Protocol I5F-IE-JSCA (v7.0)

Phase 1 Study of IMC-CS4, a Monoclonal Antibody Targeted to the CSF-1 Receptor (CSF-1R), In Subjects With Advanced Solid Tumors Refractory to Standard Therapy or for Which No Standard Therapy is Available

NCT01346358

Approval Date: 03-Sep-2015

Clinical Trial Protocol

IMCL CP24-1001

I5F-IE-JSCA

Study Title:	Phase 1 Study of IMC-CS4, a Monoclonal Antibody Targeted to the CSF-1 Receptor (CSF-1R), in Subjects With Advanced Solid Tumors Refractory to Standard Therapy or for Which No Standard Therapy Is Available
Study Number:	IMCL CP24-1001 (I5F-IE-JSCA)
Study Phase:	Phase 1
Product Name:	IMC-CS4 (LY3022855)
IND Number:	110490
Indication:	Advanced Solid Tumors
Investigators:	Multicenter
Sponsor:	Eli Lilly and Company Indianapolis, Indiana USA 46285

Protocol Amendment Version 7.0: Electronically signed and approved by Eli Lilly and Company on date provided below.

Approval Date: 03-Sep-2015 GMT

PROTOCOL CHANGES FROM VERSION 6.0 TO VERSION 7.0

Overview

Protocol IMCL CP24-1001 Phase 1 Study of IMC-CS4, a Monoclonal Antibody Targeted to the CSF-1 Receptor (CSF-1R), in Subjects With Advanced Solid Tumors Refractory to Standard Therapy or for Which No Standard Therapy Is Available has been amended. The new protocol is indicated by Amendment Version 7.0 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:

- Updated Sponsor name and address, including deletion of ImClone logo on cover page, for consistency with the current template.
- Revised confidentiality statement (cover page), for consistency with required language.
- Added LY number (document header), for consistency with the current template.
- Added clinical experience for Cohorts 4 and 5 (Section 1.4.3).
- Increased the number of study sites from approximately 3 to approximately 6 (Section 4.1).
- Deleted information throughout the protocol regarding weight-based dosing Cohorts 6, 7, and 8, since these cohorts will not be examined as was planned in Protocol Amendment Version 6.0.
- (MAIN REASON FOR AMENDMENT) Added information throughout the protocol regarding new non-weight-based dosing Cohorts 6a (and 6b and 6c), 7a (and 7b and 7c), and 8a (and 8b and 8c), including a justification for non-weight-based dosing (new Section 1.4.4).
- Added details for Parts A and B throughout the protocol, where Part A comprises Cohorts 1 through 5 (weight-based dosing) and Part B comprises new Cohorts 6a (and 6b and 6c), 7a (and 7b and 7c), and 8a (and 8b and 8c) (non-weight-based dosing). This includes revisions to Sections 1.4.4, 1.5, 4.1, 5.1.1, 7.2, 7.6, 7.7, and 10.1.2.
- Added the definition of evaluable subjects (Section 4.1.1).
- Revised the secondary objective to define the recommended Phase 2 dose (RP2D) as 2 objectives in which an RP2D will be defined for each of Parts A and B (Section 2.2).
- Revised the following entry criteria (Section 3.3):
    - Inclusion of subjects who agree to undergo mandatory biopsies (pretreatment and posttreatment) was clarified by the addition of a separate criterion.

  - Exclusion of subjects with clinically significant hypercalcemia within 28 days prior to first dose of study therapy was deleted. Hypercalcemia has not been a safety concern.
  - Exclusion of subjects who received treatment with any monoclonal antibodies was revised from "within 6 weeks prior to first dose of study therapy" to "within 4 weeks prior to first dose of study therapy" for consistency with Exclusion Criterion [6].
  - Exclusion of subjects receiving radiotherapy was revised from "within 4 weeks prior to study entry" to "within 2 weeks prior to first dose of study entry." This revision will enhance accrual and 2 weeks is sufficient to recover from side effects of radiotherapy.
  - Exclusion of subjects who received treatment with agents specifically targeting CSF-1 or CSF-1R was deleted. This revision will enhance accrual and excluding these subjects is not necessary where safety is the primary objective.

- Revised number of subjects planned to be enrolled from 47 to 72 (Sections 4.1 and 12), based on the addition of new non-weight-based cohorts.
- Added language regarding examination of the maximum tolerated dose (MTD) for each regimen (weight-based and non-weight-based dosing), in place of RP2D (Section 4.1), to establish the safety profile of IMC-CS4.
- Clarified that the observation period for Cycle 1 is for Part A only, not for Part B.
- Revised RP2D determination (Section 4.1.2), so that once an RP2D is reached, options will be to expand at the RP2D OR to conclude (end) enrollment (whereas, prior to this amendment, the only option was to expand at the RP2D).
- Revised dose-limiting toxicity (DLT) definition for nonhematologic toxicity (Section 4.1.4), making exceptions for certain liver function test abnormalities, transient bilirubin elevations, and laboratory abnormalities in order to allow flexibility for continued dosing in the event of certain non-drug-related laboratory abnormalities. Additionally, language has been included to permit the treatment of immune-related adverse events (irAEs) with steroids for 7 days before an irAE is considered a DLT.
- Revised "extension period" to "continued access period" (Section 4.4), for consistency with the current template.
- Revised assessment of troponin T to also permit assessment of troponin I or whatever is the institutional standard (Sections 6.5, 6.8.4, 7.1, 7.2.1, 7.2.2.4, 7.3, 7.4, and 7.7), since not all institutions use the same assessment.
- Revised tissue sampling (Section 6.7), so that fine needle aspiration (FNA) and previously acquired tumor tissue are no longer permitted as assessments of pharmacodynamic effect. To improve the scientific validity of this study, only prospective core needle or excisional biopsy specimens will be permitted as assessments of pharmacodynamic effect moving forward, with skin punch biopsy as an acceptable posttreatment biopsy alternative for subjects unable to tolerate core needle or excisional biopsy.

- Revised language regarding retention of tissue samples (Sections 6.7 and 6.11.1), to align with the protocol template language.
- Revised language regarding validation of analytical methods (Section 6.8.1) to align with the current PK template language.
- Revised language so that triplicