~~IMC-CS4~~ was conducted in cynomolgus monkeys. This species was considered a relevant model for the nonclinical safety evaluation of LY3022855~~IMC-CS4~~, based on a preliminary cross-species evaluation of tissue/receptor binding and/or functional in vitro pharmacological activity in human and cynomolgus monkey test systems and in a subsequent comprehensive tissue cross-reactivity study using full panels of monkey and human tissues. The toxicology studies conducted with LY3022855~~IMC-CS4~~ included an exploratory single-dose toxicity and toxicokinetic (TK) dose range-finding study and a pivotal 4-week repeat-dose good laboratory practice toxicity, TK, and immunogenicity study with a 6-week recovery period. Animals were administered LY3022855~~IMC-CS4~~ by I.V. infusion, the intended clinical method of administration, using the dosing schedule (once weekly) in the planned initial clinical investigations of LY3022855~~IMC-CS4~~. The pivotal study included evaluations of relevant safety pharmacology parameters. Because of an anticipated effect of LY3022855~~IMC-CS4~~ on circulating levels of the target ligand, CSF-1, the levels of CSF-1 were also measured in the study animals as a potential marker of the pharmacodynamic activity of the antibody. A thorough assessment of peripheral blood and spleen mononuclear cell subsets and an immunohistochemical analysis of CD68+ cells (cellular marker of monocytes/macrophages) in liver and spleen were also included to determine the effects that blockade of the CSF-1 receptor might have on these endpoints.

Assessment of the genotoxicity potential of monoclonal antibodies is not relevant and was, therefore, not studied. Based on the early stage of clinical development and the oncology indication, reproductive toxicity studies of LY3022855~~IMC-CS4~~ have not been conducted.

5.4.4.1. Single-Dose Toxicity

Single-dose administration of LY3022855~~IMC-CS4~~ at dose levels of 10, 40, and 140 mg/kg administered by I.V. infusion over a 15-minute period was well tolerated in cynomolgus monkeys (2 monkeys/sex/group) during the 14-day observation period. Sustained dose-proportional exposure to LY3022855~~IMC-CS4~~ was generally observed throughout the 14-day

observation period at all dose levels following administration, with no apparent sex differences.

CCI [redacted]

CCI [redacted] Similar elevations in serum enzyme levels have also been observed when treating with other pharmacological agents targeting CSF-1R (Wang et al. 2011) or CSF-1 (Radi et al. 2011).

No other adverse clinical signs or effects on food consumption, body weight, hematology, and organ weights were associated with administration of LY3022855~~IMC-CS4~~.

CSF-1 serum levels increased relatively quickly after LY3022855~~IMC-CS4~~ administration and remained sustained throughout the 14-day observation period. CSF-1 was not detected in any control animals at any time. The maximum levels of CSF-1 reached were comparable across dose groups, suggesting that a maximal pharmacodynamic effect of LY3022855~~IMC-CS4~~ on this parameter was achieved at even the lowest dose level in the study.

The no-observed-adverse-effect level (NOAEL) in this study was considered to beCCI [redacted] This dose corresponded to a dosing Day 1 CCI [redacted]

5.4.4.2. Repeat-Dose Toxicity

In the pivotal repeat-dose toxicity, TK, and immunogenicity study of LY3022855~~IMC-CS4~~, doses of 0, 20, 60, and 180 mg/kg/dose LY3022855~~IMC-CS4~~ were administered by I.V. infusion once weekly to cynomolgus monkeys (5/sex/group) for 4 weeks, followed by a 6-week recovery period. Standard toxicological and relevant safety pharmacology (cardiovascular, central nervous [CNS], and respiratory systems) endpoints were assessed. As in the single-dose study, circulating levels of CSF-1 were measured. A thorough assessment of peripheral blood and spleen mononuclear cell subsets and an immunohistochemical analysis of CD68+ mononuclear cells in liver and spleen were also conducted.

Intravenous infusion of LY3022855~~IMC-CS4~~ was generally well tolerated at all dose levels. Sustained dose-proportional to slightly-greater-than-dose-proportional increases in exposure to LY3022855~~IMC-CS4~~ were generally observed, and no sex differences in exposure were

apparent. Moderate accumulation (approximately 2-fold) of LY3022855~~IMC-CS4~~ occurred after repeated administration. CCI

[redacted]

As noted in the single-dose exploratory study, circulating concentrations of CSF-1 increased shortly after LY3022855~~IMC-CS4~~ administration. CSF-1 was not detected in any control animals. In contrast to LY3022855~~IMC-CS4~~, the concentration of CSF-1 did not vary with dose, as comparable maximum levels were reached in all 3 dose groups. Towards the end of the recovery period, CSF-1 levels generally decreased in the 20- and 60-mg/kg dose groups, but remained elevated in the 180-mg/kg dose group.

The key toxicological findings attributed to LY3022855~~IMC-CS4~~ administration in this study were periorbital swelling, increases in serum transaminases as noted in the exploratory study, changes in leukocyte populations (monocytes, neutrophils, CD68+ mononuclear cells, natural killer [NK] cells), and target organ effects in liver (Kupffer cell hypertrophy/hyperplasia), spleen (follicular hypertrophy/dendritic cell hyperplasia), and bone marrow (hypercellularity). The immunomodulatory effects on leukocytes, Kupffer cells, spleen, and bone marrow likely reflect an exaggerated pharmacological response to LY3022855~~IMC-CS4~~, possibly associated with elevations in circulating CSF-1 levels noted during the study.

Elevations in ALT after the last dosing of LY3022855~~IMC-CS4~~ were generally minimal in the lowest dose group (20 mg/kg) and minimal to moderate at the 60- and 180-mg/kg dose levels. AST levels were minimally to moderately increased at all dose levels. ALT and AST returned to baseline in the 20-mg/kg group and trended towards baseline in the 60- and 180-mg/kg groups during the recovery period, but remained increased in some individual animals compared with baseline. No histological changes in the liver were noted to correlate with the transaminase increases, nor were any changes noted in liver functional parameters (that is, AP, bilirubin, and coagulation). Therefore, based on the small magnitude of the elevations and the absence of histological or functional changes, the increases in ALT and AST were not considered adverse.

Increases in circulating white blood cells due to increases in neutrophils and monocytes were observed in both sexes at 60 and 180 mg/kg. Flow cytometry analysis of spleen and peripheral blood revealed increases in monocytes in spleen and blood at 60 and 180 mg/kg and reductions in splenic NK cells in all LY3022855~~IMC-CS4~~ treated groups. Variability in NK cell numbers in the peripheral blood of animals in all dose groups (including control) precluded assigning a definitive relationship with LY3022855~~IMC-CS4~~ treatment. These changes in white blood cell counts, in conjunction with minimal reversible increases in serum globulin concentrations with a corresponding decrease in albumin to globulin ratio, are consistent with the presence of an inflammatory response. However, no histopathologic evidence of inflammation was observed. The monocyte, neutrophil, and globulin changes were reversible by the end of the recovery

period, while the splenic NK cell reductions were still apparent in some animals. These changes were not considered adverse because of their small magnitude.

Anatomic pathology changes attributed to the administration of LY3022855~~IMC-CS4~~ at the end of the dosing period included increased spleen weights in females (all dose groups), which generally correlated with splenic follicular hypertrophy (males at 60 and 180 mg/kg; females at 20 and 180 mg/kg), bone marrow hypercellularity (all female dose groups, one male at 60 mg/kg), bone marrow lymphoid aggregates (one male, one female at 180 mg/kg), and Kupffer cell hypertrophy/hyperplasia (primarily minimal, all male dose groups, one female at 60 mg/kg). Immunohistochemical analyses confirmed the presence of increased size or number of CD68+ Kupffer cells in the liver and increased numbers of CD68+ mononuclear cells in the spleen at all dose levels. The CD68+ cells in the spleen were likely follicular dendritic cells. The immunohistochemical findings in liver and spleen generally correlated with the histopathologic diagnoses of Kupffer cell hypertrophy/hyperplasia and splenic follicular hypertrophy. Similar anatomic pathology findings in spleen, liver, and bone marrow were observed after the recovery period. These changes were not considered adverse because of their small magnitude.

Slight to moderate periorbital swelling was observed primarily during the recovery phase in all LY3022855~~IMC-CS4~~-treated groups (20, 60, and 180 mg/kg/dose). This clinical sign has been reported to occur in humans with another antibody to CSF-1 (Sadis et al. 2009) and may thus represent a delayed response to LY3022855~~IMC-CS4~~ in the treated monkeys. Watery feces was observed only in the 60-mg/kg/dose animals, but is considered possibly related to the administration of LY3022855~~IMC-CS4~~. These clinical signs were not considered adverse based on their limited impact to the overall health of the animal. No adverse effects were noted in assessments of the central nervous (neurological behavioral examination), respiratory (rate), or cardiovascular (heart rate, blood pressure, electrocardiogram [ECG]) systems. In addition, no evidence of an adverse reaction or intolerance attributable to LY3022855~~IMC-CS4~~ was apparent at the injection sites after I.V. infusion in the cynomolgus monkey repeat-dose toxicity studies.

Based on the absence of any definitive LY3022855~~IMC-CS4~~-related adverse findings, the NOAEL for LY3022855~~IMC-CS4~~ administered via 15-minute I.V. infusion weekly on 4 occasions was considered to be 180 mg/kg/dose. The dose corresponded to a dosing Day 22 mean C_{max} of 7985 µg/mL, C_{168hr} of 2945 µg/mL, and mean $AUC_{(0\text{-}168hr)}$ of 711340 µg· hr/mL.

5.4.5. Clinical Experience

Clinical experience with LY3022855 comprises 43 patients (as of 28 January 2016) who received the following doses I.V. in 2 ongoing Lilly-sponsored Phase 1 studies (I5F-IE-JSCA [JSCA] and I5F-MC-JSCB [JSCB]): 2.5 mg/kg QW (n=6), 0.3 mg/kg QW (n=4), 0.6 mg/kg QW (n=3), 1.25 mg/kg Q2W (n=20), 1.25 mg/kg QW (n=5), and 1 mg/kg on Weeks 1, 2, 4, and 5 of every 6-week cycle (n=5). At the first human dose studied, 2.5 mg/kg QW (Study JSCA), which was also the highest dose administered, laboratory abnormalities, including Grade 2-3 creatine kinase (CK) and Grade 2-3 AST elevations, were noted in 5 patients but were not classified as dose-limiting toxicities (DLTs) due to the lack of clinical signs or symptoms of

organ toxicity. Because of these laboratory abnormalities, the protocol for Study JSCA was amended and dose escalation was restarted at a lower dose, 0.3 mg/kg QW.

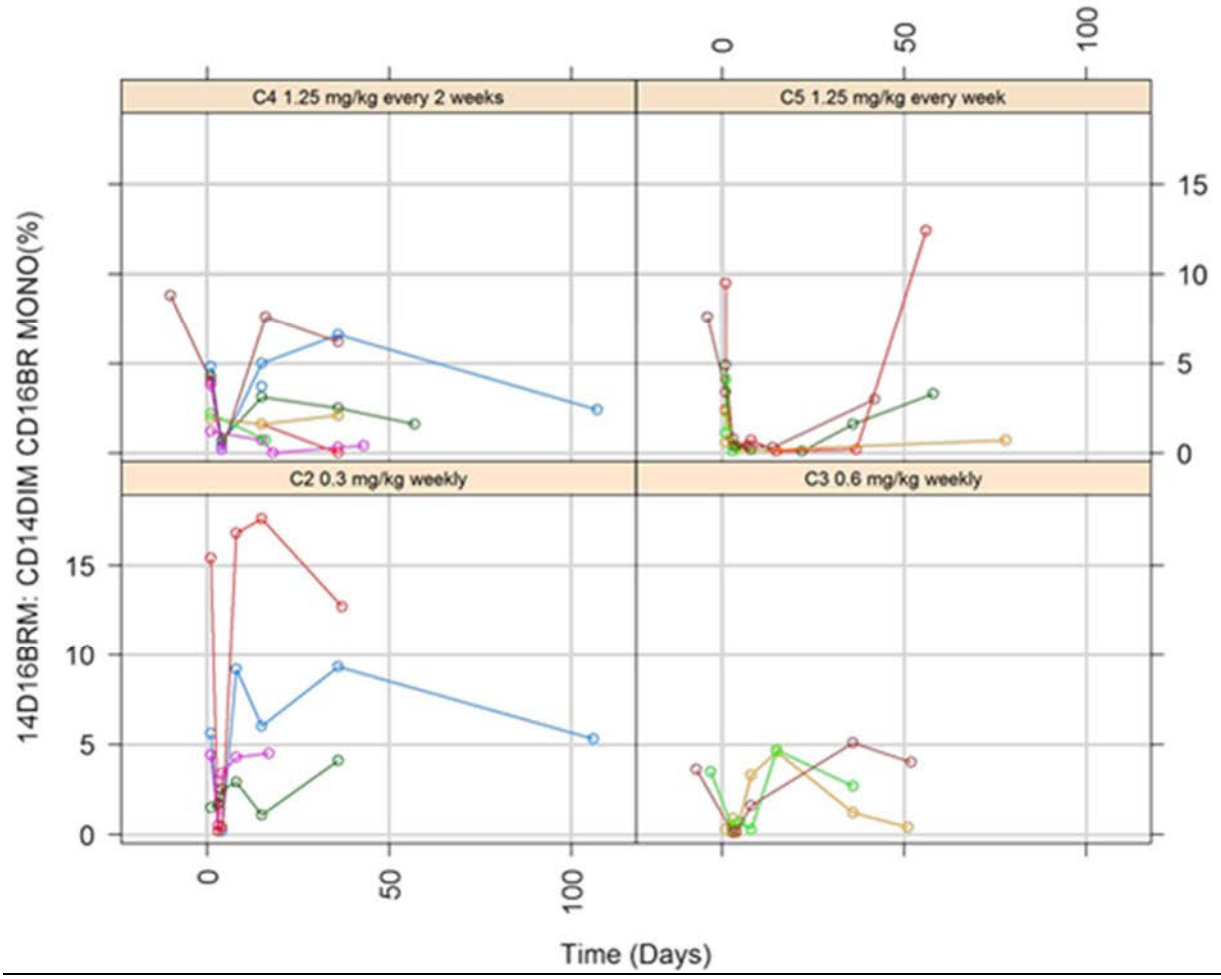
Elevated levels of CK and AST, in the absence of clinical signs or symptoms or other laboratory abnormalities suggestive of end-organ damage are, in retrospect, believed to be pharmacodynamic indicators of target engagement, rather than markers of drug-related toxicity. This belief is strengthened by findings of Radi et al. (2011), in which preclinical models support the hypothesis that increases in the levels of serum enzymes can be the result of decreases in Kupffer cells, in the apparent absence of hepatic or skeletal muscle injury. In all cases where elevated enzymes were observed following LY3022855 administration in Study JSCA, the levels decreased to Grade <2 upon discontinuation of LY3022855, indicating that these effects were reversible.

As of 12 October 2016, four DLTs have been observed in Study JSCA: an event of left ventricular dysfunction (Cohort 4, 1.25 mg/kg Q2W), an event of pancreatitis (a patient in Cohort 5, 1.25 mg/kg QW), an event of rhabdomyolysis (another patient in Cohort 5), and an event of Grade 3 CK elevation (Cohort 7a, 150 mg QW). The patient with the DLT of left ventricular dysfunction had a baseline left ventricular ejection fraction (LVEF) of 35%, which obfuscated the relationship between LY3022855 and the DLT event; therefore, the patient was considered to be a suboptimal candidate for study participation. The patient in Cohort 5 who experienced pancreatitis had a medical history significant for irritable bowel syndrome and gastroesophageal reflux disease (GERD), rendering the patient prone to nausea and abdominal pain. During the course of treatment in Study JSCA, this patient's serum levels of lipase gradually increased, from 21 U/L (baseline) to 138 U/L (Cycle 1, Week 6 [C1W6]) (C1W2 = 79 U/L, C1W3 = 90 U/L, C1W4 = 121 U/L, C1W5 = 149 U/L). Following the C1W3 administration of LY3022855, the patient's treatment with study drug was held due to rising lipase levels. Steroids were not initiated until the patient presented for medical attention with complaints of nausea, vomiting, and abdominal pain on C1W6, at which time the patient was diagnosed with Grade 3 pancreatitis. The symptoms improved with hospitalization, supportive therapy, and systemic steroids. Although this particular case resulted in a DLT, the relationship between elevated lipase and gastrointestinal symptoms is not clear, given the patient's history of irritable bowel syndrome and GERD.

Following the occurrence of the 2 DLTs in Cohort 5 of Study JSCA, dose escalation was temporarily halted. Subsequent PK and pharmacodynamic analyses revealed the following:

- A lack of correlation between body weight and LY3022855 clearance (Figure JSCB.1)
- Intermittent inhibition of CSF-1R signaling with Q2W dosing of LY3022855, as evidenced by levels of both circulating CSF-1 and peripheral $CD14^{dim}CD16^{bright}$ cells by fluorescence-activated cell sorting (FACS) (Figure JSCB.2)
- Sustained inhibition of CSF-1R signaling with 2.5 mg/kg QW and 1.25 mg/kg QW dosing (Study JSCA Cohorts 1 and 5, respectively) of LY3022855, as evidenced by levels of both circulating CSF-1 and peripheral $CD14^{dim}CD16^{bright}$ cells by FACS (Figure JSCB.2)

Based on these observations, the protocol for Study JSCA was amended to: (1) examine fixed (non-weight-based) dosing of LY3022855 on weekly administration schedules to optimize the biological effects of LY3022855 on CSF-1R inhibition, (2) redefine a DLT as any LY3022855-related AE that occurs during Cycle 1 and does not improve to Grade ≤2, unless stated otherwise, despite medical management, including steroids (if applicable) within 7 days of documented occurrence, and (3) incorporate management guidelines for immune-related AEs. Dosing in Study JSCA resumed at a fixed dose of 100 mg QW, which is comparable to 1.33 mg/kg in a 75-kg person and within the coefficient of variation in exposure (34% to 49%). As of 12 October 2016, 3 patients in Study JSCA have received 100 mg QW for 6 weeks (Cycle 1, DLT assessment period) without experiencing a DLT. Of the 3 patients treated at the next higher dose level of 150 mg QW, 1 patient experienced a DLT of Grade 3 CK elevation associated with elevated serum and urine myoglobin.



Abbreviation: C = cohort.

Figure JSCB.2. $CD14^{dim}CD16^{bright}$ (relative percentage of $CD45^{+}$ HLA-DR^{+} $CD14^{+}$) in the blood of patients from Study JSCA.

~~There is currently one IMC-CS4 study, Study JSCA, an ongoing Phase 1 dose-escalation study of single-agent therapy in advanced solid tumors that are refractory to standard therapy or for which no standard therapy is available. As of 22 February 2015, IMC-CS4 has been administered by I.V. infusion over 6-week cycles to 26 patients in this study. This includes:~~

- ~~6 patients dosed at the starting dose of 2.5 mg/kg weekly (Cohort 1),~~
- ~~4 patients dosed at 0.3 mg/kg weekly (Cohort 2),~~
- ~~3 patients dosed at 0.6 mg/kg weekly (Cohort 3),~~
- ~~6 patients dosed at 1.25 mg/kg every 2 weeks (Cohort 4),~~
- ~~5 patients dosed at 1.25 mg/kg weekly (Cohort 5), and~~
- ~~2 patients dosed at 1.25 mg/kg every 2 weeks (expansion cohort).~~

~~In Cohort 1 (2.5 mg/kg weekly), laboratory findings consistently reported for the 6 treated patients included serum elevations of creatine kinase (CK; also known as creatine phosphokinase), AST, and LDH. None of these findings were considered to be dose-limiting toxicities (DLTs), due to the lack of clinical signs and symptoms of organ toxicity and because enzyme levels decreased upon discontinuation of IMC-CS4, indicating that this effect was temporary and reversible. However, based on these findings, the planned dose-escalation scheme for Cohorts 2 and beyond was revised (via dose reductions and prolonged administration intervals) to better characterize the IMC-CS4 dose-response effect on the monocyte/macrophage system and on various serologic and hematologic parameters.~~

~~No DLTs were observed in Cohorts 2 and 3. In Cohort 4, one patient with a history of cardiac dysfunction developed a Grade 3 left ventricular systolic dysfunction (verbatim) after one dose of IMC-CS4; the event was considered by the investigator to be related to IMC-CS4. Because a DLT could not be ruled out for this event, 2 additional patients were enrolled into Cohort 4 and completed the cycle without experiencing a DLT.~~

~~Five patients were subsequently enrolled into Cohort 5, of whom 2 developed DLT events:~~

- ~~One patient developed rhabdomyolysis, complicated by acute renal failure, after one dose. No clear contributing or inciting factors were identified other than possible dehydration caused by physical activity in hot humid weather 5 days after receiving IMC-CS4.~~
- ~~One patient was diagnosed with pancreatitis after 3 weekly doses. No clear inciting factors could be identified other than study drug administration; however, the diagnosis of pancreatitis was obfuscated by concurrent medical issues, including irritable bowel syndrome and baseline Grade 1 nausea.~~

~~Due to these 2 DLTs, dose escalation was discontinued and enrollment to a 6-patient expansion cohort (to be dosed at 1.25 mg/kg every 2 weeks) was initiated.~~

~~As of 28 January 2014 (the cutoff date for the 2014 IB for IMC-CS4), the most commonly reported treatment-emergent adverse events (TEAEs) (≥20% patients) regardless of grade or relationship to IMC-CS4 were: fatigue (11 patients); hypoalbuminemia (8 patients); nausea, aspartate aminotransferase increased, and decreased appetite (6 patients each); cough and blood creatine phosphokinase increased (5 patients each); and lymphopenia, blood alkaline phosphatase increased, lymphocyte count decreased, weight decreased, hypocalcemia, hyponatremia, and hypertension (4 patients each). Six patients who received at least 1 dose of IMC-CS4 in Study JSCA experienced the following Grade 3 or Grade ≥4 adverse events (AEs) regardless of relationship to IMC-CS4: Grade 3 AEs of anemia, tachycardia, left ventricular dysfunction, ascites, fatigue, subcutaneous abscess, aspartate aminotransferase increased, blood creatine phosphokinase increased, blood alkaline phosphatase increased, lymphocyte count decreased, hypokalemia, pneumothorax, and hypotension; and Grade ≥4 sudden death.~~

~~Results from Study JSCA indicate that IMC-CS4 demonstrates a safety and toxicity profile that supports further testing of IMC-CS4 as single-agent therapy in advanced solid tumors that are refractory to standard therapy or for which no standard therapy is available.~~

~~For additional information, see the current IMC-CS4 IB.~~

More information about the known and expected benefits, risks, and reasonably anticipated AEs may be found in the IB. Information on AEs expected to be related to the investigational product may be found in Section 7 (Development Core Safety Information) of the IB. Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

5.5. Rationale for Selection of Dose

The optimal dose and ~~regimen~~ schedule of LY3022855~~IMC-CS4~~ in humans are not known. The protocol will utilize ~~4~~2 dosages of LY3022855~~IMC-CS4~~, where Dosages A and B are weight based, while Dosages C and D are non-weight based (that is, fixed), as prior data suggest that weight-based dosing does not affect exposure (Section 5.4.3). ~~Dosage A will be 1.25 mg/kg administered every 2 weeks of a 6-week cycle, and Dosage B will be 1 mg/kg on Weeks 1, 2, 4, and 5 of a 6-week cycle.~~Refer to Table JSCB.1 for a summary of the LY3022855 dosages to be used in this study.

Table JSCB.1. Summary of LY3022855 Dosages in Study JSCB

Dosage	Dose	Schedule (based on a 6-week cycle)
Dosage A (weight based dose)	1.25 mg/kg	Q2W
Dosage B (weight based dose)	1 mg/kg	Weeks 1, 2, 4, and 5 of a 6-week cycle
Dosage C (non-weight based/fixed dose)	100 mg	QW
Dosage D (non-weight based/fixed dose)	100 mg	Q2W

Abbreviations: QW = weekly; Q2W = every 2 weeks (Weeks 1, 3, and 5).

The rationale for each dosage is presented as follows.

Dosage A is based on the following observations from Study JSCA:

- A dosage of 1.25 mg/kg every 2 weeks was the lowest dosage tested in Study JSCA that demonstrated a significant increase in the 2 ligands of CSF-1R (CSF-1, IL-34).
- Results demonstrated an acceptable clinical safety profile of LY3022855~~IMC-CS4~~ at a dose of 1.25 mg/kg every 2 weeks.

Dosage B ~~is based on the following~~ rationale:

- PK parameters from Study JSCA revealed a 34% to 49% coefficient of variation in exposure ($AUC_{0-\infty}$) for patients administered LY3022855~~IMC-CS4~~ at 1.25 mg/kg every 2 weeks or 1.25 mg/kg weekly. Dosage B at 1 mg/kg on Weeks 1, 2, 4, and 5 of a 6-week cycle will result in a cumulative dose of 4 mg/kg every 6 weeks, which is 0.25 mg/kg (6.7%) greater than the cumulative dose per (6-week) cycle of Dosage A (1.25 mg/kg every 2 weeks). However, a 6.7% increase in exposure is within the variation of exposure documented in Cohorts 4 and 5. Thus, Dosage B is a reasonable dose and schedule in terms of safety. Additionally, dosing 2 consecutive weeks is expected to enhance inhibition of CSF-1R, based upon preliminary pharmacodynamic data (CSF-1 and IL-34) from Cohorts 4 and 5. Furthermore, interruption of dosing every 3 weeks provides an opportunity for LY3022855~~IMC-CS4~~-associated laboratory abnormalities to normalize prior to resumption of dosing, as has been observed in the Phase 1 dose-escalation Study JSCA.

Dosage C rationale:

- Pharmacodynamic data (Section 5.4.5) suggest that weekly administration of LY3022855 results in enhanced target engagement. Thus, Dosage C will be implemented to examine weekly administration of LY3022855.

Dosage D rationale:

- It has been observed that all patients who were treated with LY3022855 and experienced antitumor activity (as evidenced by tumor shrinkage or stability) as of 24 August 2016 were treated on a Q2W schedule. Thus, Dosage D will be implemented to continue exploring Q2W dosing, but at a fixed (non-weight-based) dose. Furthermore, the Q2W schedule may be preferable for quality of life, because the patient will require fewer clinic visits.

6.1. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may ~~not~~ be re-screened if agreed upon by the sponsor. If a patient discontinues prior to the second biopsy, the patient will be replaced.

6.1.1. Inclusion Criteria

[6] Have a performance status of ≤2 on the Eastern Cooperative Oncology Group (ECOG) scale. See Attachment 8~~Attachment 6~~.

[9b] Female patients:

are women of child-bearing potential who test negative for pregnancy within 7 days prior to enrollment based on a urine or serum pregnancy test and agree to use a reliable method of birth control during the study and for 12 weeks following the last dose of the study drug and also must not be breastfeeding,

10] Have an estimated life expectancy that, in the judgment of the investigator, ~~that~~ will permit the patient to complete 1 cycle of treatment.

6.1.2. Exclusion Criteria

14] Have symptomatic CNS malignancy or metastasis (screening not required).

Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids (to control CNS edema) ~~and/or anticonvulsants~~, and their disease is asymptomatic for at least 28 days prior to enrollment. Magnetic resonance imaging (MRI) documenting disease stability within 60 days prior to enrollment is also required.

[16] Have any of the following cardiovascular conditions ~~a history of and/or current~~:

a) symptomatic coronary artery disease currently or within the past 6 months,

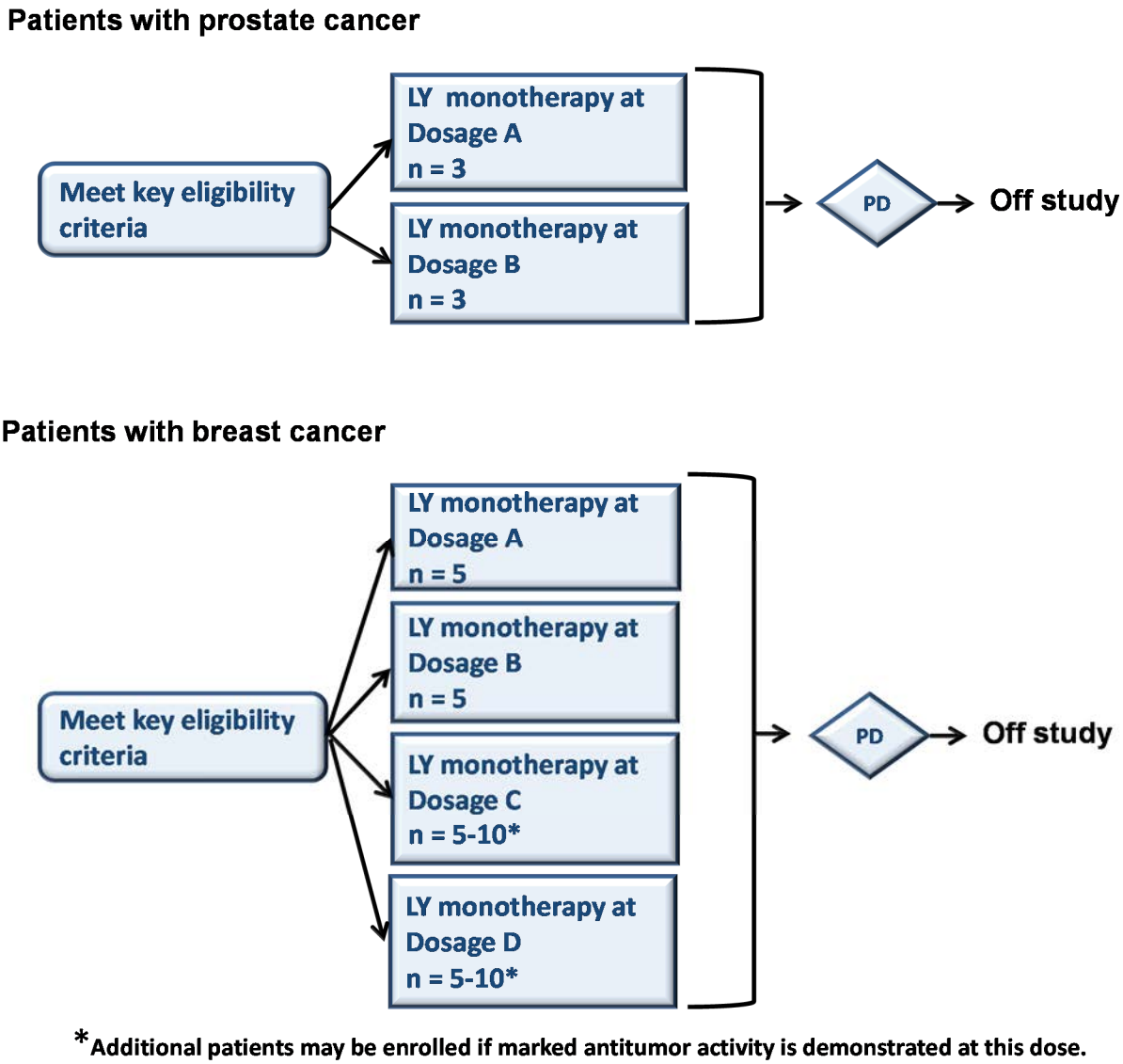
b) confirmed left ventricular ejection fraction ≤50% or any cardiac insufficiency > New York Heart Association (NYHA) class II~~,~~* currently or within the past 6 months,

c) uncontrolled hypertension (>170/100 mm Hg) currently or within the past 7 days, or

d) serious cardiac arrhythmia (well-controlled atrial fibrillation is permitted) currently or within the past 6 months.

6.2. Summary of Study Design

Study I5F-MC-JSCB (JSCB) is a single-center, open-label, nonrandomized, noncontrolled Phase 1 study of I.V. LY3022855~~IMC-CS4~~ in patients with advanced, refractory breast or prostate cancer. Eligible patients will receive LY3022855~~IMC-CS4~~ as an infusion, suggested to be administered over approximately 90 minutes for the first infusion, decreasing by 30 minutes for subsequent infusions, until administered over 30 minutes (refer to Section 7.2 for further details of study drug administration). Study JSCB is intended to explore clinical response and immunological activity of single-agent LY3022855~~IMC-CS4~~ in approximately 40~~20~~ patients (enrolled, of whom 36~~16~~ will be evaluable), by assessment of biomarkers, cytokines, and immune cells. The study schema is shown in Figure JSCB.3.



Abbreviations: ~~Ca = cancer;~~ LY = LY3022855 (IMC-CS4); PD = progressive disease~~;~~ ~~Pts = patients~~.

Figure JSCB.3. Study JSCB study design.

Enrollment will be sequential, starting with the assignment of patients to Dosage A (LY3022855~~IMC-CS4~~, 1.25 mg/kg every 2 weeks [Q2W] of a 6-week cycle), then the assignment of patients to Dosage B (LY3022855~~IMC-CS4~~, 1.0 mg/kg on Weeks 1, 2, 4, and 5 of a 6-week cycle) once the Dosage A cohort ~~of the study~~ is fully enrolled. Once the Dosage B breast cancer cohort is fully enrolled, patients with breast cancer will be assigned by the sponsor to Dosage C (LY3022855, 100 mg QW of a 6-week cycle) or D (LY3022855, 100 mg Q2W of a 6-week cycle) on an alternating basis until 5 patients are enrolled to each of Dosages C and D. Once 5 patients are enrolled to each of Dosages C and D, the sponsor and the investigators will

review clinical data to determine if enrollment of an additional 5 patients to each of Dosages C and D is warranted (refer to Section 10 for details regarding sample size).

Patients will receive Dosage A, ~~or Dosage~~ B, C, or D for one 6-week cycle or until the patient meets one or more criteria for study discontinuation. After 1 cycle, patients who are benefitting from study treatment (that is, no disease progression or unacceptable toxicity) may continue to receive study treatment at the same dose and schedule until there is clear (confirmed) evidence of disease progression or other withdrawal criteria are met. At the time of study completion, if a patient continues to benefit from study treatment, that patient may enter the continued access period.

Immune studies will include evaluations of changes in baseline over time in: (1) 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, as well as (2) serum cytokines, as determined by MSD multiplex cytokine immunoassay technology or ELISA, and that may include but not be limited to CSF-1, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-34, and TNF-α. Blood samples for the immunomodulatory studies will be taken as described in Attachment 4, Attachment 5, and Attachment 6.

In addition, for all patients, 2 separate tumor biopsy procedures will be performed (attempted): the first will be performed at baseline (predose), within 14 days prior to dosing on Cycle 1, Day 1, and the second will be performed within 14 days prior to dosing on Cycle 2, Day 1. Biopsy samples will be flash frozen, for exploratory biomarker research, to be used in understanding the pharmacodynamic effects of LY3022855~~IMC-CS4~~. To ensure adequate enrollment for the immune studies, additional patients will be enrolled as needed to replace a patient who either: (1) discontinues from the study prior to the second biopsy procedure, or (2) does not have sufficient tumor tissue for the second biopsy procedure and in the opinion of the investigator is benefitting from study treatment (in which case, the patient will be allowed to remain on study treatment). In addition to the required blood and tumor samples previously noted, optional tumor biopsies and/or blood samples for biomarker research may be obtained at the investigator's discretion in discussion with the patient, such as at the time of radiographic response or treatment progression.

To document the immunomodulatory activity of LY3022855~~IMC-CS4~~ treatment in patients with advanced, refractory breast or prostate cancers, an adequate sample size is required (refer to Section 10). ~~A sufficient sample size will allow for 16 evaluable patients. This sample size is estimated to be approximately 20 patients. This assumes 20% of enrolled (treated) patients will be inevaluable. The sample size is based on the observation that 14 of 17 patients evaluated in Study JSCA demonstrated a more than 2-fold (>100%) increase in CSF-1 levels 8 hours after administration of IMC-CS4.~~

6.2.1. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) when 3616 evaluable patients* are attained. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient.

6.3.1. Discontinuation of Patients

- The patient has confirmed evidence of progressive disease.
    - Exceptions for continuing with study treatment beyond confirmed radiographic progression may be made on a case-by-case basis for patients who are believed to be clinically benefiting from protocol therapy and both the iInvestigator and sSponsor (the CRP/clinical research scientist [CRS]) agree that continuing protocol therapy is in the patient's best interest.
- The patient experiences unacceptable toxicity.
- The patient experiences a Grade 3 or 4 infusion-related reaction (IRR) to LY3022855IMC-CS4.

7.1. Materials and Supplies

LY3022855IMC-CS4 for Injection is supplied at 5 mg/mL strength as a solution dosage, packaged in glass vials with an elastomeric closure. Each vial of LY3022855IMC-CS4 for Injection contains 20 mL of the drug product (100 mg/20-mL vial). Vials of LY3022855IMC-CS4 for Injection should be stored refrigerated at 2°C to 8°C. The drug product is formulated to contain the active LY3022855IMC-CS4 in 10mM histidine, 100mM glycine, 100mM arginine, and 0.01% polysorbate 80 at pH 6.0. LY3022855IMC-CS4 is a clear or slightly opalescent and colorless or slightly yellow liquid without visible particles.

LY3022855IMC-CS4 will be administered as an I.V. infusion. The dose is prepared and infused at room temperature (23°C-27°C). LY3022855IMC-CS4 will be diluted in normal saline to a final volume of 250 mL. Lilly instructions regarding dilution requirements should be followed.

7.2. Study Drug Administration

TwoFour dosages of LY3022855IMC-CS4 will be administered in this study. Refer to Table JSCB.1 for a summary of the LY3022855 dosages to be used.: Dosage A (1.25 mg/kg every 2 weeks of a 6-week cycle) and Dosage B* (1 mg/kg on Weeks 1, 2, 4, and 5 of every 6-week cycle) Eligible patients will receive LY3022855IMC-CS4 as an I.V. infusion administered over a minimum duration of 30 minutes and a maximum duration of 4 hours, based on the known safety and stability of the prepared drug. The infusion rate should not exceed 25 mg/minute.

For Dosages A and B, tThe first dose of LY3022855IMC-CS4 is dependent upon the patient's baseline body weight in kilograms. Subsequent doses of LY3022855IMC-CS4 must be recalculated if there is a ≥10% change (increase or decrease) in body weight from baseline; subsequent doses may be recalculated if there is a <10% change (increase or decrease) in body weight from baseline.

For patients with fluid retention, the estimated dry weight, instead of the actual body weight, should be used for dose calculation or recalculation (in the setting of substantial fluid retention, the Lilly CRP or designee should be consulted regarding optimal assessment of dry weight).

Dosages C and D are to be non-weight based (fixed dosing).

7.2.1. Dose Adjustments and Delays

If benefitting from treatment (that is, no disease progression or other withdrawal criteria), a patient who experiences a toxicity may continue to receive LY3022855~~IMC-CS4~~ upon agreement of the sponsor and according to the dose reduction guidelines for this study (Table JSCB.2~~Table JSCB.1~~). For any given patient in the study, their dose may be reduced up to a maximum of ~~2~~ 3 times.

Table JSCB.2~~1~~. General Dose Reduction Guidelines

Dosage	Starting Dose and Schedule	First Reduction	Second Reduction	Third Reduction
A	1.0 mg/kg (Weeks 1, 2, 4, and 5)	0.6 mg/kg (~~qw~~QW)	0.3 mg/kg (~~qw~~QW)	0.3 mg/kg (Q2W)
B	1.25 mg/kg (~~q2w~~Q2W)	0.6 mg/kg (~~qw~~QW)	0.3 mg/kg (~~qw~~QW)	0.3 mg/kg (Q2W)
C	100 mg (QW)	75 mg (QW)	50 mg (QW)	40 mg (QW)
D	100 mg (Q2W)	75 mg (Q2W)	50 mg (Q2W)	40 mg (Q2W)

Abbreviations: QW~~qw~~ = weekly; Q2W~~q2w~~ = every 2 weeks (Weeks 1, 3, and 5).

In the case of the toxicities listed in Table JSCB.3~~Table JSCB.2~~, study treatment may be held (if appropriate, in the opinion of the investigator and upon agreement with the sponsor) for a maximum of ~~3~~4 weeks, until resolution to baseline or improvement to Grade <2. Upon resolution to baseline or improvement to Grade <2, study treatment may be administered at a reduced dose (according to Table JSCB.2~~Table JSCB.1~~), beginning with the next cycle, if appropriate, in the opinion of the investigator and upon agreement with the sponsor. If toxicity does not resolve to baseline or improve to Grade <2 within ~~3~~ 4 weeks following the last administered dose, study treatment should be permanently discontinued and the patient should be discontinued from the trial.

Once a patient has had a dose reduction (has started a new cycle at the reduced dose), all subsequent infusions will be at the reduced dose level; there will be no resumption to prior dose level(s). Any patient experiencing toxicity that would necessitate more than 3~~2~~ dose reductions must discontinue treatment. Dose reductions must be confirmed by the sponsor.

Table JSCB.32. Toxicities for Which Dose Adjustments and Delays Apply

- Grade 4 hematologic toxicity
- Grade 3 hematologic toxicity lasting >7 days
- Grade 3 or 4 nonhematologic toxicity. Exceptions maybe be made for the following, if agreed upon by the sSponsor AND the iInvestigator:
  - Grade ≥3 liver function test (LFT) abnormality, such as alkaline phosphatase, gamma glutamyl transferase (GGT), AST, and ALT, not suspected to be drug related
  - Transient Grade ≥2 bilirubin elevation in the presence of known liver metastases lasting ≤7 days~~,~~
  - Laboratory abnormalities that improve to Grade <2 or baseline levels within 7 days after initial documentation ~~or that are deemed not clinically significant~~
  - {note that this bullet was promoted one level during this amendment} Laboratory abnormalities ≥Grade 3 that are deemed not clinically significant ~~do not require dose delay~~
  - Grade ≥3 asymptomatic elevation of CK **WITHOUT** elevation in serum and urine myoglobin ~~does not require dose modification~~.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; CRP = clinical research physician.

Refer to Section 7.2.1.1 (Infusion-Related Reactions) regarding dose adjustment, delay, and discontinuation of study treatment due to LY3022855~~IMC-CS4~~ IRRs.

7.2.1.1. Infusion-Related Reactions

If a patient experiences **Grade 1** IRR/allergic reaction, the infusion rate should be decreased by 50% for the duration of the infusion. In case of a **Grade 2** IRR/allergic reaction, the infusion must be stopped until resolution to Grade ≤1; the infusion may then be resumed at 50% of the prior infusion rate (the duration of the infusion should not exceed 3 hours). Once the infusion rate has been reduced for a Grade 1 or 2 IRR, it is recommended to maintain the lower infusion rate for all subsequent infusions (premedication must be provided prior to any subsequent doses of LY3022855~~IMC-CS4~~ if the patient has experienced a Grade 1 or 2 IRR). Occurrence of a **Grade 3 or 4** IRR requires immediate and permanent discontinuation of LY3022855~~IMC-CS4~~.

During Cycles 1 and 2 only, patients are to be observed closely for any potential AEs, from the start of the infusion until at least 1 hour after the end of the infusion of LY3022855~~IMC-CS4~~. This observation is to be done in an area with resuscitation equipment and medications necessary for advanced life support and cardiopulmonary resuscitation, such as bronchodilators, vasopressor agents (for example, epinephrine), oxygen, glucocorticoids, antihistamines, and I.V. fluids, etc.

CAUTION: Infusion-related reactions may occur during or following LY3022855~~IMC-CS4~~ administration.

Premedication is not recommended to be administered prior to the first infusion of LY3022855~~IMC-CS4~~. However, if the patient experiences a Grade 1 or 2 IRR, premedication must be provided prior to any subsequent doses of LY3022855~~IMC-CS4~~. The choice of premedication is to be made after discussion and agreement between the investigator and the

Lilly CRP. In such cases (Grade 1 or 2 IRRs), administration of steroids should be avoided, if possible. Any premedication administered should be documented in the eCRF, including dose and route of administration.

If at any time a patient experiences an IRR to LY3022855~~IMC-CS4~~, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of IRRs.

For further details regarding IRRs, including characterization according to CTCAE v4.0 and treatment guidelines, refer to the LY3022855~~IMC-CS4~~ IB.

7.2.1.2. Other Adverse Events

Based on observations in nonclinical toxicological studies with LY3022855~~IMC-CS4~~ and/or observations in one clinical trial with another monoclonal antibody targeting CSF-1 (Sadis et al. 2009), patients receiving LY3022855~~IMC-CS4~~ should be closely monitored for signs indicative of hepatic function impairment (for example, increases in transaminases, LDH, bilirubin, coagulation disorders), inflammation (for example, leukocyte alterations, C-reactive protein), CK increases, and periorbital swelling. For details, refer to the LY3022855~~IMC-CS4~~ IB.

7.2.1.2.1. Immune-Related Adverse Events (irAEs)

Symptoms occurring during or following infusion of investigational therapy will be defined according to the NCI-CTCAE, Version 4.0.

In the setting of symptoms consistent with irAEs occurring following infusion of investigational therapy, investigators are encouraged to refer to Attachment 10 as a guideline for the management of potential toxicities encountered with immuno-oncology agents. Due to the potential of rapid and serious sequelae associated with irAEs, early intervention with immunomodulatory agents as indicated is encouraged, concurrent with further diagnostic medical evaluations for possible non-immune-related causes of AEs. Attachment 10 is a guideline for the management of irAEs; local standards may supersede recommendations when deemed appropriate by the investigator.

7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive LY3022855~~IMC-CS~~4 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 for each patient.

7.6. Treatment Compliance

LY3022855~~IMC-CS4~~ will be administered I.V. 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 eCRF.

7.6.1. Evaluable Patients

Any patient who does not complete 1 cycle of LY3022855~~IMC-CS4~~ treatment, undergo 1 baseline and 1 posttreatment tumor biopsy procedure (ie, attempted, whether the biopsy is successful or not), and complete immune blood studies for 1 cycle will be deemed nonevaluable for assessment of a dose level.

Patients who complete 1 cycle of LY3022855~~IMC-CS4~~ treatment, undergo 1 baseline and 1 posttreatment tumor biopsy procedure (ie, attempted, whether the biopsy is successful or not), and complete immune blood studies for 1 cycle will be considered evaluable for the assessment of a dose level. Nonevaluable patients may be replaced to ensure that ~~16~~ 36 evaluable patients are attained.

8.1. Safety Evaluations

The safety and tolerability of LY3022855~~IMC-CS4~~ have been assessed in nonclinical toxicology studies and the results from these studies are detailed in the IB. This Phase 1 study contains detailed safety monitoring that will permit further characterization of the safety profile of LY3022855~~IMC-CS4~~ in patients, beyond that initially characterized in Phase 1 study JSCA. Study procedures and their timing, including collection of blood and urine samples, are described in the Study Schedule (Attachment 1).

8.1.1. Safety Data Collection and Review

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JSCB.4~~Table JSCB.3~~ presents a summary of AE and SAE reporting guidelines. Table JSCB.4~~Table JSCB.3~~ also shows which database or system is used to store AE and SAE data.

8.1.2.2. Adverse Event and Serious Adverse Event Reporting

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System (see Attachment 7~~Attachment 5~~ for reporting recommendations).

8.1.2.2.1. Prior to Administration of Study Drug(s)

During screening, all AEs and SAEs (regardless of relatedness to protocol procedures) are collected after the patient has signed the informed consent form (ICF). For patients who do not enroll in the trial (that is, have not received at least one dose of LY3022855~~IMC-CS4~~), only AEs and SAEs related to protocol procedures are required to be collected.

8.1.2.4. Summary of AE/SAE Reporting Guidelines

The AE and SAE reporting guidelines are summarized in Table JSCB.4~~Table JSCB.3~~.

Table JSCB.4~~3~~. Adverse Event and Serious Adverse Reporting Guidelines for Study JSCB

8.2. Sample Collection and Testing

Attachment 4, Attachment 5, and Attachment 6 lists~~s~~ the detailed schedules for sample collections specifically for PK, pharmacodynamics, and immunogenicity in this study.

~~Attachment 7 provides a summary of the estimated maximum number and volume of invasive samples for all sampling during the study.~~

8.2.2. Samples for Drug Concentration Measurements Pharmacokinetics/Pharmacodynamics

Pharmacokinetic and pharmacodynamic samples will be collected as specified in ~~the Pharmacokinetic, Pharmacodynamic, and Immunogenicity Blood Sampling Schedule~~ (Attachment 1~~)~~.

8.2.2.1. Pharmacokinetic Samples

At the visits and times specified in the sampling schedule (Attachment 4, Attachment 5, and Attachment 6), venous blood samples of approximately 3 to 6 mL each will be collected to determine the serum concentrations of LY3022855~~IMC-CS4~~. If a patient remains on study until Cycle 3, additional samples will be drawn at that time. Additional samples may be drawn at additional time points during the study, if warranted and agreed upon by the investigator, Lilly, and the patient. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time of each sampling must be clearly and accurately recorded.

These samples will be analyzed at a laboratory designated by the sponsor. Serum concentrations of LY3022855~~IMC-CS4~~ will be assayed using a validated ELISA method.

8.2.2.2. Pharmacodynamic Samples

The following pharmacodynamic assessments are based on the primary study objective and are, therefore, required assessments. Samples will be tested for changes from baseline over time in peripheral blood immune cell subsets and in serum cytokines to document the immunomodulatory activity of LY3022855~~IMC-CS4~~ treatment in patients with advanced, refractory breast or prostate cancers. Flow cytometric analysis using an antibody panel that may include, but not be limited to markers Live-Dead, CD3, CD4, CD8, CD14, CD16, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS will be used to evaluate T-cell and monocyte subsets from peripheral blood. In addition, serum cytokine levels will be determined by MSD multiplex cytokine immunoassay technology or ELISA, and may include, but not be limited to CSF-1, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, IL-34, and TNF-α.

Required samples for biomarker research to be collected from all patients in this study are the following:

- blood (for exploratory analysis of serum biomarkers that may be relevant to the mechanism of action of LY3022855~~IMC-CS4~~, CCI [redacted])
- tumor tissue (for exploratory analysis of the immunomodulatory effects of LY3022855~~IMC-CS4~~ administration, including the understanding of the pharmacodynamic effects of LY3022855~~IMC-CS4~~)

8.2.3. Samples for Tailoring Biomarkers

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY3022855~~IMC-CS4~~. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

Refer to Section 8.2.2.2, Pharmacodynamic Samples, for details of samples collected for other biomarker research that is part of this study. These other samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to CSF-1, CSF-1R, and/or the mechanism of action of study drugs (LY3022855~~IMC-CS4~~).

8.2.4. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against LY3022855~~IMC-CS4~~. Immunogenicity will be assessed by a validated assay designed to detect ADA in the presence of LY3022855~~IMC-CS4~~. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY3022855~~IMC-CS4~~.

In addition to planned sampling for immunogenicity testing, if at any time a patient experiences an IRR to LY3022855~~IMC-CS4~~, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of IRRs.

Samples may be stored for a maximum of 15 years following last patient visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to LY3022855~~IMC-CS4~~. The duration allows the sponsor to respond to regulatory requests related to LY3022855~~IMC-CS4~~.

8.3. Efficacy Evaluation

Each patient's full extent of disease will also be assessed as follows:

- For patients with measurable disease defined by RECIST, tumor measurements are to be assessed by RECIST 1.1 (Eisenhauer et al. 2009; Attachment 9~~Attachment 8~~) and irRECIST (~~Wolchok et al. 2009~~Nishino et al. 2013).

10. Data Analyses

For this study, approximately 40~~20~~ patients will be enrolled.~~,~~ ~~each~~Patients with prostate cancer will~~to~~ be treated at 1 of 2 dosages of LY3022855, and patients with breast cancer will be treated at 1 of 4 dosages of LY3022855~~IMC-CS4~~. Of those enrolled patients, approximately ~~16~~36 patients will be evaluable: ~~10~~ 30 patients with advanced, refractory breast cancer and 6 patients with advanced, refractory prostate cancer. Refer to Section 6.1 for the definition of an evaluable patient.

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.

~~On the other hand~~However, when the effect size is as small as 1 for the ~~other unknown~~ 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.

All data collected will be summarized using descriptive statistics or graphics, if appropriate, and will also be listed. ~~A detailed description of data analyses will be provided in separate statistical analysis plans for this study.~~

10.3. Patient Characteristics

Patient characteristics will include the following:

- Patient demographics ~~will be reported.~~
- Baseline disease characteristics

10.4. Safety Analyses

All patients who receive at least one dose of LY3022855~~IMC-CS4~~ will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE v4.0.

10.5. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on patients who have received at least one dose of the study drug and have had samples collected, and PK serum concentrations of LY3022855~~IMC-CS4~~ will be determined.

The parameters for analysis will include but not be limited to maximum concentration (C_{max}) and trough concentration (C_{trough}) of LY3022855~~IMC-CS4~~. 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. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

10.6. Pharmacodynamic Analyses

To study the impact of the study drug and the dose levels on the patients, the changes from baseline over time in peripheral blood immune cell subsets will be documented. The immunomodulatory activity of LY3022855~~IMC-CS4~~ will be documented by examining markers that include, but are not limited to: Live-Dead, CD3, CD4, CD8, CD14, CD16, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS. The expression of those markers will be quantified by flow cytometric analysis with an antibody panel.

Biomarker measures of protein expression, based on flow cytometry, MSD, and ELISA, will be summarized by tumor type and/or dosage, based on enrolled patients. Summary statistics may include means, medians, corresponding standard errors, quartiles, and ranges. Graphics, including profile plots of markers over time, will be generated to explore potential patterns between patients. Correlation analyses between biomarkers and relative laboratory tests may be performed to further explore the activity of LY3022855~~IMC-CS4~~.

10.7. Pharmacokinetic/Pharmacodynamic Analyses

An exploratory correlative analysis of LY3022855~~IMC-CS4~~ PK and pharmacodynamics may be conducted.

10.8. Efficacy Analyses

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.

10.9. Interim Analyses

Since this is a Phase 1 study, safety data will be ~~analyzed~~reviewed 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 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 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, and the analyses on all patients including these data may not be performed.

12. References

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Amer Stat Assoc*. 1958;53(282):457-481.

Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. *Clin Cancer Res*. 2013;19(14):3936-3943.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology G~~g~~roup. *Am J Clin Oncol*. 1982;5(6):649-655.

Radi ZA, Koza-Taylor PH, Bell RR, Obert LA, Runnels HA, Beebe JS, Lawton MP, Sadis S. Increased serum enzyme levels associated with kupffer cell reduction with no signs of hepatic or skeletal muscle injury. *Am J Pathol*. 2011;179(1):240-247.

~~Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15(23):7412-7420.~~

Attachment 1. Protocol JSCB Study Schedules

Baseline and Cycle 1 Assessments (for All Dosing Schedules)

Procedure	Baseline Relative Day Prior to Day 1 of Cycle 1			Treatment Cycle 1 only						Comments
	≤28	≤14	≤7	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Eligibility Assessments										
Informed consent		X								ICF must be signed prior to performance of any protocol-specific tests/procedures.
Medical history		X								
β-hCG Pregnancy test			X							At baseline, a urine or serum pregnancy test is required for WOCBP. Thereafter, every 12 weeks after the first dose or according to local regulations, whichever is more frequent.
ECG		X				X			X	Note that in cases where ECG and blood sample collection are scheduled at the same time, all blood sampling should be performed prior to ECG assessment.
ECOG PS assessment		X		X	X	X	X	X	X	
Safety Assessments										
Physical examination		X		X	~~X~~	X	~~X~~	X	~~X~~	Includes height (at baseline only), and thoracic, abdominal, and symptom-directed examination.
Vital signs and weight measurement		X		X	X	X	X	X	X	Vital signs include temperature, pulse rate, respiration rate, and blood pressure. Vital signs will be checked and recorded prior to each infusion of LY3022855~~IMC-CS4~~, midway through each infusion, at the end of each infusion, and every 15 minutes for the first hour following each infusion, including Cycle 1, Day 1 (also to be checked and recorded at nontreatment visits during Cycle 1).
Toxicity/AE assessment		X		X	X	X	X	X	X	Any preexisting toxicity should be documented, recorded, and graded (CTCAE v4.0 grade) as a part of the baseline medical history. AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator. Data on SAEs that occur before the end of the trial will be stored in the collection database and the Lilly Safety System.
Concomitant medication assessment		X		X	X	X	X	X	X	Including those medications taken within 28 days prior to the first dose of study therapy.

Procedure	Baseline Relative Day Prior to Day 1 of Cycle 1			Treatment Cycle 1 only						Comments
	≤28	≤14	≤7	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Laboratory Tests										
HIV and viral hepatitis B and C screening	X*									Includes HIV and hepatitis B and C, per institutional standards. If done within 28 days prior to Cycle 1, Day 1 as part of standard of care, does not need to be repeated. * Should be done within 60 days prior to enrollment.
Hematology		X		X	X	X	X	X	X	Every week for the first 12 weeks on therapy.
Coagulation		X					X*			Evaluations performed as part of the baseline assessment do not need to be repeated on Cycle 1, Day 1, unless required in the opinion of the investigator. * Required within 14 days of planned posttreatment tumor biopsy.
Serum chemistry		X		X	X	X	X	X	X	Every week for the first 12 weeks on therapy.
CEA and CA 15-3	X									Applies only to breast cancer cohorts and if clinically applicable.
C-reactive protein assessment		X		X	X	X	X	X	X	Every week for the first 12 weeks on therapy, and every 2 weeks thereafter.
Urinalysis		X								Evaluations performed as part of the baseline assessment do not need to be repeated on Cycle 1, Day 1, unless required in the opinion of the investigator. Urinalysis evaluations will be performed at the beginning of each cycle (that is, approximately every 6 weeks following the first dose of study therapy). If urine dipstick >1+ for protein, obtain 24-hour urine collection for protein analysis.
Serum and urine myoglobin		X*		X*	X*	X*	X*	X*	X*	*As clinically indicated, if serum CK ≥2.5 × ULN.
Tailoring biomarkers	X									10 mL of blood to be drawn for future pharmacogenetic biomarker testing.
Blood sampling for PK, PD, IG	Refer to Attachment 4, Attachment 5, and Attachment 6.									All sampling indicated in Attachment 4, Attachment 5, and Attachment 6 is to be done only after study eligibility is met.
Efficacy Assessments										
Imaging studies (CT/MRI)	X*								X	Radiographic assessment of tumor response should be performed prior to the start of a cycle so that results are available before the patient receives a new cycle of treatment. If done within 28 days prior to Cycle 1, Day 1, as part of standard of care, does not need to be repeated prior to the start of Cycle 1. * For patients with treated CNS metastases that are eligible for this study, a baseline MRI documenting disease stability within 60 days prior to enrollment is required.
Bone scan	X								X*	**Breast cancer cohort**: A baseline bone scan is required, except in the event that a PET scan is performed within 28 days prior to the first dose of study therapy that is negative for bone disease. Routine bone scans during treatment are not required, except in the setting of bone-only disease (no lymph node, visceral, skin, or subcutaneous metastases), or as deemed appropriate by the investigator. ***Prostate cancer cohort**: Bone scans are required at baseline and (follow-up

Procedure	Baseline Relative Day Prior to Day 1 of Cycle 1			Treatment Cycle 1 only						Comments
	≤28	≤14	≤7	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
										[posttreatment]) every 6 weeks thereafter, or as clinically indicated. If done within 28 days prior to Cycle 1, Day 1, as part of standard of care, does not need to be repeated prior to the start of Cycle 1.
Tumor assessments	X								X	Radiographic assessment of tumor response should be performed prior to the start of a cycle so that results are available before the patient receives a new cycle of treatment. If done within 28 days prior to Cycle 1, Day 1, as part of standard of care, does not need to be repeated prior to the start of Cycle 1.
Tumor core needle or surgical biopsy		X						X {2 cells were merged in this amendment}		**Required**: The first tumor biopsy will be taken (attempted) at baseline (predose), within 14 days prior to dosing on Cycle 1, Day 1, and the second tumor biopsy will be taken (attempted) within 14 days prior to dosing on Cycle 2, Day 1. **Optional**: In cases of disease progression, if the patient's condition allows it, an optional tumor biopsy will be performed, as clinically indicated (refer to Section 8.2.2.2).
Ad hoc tumor tissue and blood sampling				X						**Optional**: Additional tumor tissue and/or blood samples for biomarker research may be obtained at the investigator's discretion in discussion with the patient, such as at the time of radiographic response or treatment progression. If, at any time during the study, tumor tissue is obtained through a core biopsy, surgical biopsy, or resection as routine clinical care, the sponsor requests a tissue block or unstained slides for analysis of potentially relevant surrogate biomarkers.
Study Therapy Administration										
Administer LY3022855~~IMC-CS4~~ Weekly (on Days 1, 8, 15, 22, 29, and 36)				X	X	X	X	X	X	
Administer LY3022855~~IMC-CS4~~ Every 2 Weeks (on Days 1, 15, and 29)				X		X		X		
Administer LY3022855~~IMC-CS4~~ on Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29)				X	X		X	X		

Abbreviations: β-hCG = beta human chorionic gonadotropin; AE = adverse event; CA 15-3 = cancer antigen 15-3; CEA = carcinoembryonic antigen; CK = creatine kinase; CNS = central nervous system; CT = computed tomography; CTCAE v4.0 = Common Terminology Criteria for Adverse Events, version 4.0; ECG = electrocardiogram; ECOG PS= Eastern Cooperative Oncology Group performance status; HIV = human immunodeficiency virus; ICF = informed consent form; IG = immunogenicity; MRI = magnetic

resonance imaging; PET = positron emission tomography; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event; ULN = upper limit of normal; WOCBP = women of child-bearing potential.

Cycle 2 Assessments (for All Dosing Schedules)

Procedure	Treatment Cycle 2 only						Comments
	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Safety Assessments							
β-hCG Pregnancy test							Urine or serum pregnancy test is required for WOCBP every 12 weeks after the first dose or according to local regulations, whichever is more frequent.
ECG					~~X*~~	~~X*~~	Note that in cases where ECG and blood sample collection are scheduled at the same time, all blood sampling should be performed prior to ECG assessment. ~~* As clinically indicated, prior to last infusion of treatment cycle.~~
ECOG PS assessment	X						To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29).
Physical examination	X						Includes thoracic, abdominal, and symptom-directed examination.
Vital signs and weight measurement	X						To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29). Vital signs include temperature, pulse rate, respiration rate, and blood pressure. Vital signs will be checked and recorded prior to each infusion of LY3022855~~IMC-CS4~~, midway through each infusion, at the end of each infusion, and every 15 minutes for the first hour following each infusion.
Toxicity/AE assessment	X						To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29). AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator. Data on SAEs that occur before the end of the trial will be stored in the collection database and the Lilly Safety System.
Concomitant medication assessment	X						To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29).
Laboratory Tests							
Hematology	X	X	X	X	X	X	Every week for the first 12 weeks on therapy.
Serum chemistry	X	X	X	X	X	X	Every week for the first 12 weeks on therapy.
CEA and CA 15-3	X						Applies only to breast cancer cohorts and if clinically applicable.
C-reactive protein assessment	X	X	X	X	X	X	Every week for the first 12 weeks on therapy, and every 2 weeks thereafter.

Procedure	Treatment Cycle 2 only						Comments
	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Urinalysis	X						Urinalysis evaluations will be performed at the beginning of each cycle (that is, approximately every 6 weeks following the first dose of study therapy). If urine dipstick >1+ for protein, obtain 24-hour urine collection for protein analysis.
Serum and urine myoglobin	X*	X*	X*	X*	X*	X*	*As clinically indicated, if serum CK ≥2.5 × ULN.
Blood sampling for PK, PD, IG	Refer to Attachment 4, Attachment 5, and Attachment 6.						
Efficacy Assessments							
Imaging studies (CT/MRI)						X	Radiographic assessment of tumor response should be performed prior to the start of a cycle so that results are available before the patient receives a new cycle of treatment.
Bone scan						X*	**Breast cancer cohort**: Routine bone scans during treatment are not required, except in the setting of bone-only disease (no lymph node, visceral, skin, or subcutaneous metastases), or as deemed appropriate by the investigator. ***Prostate cancer cohort**: Follow-up (posttreatment) bone scans are required every 6 weeks, or as clinically indicated.
Tumor assessments						X	Radiographic assessment of tumor response should be performed prior to the start of a cycle so that results are available before the patient receives a new cycle of treatment.
Ad hoc tumor tissue and blood sampling	X						**Optional**: Additional tumor tissue and/or blood samples for biomarker research may be obtained at the investigator's discretion in discussion with the patient, such as at the time of radiographic response or treatment progression. If, at any time during the study, tumor tissue is obtained through a core biopsy, surgical biopsy, or resection as routine clinical care, the sponsor requests a tissue block or unstained slides for analysis of potentially relevant surrogate biomarkers.
Study Therapy Administration							
Administer LY3022855~~IMC-CS4~~ Weekly (on Days 1, 8, 15, 22, 29, and 36),	X	X	X	X	X	X	
Administer LY3022855~~IMC-CS4~~ Every 2 Weeks (on Days 1, 15, and 29	X		X		X		
Administer LY3022855~~IMC-CS4~~ Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29	X	X		X	X		

Abbreviations: β-hCG = beta human chorionic gonadotropin; AE = adverse event; CA 15-3 = cancer antigen 15-3; CEA = carcinoembryonic antigen; CK = creatine kinase; CT = computed tomography; ECG = electrocardiogram; ECOG PS= Eastern Cooperative Oncology Group performance status; IG = immunogenicity; MRI = magnetic resonance

imaging; PET = positron emission tomography; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event; ULN = upper limit of normal; WOCBP = women of child-bearing potential.

Cycle 3+ Assessments (for All Dosing Schedules)

Procedure	Treatment Cycle 3 and beyond						Comments
	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Safety Assessments							
β-hCG Pregnancy test	X						Urine or serum pregnancy test is required for WOCBP 12 weeks after the first dose and every 12 weeks thereafter, or according to local regulations, whichever is more frequent.
ECG					X*	X*	Note that in cases where ECG and blood sample collection are scheduled at the same time, all blood sampling should be performed prior to ECG assessment. * As clinically indicated, prior to last infusion of treatment cycle.
ECOG PS assessment	X						To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29).
Physical examination	X						Includes thoracic, abdominal, and symptom-directed examination.
Vital signs and weight measurement	X						To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29). Vital signs include temperature, pulse rate, respiration rate, and blood pressure. Vital signs will be checked and recorded prior to each infusion of LY3022855~~IMC-CS4~~, midway through each infusion, at the end of each infusion, and every 15 minutes for the first hour following each infusion.
Toxicity/AE assessment	X						To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29). AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator. Data on SAEs that occur before the end of the trial will be stored in the collection database and the Lilly Safety System.
Concomitant medication assessment	X						To be performed only on dosing days. Dosing schedules, per protocol: Weekly (on Days 1, 8, 15, 22, 29, and 36), Every 2 Weeks (on Days 1, 15, and 29), or Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29).

Procedure	Treatment Cycle 3 and beyond						Comments
	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Laboratory Tests							
Hematology:							
For Weekly and Every-2-Week schedules	X		X		X		Cycle 3 and beyond: Every 2 weeks for patients receiving treatment on the Weekly or Every-2-Week dosing schedule (on Days 1, 15, and 29).
For Weeks 1, 2, 4, and 5 schedule	X			X			Cycle 3 and beyond: Every 3 weeks for patients receiving treatment Weeks 1, 2, 4, and 5 (on Weeks 1 and 4 [that is, Days 1 and 22]).
Serum chemistry:							
For Weekly and Every-2-Week schedules	X		X		X		Cycle 3 and beyond: Every 2 weeks for patients receiving treatment on the Weekly or Every-2-Week dosing schedule (on Days 1, 15, and 29).
For Weeks 1, 2, 4, and 5 schedule	X			X			Cycle 3 and beyond: Every 3 weeks for patients receiving treatment Weeks 1, 2, 4, and 5 (that is, on Weeks 1 and 4 [that is, Days 1 and 22]).
CEA and CA 15-3	X						Applies only to breast cancer cohorts and if clinically applicable.
C-reactive protein assessment	X		X		X		Cycle 3 and beyond: Every 2 weeks.
Urinalysis	X						Urinalysis evaluations will be performed at the beginning of each cycle (that is, approximately every 6 weeks following the first dose of study therapy). If urine dipstick >1+ for protein, obtain 24-hour urine collection for protein analysis.
Serum and urine myoglobin	X*	X*	X*	X*	X*	X*	*As clinically indicated, if serum CK ≥2.5 × ULN.
Blood sampling for PK, PD, IG	Refer to Attachment 4, Attachment 5, and Attachment 6.						
Efficacy Assessments							
Imaging studies (CT/MRI)						X	Radiographic assessment of tumor response should be performed prior to the start of a cycle so that results are available before the patient receives a new cycle of treatment.
Bone scan	X*						**Breast cancer cohort**: Routine bone scans during treatment are not required, except in the setting of bone-only disease (no lymph node, visceral, skin, or subcutaneous metastases), or as deemed appropriate by the investigator. ***Prostate cancer cohort**: Follow-up (posttreatment) bone scans are required every 6 weeks, or as clinically indicated.
Tumor assessments						X	Radiographic assessment of tumor response should be performed prior to the start of a cycle so that results are available before the patient receives a new cycle of treatment.
Ad hoc tumor tissue and blood sampling	X						**Optional**: Additional tumor tissue and/or blood samples for biomarker research may be obtained at the investigator's discretion in discussion with the patient, such as at the time of radiographic response or treatment progression. If, at any time during the study, tumor tissue is obtained through a core biopsy, surgical biopsy, or resection as routine

Procedure	Treatment Cycle 3 and beyond						Comments
	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
							clinical care, the sponsor requests a tissue block or unstained slides for analysis of potentially relevant surrogate biomarkers.
Study Therapy Administration							
Administer LY3022855~~IMC-CS4~~ Weekly (on Days 1, 8, 15, 22, 29, and 36)	X	X	X	X	X	X	For patients being treated on Dosage C and who are clinically benefitting, after the completion of Cycle 3, the dosing interval may be changed to once-every-2-week dosing after discussion with the sponsor. If a patient's dosage is changed from that of Dosage C (that is, weekly) to every-2-week dosing and then the patient develops progressive disease, the patient's dosage may then be changed back to weekly dosing if agreed upon by the investigator and sponsor.
Administer LY3022855~~IMC-CS4~~ Every 2 Weeks (on Days 1, 15, and 29)	X		X		X		
Administer LY3022855~~IMC-CS4~~ on Weeks 1, 2, 4, and 5 (on Days 1, 8, 22, and 29)	X	X		X	X		

Abbreviations: β-hCG = beta human chorionic gonadotropin; AE = adverse event; CA 15-3 = cancer antigen 15-3; CEA = carcinoembryonic antigen; CK = creatine kinase; CT = computed tomography; ECG = electrocardiogram; ECOG PS= Eastern Cooperative Oncology Group performance status; IG = immunogenicity; MRI = magnetic resonance imaging; PET = positron emission tomography; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event; ULN = upper limit of normal; WOCBP = women of child-bearing potential.

Follow-up Assessments (for All Dosing Schedules)

Procedure	30-Day Follow-up	Comments Except for the Cycle 1, Day 1 visit, allowable visit windows are ±3 days, unless indicated otherwise.
Safety Assessments		
β-hCG Pregnancy test	X	Urine or serum pregnancy test is required for WOCBP.
ECG	X	In cases where ECG and blood sample collection are scheduled at the same time, all blood sampling should be performed prior to ECG assessment.
ECOG PS assessment	X	
Physical examination	X	Includes thoracic, abdominal, and symptom-directed examination.
Vital signs and weight measurement	X	Vital signs include temperature, pulse rate, respiration rate, and blood pressure.
Toxicity/AE assessment	X	All SAEs and LY3022855~~IMC-CS4~~-related AEs will be followed until the event is resolved, stabilized, returned to baseline, deemed irreversible, or otherwise explained (frequency of follow-up evaluations is left to the discretion of the investigator). Data on SAEs that occur before the end of the trial will be stored in the collection database and the Lilly Safety System.
Concomitant medication assessment	X	
Laboratory Tests		
Hematology	X	
Serum chemistry	X	
C-reactive protein assessment	X	
Urinalysis	X	If urine dipstick > 1+ for protein, obtain 24-hour urine collection for protein analysis.
Serum and urine myoglobin	X*	*As clinically indicated, if serum CK ≥2.5 × ULN.
Blood sampling for PK, PD, IG	Refer to Attachment 4, Attachment 5, and Attachment 6.	
Efficacy Assessments		
Tumor core needle or surgical biopsy	X	**Optional**: In cases of disease progression, if the patient's condition allows it, an optional tumor biopsy will be performed, as clinically indicated (refer to Section 8.2.2.2).

Abbreviations: β-hCG = beta human chorionic gonadotropin; AE = adverse event; CK = creatine kinase; CRP = clinical research physician; ECG = electrocardiogram; ECOG PS= Eastern Cooperative Oncology Group performance status; IG = immunogenicity; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event; ULN = upper limit of normal; WOCBP = women of child-bearing potential.

Attachment 2. Protocol JSCB Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]
- Hemoglobin
- Hematocrit
- Platelets
- Leukocytes (WBC), including differential
- Neutrophils – absolute and percentage
- Lymphocytes – absolute and percentage
- Monocytes – absolute and percentage
- Eosinophils – absolute and percentage
- Basophils – absolute and percentage

Coagulation[a]
- Partial thromboplastin time (PTT)
- Prothrombin time (PT)/INR

Urinalysis[a]
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Blood
- Leukocyte esterase

Clinical Chemistry[a] **(Serum Concentrations)**
- Sodium
- Potassium
- Chloride
- Bicarbonate
- Magnesium
- Calcium
- Phosphorus
- Total bilirubin
- Direct bilirubin
- Alkaline phosphatase
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Gamma glutamyl transpeptidase
- Albumin
- Total protein
- Creatinine
- Blood urea nitrogen (BUN)
- Uric acid
- Glucose (random)
- Lipase
- Amylase
- Creatine kinase (CK)

Serum or Urine Pregnancy Test[a]

Cardiac[a]
- Troponin I or T

Serologies[a]
- HIV screening
- Viral hepatitis B and C screening

Isoenzymes[b]
- Lactate dehydrogenase (LDH)
- Creatine kinase (CK)
- Alkaline phosphatase

Serum Markers of Bone Metabolism[b]
- CTX-I

Serum Markers of Inflammation[a]
- C-reactive protein

Additional tests to be performed, as clinically indicated, at a routine follow-up visit[a]
- Serum myoglobin – if CK ≥2.5 × ULN
- Urine myoglobin – if CK ≥2.5 × ULN

Serum Tumor Markers - as clinically indicated[a]
- CEA
- CA 15-3

Abbreviations: CA 15-3 = cancer antigen 15-3; CEA = carcinoembryonic antigen; CK = creatine kinase; HIV = human immunodeficiency virus; PT/INR = International Normalized Ratio of prothrombin time; ULN = upper limit of normal; WBC = white blood cells.

[a] Local or investigator-designated laboratory.

[b] Assayed by Lilly-designated laboratory.

Attachment 4. Protocol JSCB Pharmacokinetic, Pharmacodynamic, and Immunogenicity Sample Schedule for Dosages A and B Only

Note: All sampling indicated in Attachment 4 is to be done only after study eligibility is met.

Pharmacokinetic, Pharmacodynamic, and Immunogenicity Blood Sampling Schedule for Weekly Dosing

Analyses	Prior to the first infusion (≤14 days of C1D1)	*Dosing Day* Cycle 1, Day 1 (C1D1) 1 hr (±6 min) EOI	*Dosing Day* Cycle 1, Day 1 (C1D1) 4 hr (±24 min) EOI	C1D2 24 hr (±2 hr 24 min) EOI	~~C1D3 48 hr (±5 hr 45 min) EOI~~	*Dosing Day* C1D8 Predose (±25 hr)	*Dosing Day* C1D15 Predose (±25 hr)	*Dosing Day* C1D22 Predose (±25 hr)	*Dosing Day* C1D29 Predose (±25 hr)	*Dosing Day* C1D36 Predose (±25 hr)	Comments
Pharmacokinetics	X	X	X	X	~~X~~	X		X		X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X					X		X			See Note at end of table.
Pharmacodynamics											
PD #1 - Central lab	X			X		X		X		X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab			X	X	~~X~~						PD #2=CBC with differential
PD #3 - MSKCC lab				X							PD #3=ALT, AST
PD #4 - MSKCC lab	X					X		X		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry											
FC #1 - Central lab	X			X		X		X			FC #1=CD14, CD16
FC #2 - MSKCC lab	X					X	X	X	X	X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X			X		X	X	X	X	X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab	X					X		X			CTX-I
Troponin I or T - MSKCC lab	X					X	X				

Weekly Schedule (continued)									
	Dosing Day **C2D1**	***Dosing Day*** **C3D1**			**C3D2**	~~**C3D3**~~	***Dosing Day*** **C3D8**	***Dosing Day*** **C3D22**	
Analyses	**Predose** (±25 hr)	**Predose** (±25 hr)	**1 hr** (±6 min) **EOI**	**4 hr** (±24 min) **EOI**	**24 hr** (±2 hr 24 min) **EOI**	~~**48 hr (±5 hr 45 min) EOI**~~	**Predose** (±25 hr)	**Predose** (±25 hr)	**Comments**
Pharmacokinetics	X	X	X	X	X	~~X~~	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X							See Note at end of table.
Pharmacodynamics									
PD #1 - Central lab		X			X		X	X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab				X	X	~~X~~			PD #2=CBC with differential
PD #3 - MSKCC lab					X				PD #3=ALT, AST
PD #4 - MSKCC lab		X					X	X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry									
FC #1 - Central lab		X			X		X	X	FC #1=CD14, CD16
FC #2 - MSKCC lab		X							FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X				X				AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab							X		CTX-I

Weekly Schedule (continued)			
Analyses	***Dosing Day*** **C5D1** **Predose** (±25 hr)	**30-Day Follow-up** (±7 days)	**Comments**
Pharmacokinetics	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X*	X	*To be done at this time point and every 12 weeks thereafter, until last dose. See Note at end of table.
Pharmacodynamics			
PD #1 - Central lab		X	PD #1=CSF-1, IL-34
PD #4 - MSKCC lab		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry			
FC #1 - Central lab		X	FC #1=CD14, CD16
FC #2 - MSKCC lab		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab		X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab		X	CTX-I
Troponin I or T - MSKCC lab		X*	*Only obtain for patients with cardiac symptoms.

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; C = cycle; CBC = complete blood count; CK = creatine kinase; CSF-1 = colony-stimulating factor-1; D = day; EOI = post end of infusion; FC = flow cytometry; IFN = interferon; IL = interleukin; LDH = lactate dehydrogenase; MSD = Meso Scale Discovery; MSKCC = Memorial Sloan Kettering Cancer Center; PD = pharmacodynamic(s); PK = pharmacokinetic(s); TNF = tumor necrosis factor.

Note: If at any time a patient experiences an infusion-related reaction to LY3022855~~IMC-CS4~~, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of infusion-related reactions.

Pharmacokinetic, Pharmacodynamic, and Immunogenicity Blood Sampling Schedule for Every-2-Week Dosing

Analyses	**Prior to the first infusion** (≤14 days of C1D1)	***Dosing Day*** **Cycle 1, Day1 (C1D1)** **1 hr** (±6 min) **EOI**	**4 hr** (±24 min) **EOI**	**C1D2** **24 hr** (±2 hr 24 min) **EOI**	~~**C1D3**~~ ~~**48 hr (±5 hr 45 min) EOI**~~	~~**C1D4**~~ ~~**72 hr (±8 hr 64 min) EOI**~~	**C1D8** **168 hr** (±25 hr) **EOI**	**Comments**
Pharmacokinetics	X	X	X	X	~~X~~	~~X~~	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X							See Note at end of table.
Pharmacodynamics								
PD #1 - Central lab	X			X			X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab			X	X	~~X~~	~~X~~		PD #2=CBC with differential
PD #3 - MSKCC lab				X	~~X~~	~~X~~		PD #3=ALT, AST
PD #4 - MSKCC lab	X						X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry								
FC #1 - Central lab	X			X			X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X						X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X			X			X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab	X							CTX-I
Troponin I or T - MSKCC lab	X							

Every-2-Week Schedule (continued)							
Analyses	***Dosing Day*** **C1D15** **Predose** (±50 hr)	***Dosing Day*** **C1D29** **Predose** (±50 hr)	**C1D30** **24 hr** (±2 hr 24 min) **EOI**	~~**C1D31**~~ ~~**48 hr (±5 hr 45 min) EOI**~~	~~**C1D32**~~ ~~**72 hr (±8 hr 64 min) EOI**~~	**C1D36** **168 hr** (±25 hr) **EOI**	**Comments**
Pharmacokinetics	X	X	X	~~X~~	~~X~~	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X	X					See Note at end of table.
Pharmacodynamics							
PD #1 - Central lab	X		X			X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab			X	~~X~~	~~X~~		PD #2=CBC with differential
PD #3 - MSKCC lab		X*	X	~~X~~	~~X~~		PD #3=ALT, AST * For this time point, a separate sample should not be collected for PD #3 assessment. Use the serum chemistry sample (Attachment 1) taken at this time point for the PD #3 assessment.
PD #4 - MSKCC lab	X					X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry							
FC #1 - Central lab	X		X			X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X	X				X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X	X	X			X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab	X						CTX-I
Troponin I or T - MSKCC lab	X						

Every-2-Week Schedule (continued)								
	Dosing Day **C2D1**	***Dosing Day*** **C3D1**			**C3D2**	~~**C3D3**~~	**C3D8**	
Analyses	**Predose**	**Predose**	**1 hr** (±6 min) **EOI**	**4 hr** (±24 min) **EOI**	**24 hr** (±2 hr 24 min) **EOI**	~~**48 hr (±5 hr 45 min) EOI**~~	**168 hr** (±25 hr) **EOI**	**Comments**
Pharmacokinetics	X	X	X	X	X	~~X~~	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X						See Note at end of table.
Pharmacodynamics								
PD #1 - Central lab	X	X			X		X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab				X	X	~~X~~		PD #2=CBC with differential
PD #3 - MSKCC lab							X	PD #3=ALT, AST
PD #4 - MSKCC lab	X	X					X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry								
FC #1 - Central lab	X	X				~~X~~	X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X	X					X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X	X			X		X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Troponin I or T - MSKCC lab	X							

Every-2-Week Schedule (continued)				
Analyses	***Dosing Day*** **C3D15** **Predose** (±50 hr)	***Dosing Day*** **C5D1** **Predose** (±50 hr)	**30-Day Follow-up** (±7 days)	**Comments**
Pharmacokinetics	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X*	X	*To be done at this time point and every 12 weeks thereafter, until last dose. See Note at end of table.
Pharmacodynamics				
PD #1 - Central lab	X		X	PD #1=CSF-1, IL-34
PD #4 - MSKCC lab	X		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry				
FC #1 - Central lab	X		X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab			X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab			X	CTX-I
Troponin I or T - MSKCC lab			X*	*Only obtain for patients with cardiac symptoms.

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; C = cycle; CBC = complete blood count; CK = creatine kinase; CSF-1 = colony-stimulating factor-1; D = day; EOI = post end of infusion; FC = flow cytometry; IFN = interferon; IL = interleukin; LDH = lactate dehydrogenase; MSD = Meso Scale Discovery; MSKCC = Memorial Sloan Kettering Cancer Center; PD = pharmacodynamic(s); PK = pharmacokinetic(s); TNF = tumor necrosis factor.

Note: If at any time a patient experiences an infusion-related reaction to LY3022855~~IMC-CS4~~, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of infusion-related reactions.

Pharmacokinetic, Pharmacodynamic, and Immunogenicity Blood Sampling Schedule for Weeks 1, 2, 4, and 5 Dosing

Analyses	Prior to the first infusion (≤14 days of C1D1)	*Dosing Day* Cycle 1, Day1 (C1D1) 1 hr (±6 min) EOI	4 hr (±24 min) EOI	C1D2 24 hr (±2 hr 24 min) EOI	~~C1D3 48 hr (± 5 hr 45 min) EOI~~	*Dosing Day* C1D8 Predose (±25 hr)	1 hr (±6 min) EOI	C1D15 168 hr (±25 hr) EOI	Comments
Pharmacokinetics	X	X	X	X	~~X~~	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X					X			See Note at end of table.
Pharmacodynamics									
PD #1 - Central lab	X			X		X			PD #1=CSF-1, IL-34
PD #2 - MSKCC lab			X		~~X~~				PD #2=CBC with differential
PD #3 - MSKCC lab								X*	PD #3=ALT, AST * For this time point, a separate sample should not be collected for PD #3 assessment. Use the serum chemistry sample (Attachment 1) taken at this time point for the PD #3 assessment.
PD #4 - MSKCC lab	X					X		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry									
FC #1 - Central lab	X			X		X			FC #1=CD14, CD16
FC #2 - MSKCC lab	X					X		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X			X		X		X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab	X					X			CTX-I
Troponin I or T - MSKCC lab	X								

Weeks 1, 2, 4, and 5 Schedule (continued)								
	Dosing Day **C1D22**	***Dosing Day*** **C1D29**	***Dosing Day*** **C2D1**	***Dosing Day*** **C3D1**			~~**C3D3**~~	
Analyses	**Predose** (±50 hr)	**Predose** (±25 hr)	**Predose** (±50 hr)	**Predose** (±50 hr)	**1 hr** (±6 min) **EOI**	**4 hr** (±24 min) **EOI**	~~**48 hr (±5 hr 45 min) EOI**~~	**Comments**
Pharmacokinetics	X	X	X	X	X	X	~~X~~	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X		X				See Note at end of table.
Pharmacodynamics								
PD #1 - Central lab	X	X	X	X			~~X~~	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab						X	~~X~~	PD #2=CBC with differential
PD #4 - MSKCC lab	X	X	X	X				PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry								
FC #1 - Central lab	X	X	X	X			~~X~~	FC #1=CD14, CD16
FC #2 - MSKCC lab	X	X		X				FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X	X	X	X			~~X~~	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab		X						CTX-I
Troponin I or T - MSKCC lab	X							

Weeks 1, 2, 4, and 5 Schedule (continued)							
	Dosing Day C3D8		C3D15	*Dosing Day* C3D22	*Dosing Day* C5D1	*Dosing Day* C5D29	
Analyses	**Predose** (±25 hr)	**1 hr** (±6 min) **EOI**	**168 hr** (±25 hr) **EOI**	**Predose** (±50 hr)	**Predose** (±50 hr)	**Predose** (±25 hr)	**Comments**
Pharmacokinetics	X	X	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity					X*		*To be done at this time point and every 12 weeks thereafter, until last dose. See Note at end of table.
Pharmacodynamics							
PD #1 - Central lab	X			X		X	PD #1=CSF-1, IL-34
PD #4 - MSKCC lab	X			X		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry							
FC #1 - Central lab	X						FC #1=CD14, CD16
FC #2 - MSKCC lab	X		X	X			FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab				X			AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab	X						CTX-I

Weeks 1, 2, 4, and 5 Schedule (continued)			
Analyses	***Dosing Day*** **C6D29** **Predose** (±25 hr)	**30-Day Follow-up** (±7 days)	**Comments**
Pharmacokinetics	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X	See Note at end of table.
Pharmacodynamics			
PD #1 - Central lab	X	X	PD #1=CSF-1, IL-34
PD #4 - MSKCC lab	X	X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry			
FC #1 - Central lab		X	FC #1=CD14, CD16
FC #2 - MSKCC lab		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab		X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab		X	CTX-I
Troponin I or T - MSKCC lab		X*	*Only obtain for patients with cardiac symptoms.

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; C = cycle; CBC = complete blood count; CK = creatine kinase; CSF-1 = colony-stimulating factor-1; D = day; EOI = post end of infusion; FC = flow cytometry; IFN = interferon; IL = interleukin; LDH = lactate dehydrogenase; MSD = Meso Scale Discovery; MSKCC = Memorial Sloan Kettering Cancer Center; PD = pharmacodynamic(s); PK = pharmacokinetic(s); TNF = tumor necrosis factor.

Note: If at any time a patient experiences an infusion-related reaction to LY3022855~~IMC-CS4~~, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of infusion-related reactions.

Attachment 5. Protocol JSCB Pharmacokinetic, Pharmacodynamic, and Immunogenicity Sampling Schedule for Dosage C Only

Note: All sampling indicated in Attachment 5 is to be done only after study eligibility is met.

Pharmacokinetic, Pharmacodynamic, and Immunogenicity Blood Sampling Schedule for Weekly Dosing

Analyses	Prior to the first infusion (≤14 days of C1D1)	*Dosing Day* Cycle 1, Day 1 (C1D1) 1 hr (±6 min) EOI	*Dosing Day* Cycle 1, Day 1 (C1D1) 4 hr (±24 min) EOI	C1D2 24 hr (±2 hr 24 min) EOI	*Dosing Day* C1D8 Predose (±25 hr)	*Dosing Day* C1D15 Predose (±25 hr)	*Dosing Day* C1D22 Predose (±25 hr)	*Dosing Day* C1D29 Predose (±25 hr)	*Dosing Day* C1D36 Predose (±25 hr)	Comments
Pharmacokinetics	X	X	X	X	X	X	X		X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X				X		X			See Note at end of table.
Pharmacodynamics										
PD #1 - Central lab	X			X	X		X		X	PD #1=CSF-1, IL-34
PD #3 - MSKCC lab				X						PD #3=ALT, AST
PD #4 - MSKCC lab	X				X		X		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry										
FC #1 - Central lab	X			X	X		X			FC #1=CD14, CD16
FC #2 - MSKCC lab	X				X	X	X	X	X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X			X	X	X	X	X	X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab	X									CTX-I
Troponin I or T - MSKCC lab	X					X				

Weekly Schedule (continued)								
	Dosing Day C2D1	*Dosing Day* C3D1			C3D2	*Dosing Day* C3D8	*Dosing Day* C3D22	
Analyses	**Predose** (±25 hr)	**Predose** (±25 hr)	**1 hr** (±6 min) **EOI**	**4 hr** (±24 min) **EOI**	**24 hr** (±2 hr 24 min) **EOI**	**Predose** (±25 hr)	**Predose** (±25 hr)	**Comments**
Pharmacokinetics	X	X	X	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X						See Note at end of table.
Pharmacodynamics								
PD #1 - Central lab		X			X	X	X	PD #1=CSF-1, IL-34
PD #3 - MSKCC lab					X			PD #3=ALT, AST
PD #4 - MSKCC lab		X				X	X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry								
FC #1 - Central lab		X			X	X	X	FC #1=CD14, CD16
FC #2 - MSKCC lab		X						FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X				X			AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes

Weekly Schedule (continued)			
Analyses	***Dosing Day*** **C5D1** **Predose** (±25 hr)	**30-Day Follow-up** (±7 days)	**Comments**
Pharmacokinetics	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X*	X	*To be done at this time point and every 12 weeks thereafter, until last dose. See Note at end of table.
Pharmacodynamics			
PD #1 - Central lab		X	PD #1=CSF-1, IL-34
PD #4 - MSKCC lab		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry			
FC #1 - Central lab		X	FC #1=CD14, CD16
FC #2 - MSKCC lab		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab		X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab		X	CTX-I
Troponin I or T - MSKCC lab		X*	*Only obtain for patients with cardiac symptoms.

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; C = cycle; CBC = complete blood count; CK = creatine kinase; CSF-1 = colony-stimulating factor-1; D = day; EOI = post end of infusion; FC = flow cytometry; IFN = interferon; IL = interleukin; LDH = lactate dehydrogenase; MSD = Meso Scale Discovery; MSKCC = Memorial Sloan Kettering Cancer Center; PD = pharmacodynamic(s); PK = pharmacokinetic(s); TNF = tumor necrosis factor.

Note: If at any time a patient experiences an infusion-related reaction to LY3022855~~IMC-CS4~~, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of infusion-related reactions.

Attachment 6. Protocol JSCB Pharmacokinetic, Pharmacodynamic, and Immunogenicity Sampling Schedule for Dosage D Only

Note: All sampling indicated in Attachment 6 is to be done only after study eligibility is met.

Pharmacokinetic, Pharmacodynamic, and Immunogenicity Blood Sampling Schedule for Every-2-Week Dosing

Analyses	Prior to the first infusion (≤14 days of C1D1)	*Dosing Day* Cycle 1, Day1 (C1D1) 1 hr (±6 min) EOI	*Dosing Day* Cycle 1, Day1 (C1D1) 4 hr (±24 min) EOI	C1D2 24 hr (±2 hr 24 min) EOI	C1D8 168 hr (±25 hr) EOI	Comments
Pharmacokinetics	X	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X					See Note at end of table.
Pharmacodynamics						
PD #1 - Central lab	X			X	X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab			X	X		PD #2=CBC with differential
PD #3 - MSKCC lab				X		PD #3=ALT, AST
PD #4 - MSKCC lab	X				X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry						
FC #1 - Central lab	X			X	X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X				X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X			X	X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab	X					CTX-I
Troponin I or T - MSKCC lab	X					

Every-2-Week Schedule (continued)					
	Dosing Day **C1D15**	***Dosing Day*** **C1D29**	**C1D30**	**C1D36**	
Analyses	**Predose** (±50 hr)	**Predose** (±50 hr)	**24 hr** (±2 hr 24 min) **EOI**	**168 hr** (±25 hr) **EOI**	**Comments**
Pharmacokinetics	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity	X	X			See Note at end of table.
Pharmacodynamics					
PD #1 - Central lab	X		X	X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab			X		PD #2=CBC with differential
PD #3 - MSKCC lab		X*	X		PD #3=ALT, AST * For this time point, a separate sample should not be collected for PD #3 assessment. Use the serum chemistry sample (Attachment 1) taken at this time point for the PD #3 assessment.
PD #4 - MSKCC lab	X			X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry					
FC #1 - Central lab	X		X	X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X	X		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X	X	X	X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Troponin I or T - MSKCC lab	X				

Every-2-Week Schedule (continued)							
	Dosing Day C2D1	*Dosing Day* C3D1			C3D2	C3D8	
Analyses	**Predose**	**Predose**	**1 hr** (±6 min) **EOI**	**4 hr** (±24 min) **EOI**	**24 hr** (±2 hr 24 min) **EOI**	**168 hr** (±25 hr) **EOI**	**Comments**
Pharmacokinetics	X	X	X	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X					See Note at end of table.
Pharmacodynamics							
PD #1 - Central lab	X	X			X	X	PD #1=CSF-1, IL-34
PD #2 - MSKCC lab				X	X		PD #2=CBC with differential
PD #3 - MSKCC lab						X	PD #3=ALT, AST
PD #4 - MSKCC lab	X	X				X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry							
FC #1 - Central lab	X	X				X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X	X				X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab	X	X			X	X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Troponin I or T - MSKCC lab	X						

Every-2-Week Schedule (continued)				
Analyses	***Dosing Day*** **C3D15** **Predose** (±50 hr)	***Dosing Day*** **C5D1** **Predose** (±50 hr)	**30-Day Follow-up** (±7 days)	**Comments**
Pharmacokinetics	X	X	X	The date and the time of all sampling must be clearly and accurately recorded.
Immunogenicity		X*	X	*To be done at this time point and every 12 weeks thereafter, until last dose. See Note at end of table.
Pharmacodynamics				
PD #1 - Central lab	X		X	PD #1=CSF-1, IL-34
PD #4 - MSKCC lab	X		X	PD #4=MSD assay for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα
Flow cytometry				
FC #1 - Central lab	X		X	FC #1=CD14, CD16
FC #2 - MSKCC lab	X		X	FC #2=Live-Dead, CD3, CD4, CD8, FoxP3, PD-1, Ki-67, CTLA-4, TIM-3, LAG-3, and ICOS
Isoenzymes - Central lab			X	AP isoenzymes, total CK, CK isoenzymes, total LDH, LDH isoenzymes
Bone marker - Central lab			X	CTX-I
Troponin I or T - MSKCC lab			X*	*Only obtain for patients with cardiac symptoms.

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; C = cycle; CBC = complete blood count; CK = creatine kinase; CSF-1 = colony-stimulating factor-1; D = day; EOI = post end of infusion; FC = flow cytometry; IFN = interferon; IL = interleukin; LDH = lactate dehydrogenase; MSD = Meso Scale Discovery; MSKCC = Memorial Sloan Kettering Cancer Center; PD = pharmacodynamic(s); PK = pharmacokinetic(s); TNF = tumor necrosis factor.

Note: If at any time a patient experiences an infusion-related reaction to LY3022855, all attempts will be made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. A portion of the sample taken for immunogenicity testing may be used for PK analysis, in the setting of infusion-related reactions.

~~Attachment 9. Protocol JSCB Sampling Summary~~

~~The following 3 tables summarize the maximum number of samples (venipunctures, tissue biopsies), volumes for all sampling, and tests (study qualification, health monitoring, pharmacodynamics, drug concentration, tailoring biomarkers, and immunogenicity) during the study for each of the dosing schedules. Estimates are provided; more samples could be required in the case of retests, additional health monitoring (if needed), or for patients continuing treatment beyond the protocol-specified number of cycles in the study. Fewer samples may actually be taken (for example, patients who discontinue from the study).~~

Protocol JSCB Sampling Summary - Weekly Dosing Schedule (includes samples for Cycle 1 [only] and 30-Day Follow-up)

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Study qualification, which includes the following:[a]	Blood			
CBC		2 mL	1	2 mL
Chemistries		7.5 mL	1	7.5 mL
Coagulation		1.8 mL	1	1.8 mL
Health monitoring (may be more than 1 tube), which includes the following:[b]	Blood			
CBC		2 mL	7	14 mL
Chemistries		7.5 mL	7	52.5 mL
Troponin		2 mL	4	8 mL
Coagulation		1.8 mL	1	1.8 mL
Pharmacodynamics	Tissue biopsy	Varies, 5–10 mm	Up to 12 cores	120 mm
Drug concentration (PK)	Blood	3 mL	9	27 mL
Tailoring biomarkers	Blood	10 mL	1	10 mL
Immunogenicity	Blood	10 mL	4	40 mL
Biomarkers, which includes the following:	Blood			
Cytokine analysis		6 mL	11	66 mL
Flow cytometry		8 mL	12	96 mL
Bone markers of metabolism		3.5 mL	4	14 mL
Isoenzymes		5 mL + 3.5 mL	8 + 8	68 mL
AST/ALT – MSKCC lab		5 mL	1	5 mL
CBC – MSKCC lab		2 mL	3	6 mL
Total [for each tissue sample type, rounded to nearest 10 mm]	Blood Tissue		83 Up to 12 cores	422 mL 120 mm

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; MSKCC = Memorial Sloan Kettering Cancer Center; PK = pharmacokinetic(s).

[a] Additional samples may be drawn if needed for safety purposes.

[b] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with the designated medical monitor.

Protocol JSCB Sampling Summary – Every-2-Week Dosing Schedule (includes samples for Cycle 1 [only] and 30-Day Follow-up)

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Study qualification, which includes the following:[a]	Blood			
CBC		2 mL	1	2 mL
Chemistries		7.5 mL	1	7.5 mL
Coagulation		1.8 mL	1	1.8 mL
Health Monitoring (may be more than 1 tube), which includes the following:[b]	Blood			
CBC		2 mL	7	14 mL
Chemistries		7.5 mL	7	52.5 mL
Troponin		2 mL	3	6 mL
Coagulation		1.8 mL	1	1.8 mL
Pharmacodynamics	Tissue biopsy	Varies, 5–10 mm	Up to 12 cores	120 mm
Drug concentration (PK)	Blood	3 mL	14	42 mL
Tailoring biomarkers	Blood	10 mL	1	10 mL
Immunogenicity		10 mL	4	40 mL
Biomarkers, which includes the following:	Blood			
Cytokine analysis		6 mL	12	72 mL
Flow cytometry		8 mL	13	104 mL
Bone markers of metabolism		3.5 mL	3	10.5 mL
Isoenzymes		5 mL + 3.5 mL	8 + 8	68 mL
AST/ALT – MSKCC lab		5 mL	7	35 mL
CBC – MSKCC lab		2 mL	8	16 mL
Total [for each tissue sample type, rounded to nearest 10 mm]	Blood Tissue		99 Up to 12 cores	482 mL 120 mm

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; MSKCC = Memorial Sloan Kettering Cancer Center; PK = pharmacokinetic(s).

[a] Additional samples may be drawn if needed for safety purposes.

[b] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with the designated medical monitor.

Protocol JSCB Sampling Summary - Weeks 1, 2, 4, and 5 Dosing Schedule (includes samples for Cycle 1 [only] and 30-Day Follow-up)

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Study qualification, which includes the following:[a]	Blood			
CBC		2 mL	1	2 mL
Chemistries		7.5 mL	1	7.5 mL
Coagulation		1.8 mL	1	1.8 mL
Health Monitoring (may be more than 1 tube), which includes the following:[b]	Blood			
CBC		2 mL	7	14 mL
Chemistries		7.5 mL	7	52.5 mL
Troponin		2 mL	3	6 mL
Coagulation		1.8 mL	1	1.8 mL
Pharmacodynamics	Tissue biopsy	Varies, 5–10 mm	Up to 12 cores	120 mm
Drug concentration (PK)	Blood	3 mL	11	33 mL
Tailoring biomarkers	Blood	10 mL	1	10 mL
Immunogenicity		10 mL	4	40 mL
Biomarkers, which includes the following:	Blood			
Cytokine analysis		6 mL	12	72 mL
Flow cytometry		8 mL	12	96 mL
Bone markers of metabolism		3.5 mL	4	14 mL
Isoenzymes		3.5 mL + 5 mL	7 + 7	59.5 mL
CBC – MSKCC lab		2 mL	2	4 mL
Total [for each tissue sample type, rounded to nearest 10 mm]	Blood Tissue		81 Up to 12 cores	412 mL 120 mm

Abbreviations: CBC = complete blood count; MSKCC = Memorial Sloan Kettering Cancer Center; PK = pharmacokinetic(s).

[a] Additional samples may be drawn if needed for safety purposes.

[b] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with the designated medical monitor.

Attachment 10. Protocol JSCB Guidelines for the Management of Immune-Related Adverse Events

Guidelines for the Management of Potential Toxicities Encountered with Immuno-Oncology Agents

System Organ Class	Adverse Event	CTCAE, Version 4.0 Grade (if applicable) and/or Symptoms[a]		Treatment Plan[b]
		Grade	Symptoms	
Endocrine	Thyroid issues		Asymptomatic, with TSH <0.5 × LLN or >2 × ULN	Continue drug and include free T4 in subsequent cycles.
			Symptomatic	Continue drug. Administer thyroid replacement.
	Hypotension, altered mental status, headache, fatigue		Endocrine issues aside from thyroid (for example, hypophysitis, diabetes mellitus)	Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Resume drug when symptoms resolve and are stable on hormone replacement. In case of adrenal crisis, administer stress-dose steroids. Permanently discontinue for Grade 3 or 4.
Gastrointestinal	Diarrhea, abdominal pain, blood in stool	2		Withhold drug for 1 wk. Administer antidiarrheal medication and check etiology. Resume drug when symptoms resolve to Grade <1. If >5 days' duration despite antidiarrheals, begin steroids (0.5 mg/kg/d prednisone); can resume drug during taper when symptoms resolve to Grade <1.
	Diarrhea, ileus, perforation	≥3		Withhold drug and administer 1-2 mg/kg/day prednisone (no steroids if possible perforation); discontinue drug if Grade 3 persists or Grade 4. If >3 days despite steroids, add nonsteroid immunosuppressive.
	Symptomatic pancreatitis	1 or 2		Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Can resume drug during taper.
		≥3		Permanently discontinue drug. Administer steroids (1-2 mg/kg/d prednisone). Can resume drug during taper.

System Organ Class	Adverse Event	CTCAE, Version 4.0 Grade (if applicable) and/or Symptoms[a]		Treatment Plan[b]
		Grade	Symptoms	
Hepatobiliary	Liver abnormality		AST or ALT >5 × ULN but ≤20 × ULN AND total bilirubin ≤ULN	Discuss with sponsor and consider continuing protocol treatment provided patient remains without other evidence of liver toxicity.
			AST or ALT >20 × ULN AND total bilirubin ≤ULN	Discuss with sponsor and consider holding protocol treatment until AST/ALT becomes ≤20 × ULN.
			AST or ALT >5 × ULN AND total bilirubin >ULN	Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Consider resuming protocol treatment once total bilirubin ≤ULN. Discontinue protocol therapy permanently if bilirubin does not return to below the ULN within 3 wk of holding drug.
		3 or 4	GGT or alkaline phosphatase	Continue protocol treatment provided patient remains without other evidence of liver toxicity.
Musculoskeletal	Muscle abnormality		CK >2.5 × but ≤10 ULN AND Serum and urine myoglobin ≤ULN	Discuss with sponsor and consider continuing protocol treatment provided patient remains without other evidence of muscle or renal toxicity.
			CK ≥2.5 × ULN AND Serum and urine myoglobin >ULN	Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Consider resuming protocol treatment once serum and urine myoglobin ≤ULN. Discontinue protocol therapy permanently if serum and urine myoglobin does not return to below the ULN within 3 wk of holding drug.

System Organ Class	Adverse Event	CTCAE, Version 4.0 Grade (if applicable) and/or Symptoms[a]		Treatment Plan[b]
		Grade	Symptoms	
Nervous	Weakness, paresthesia (for example, Guillain-Barré syndrome, myasthenia gravis)		No impact on activities of daily living (ADL)	Withhold drug. Resume drug when symptoms resolve.
			Impact on ADL	Withhold drug. Administer appropriate medical intervention and steroids (1-2 mg/kg/d prednisone). Can resume drug during taper and after discussion with ponsor.
Respiratory	Dyspnea, hypoxia, pneumonitis	1		Consider to withhold drug. Resume drug when stable.
		2	Mild to moderate symptoms	Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Can resume drug during taper.
		≥3	Severe	Permanently discontinue drug. Administer steroids (1-2 mg/kg/d prednisone). If >2 days despite steroids, add nonsteroid immunosuppressive.
Renal and urinary	Elevated creatinine, decreased urine output, blood in urine, edema	1	<1.5 × baseline	Continue drug.
		2 to 3	>1.5 × ULN but <6 × ULN OR >1.5 × baseline	Withhold drug. Administer steroids (1- 2 mg/kg/d prednisone).If symptoms resolve to Grade ≤1, taper steroids over 1 month. Can resume drug during taper. If elevations persist >7 days or worsen treat with Grade 4 recommendations.
		4	>6 × ULN	Permanently discontinue drug. Administer steroids (1-2 mg/kg/d prednisone).
Skin	Rash, pruritus		≤50% skin affected	Withhold drug. Start supportive medications for pruritus, for example, hydroxyzine/loratadine. If symptoms persist or worsen after 1 wk, administer topical or systemic steroids. Resume drug if rash improves to mild (localized) and steroid dose <7.5 mg.
			Stevens-Johnson syndrome, toxic epidermal necrolysis, necrosis, bullous or hemorrhagic lesions	Permanently discontinue drug. Begin steroids (1-2 mg/kg/d prednisone).

Abbreviations: ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; I.V. = intravenous(ly); LLN = lower limit of normal; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] If definition of grade not specified, use CTCAE, Version 4.0 definition.

[b] Treatment plan should always include a thorough workup of the issue to rule out other potential etiologies.

Note: Other steroid options can be given at equivalent doses. For severe cases, recommend using IV steroids. For adrenal crisis, mineralocorticoid also needs to be added to stress-dose IV steroids. Also, steroids should be tapered over 1 month once symptoms improve to ≤ grade 1, and drug should not be restarted until taper over at least 1 month complete. During steroid use, add prophylactic antibiotics for opportunistic infections. Immunosuppressive refers to infliximab or cyclophosphamide.

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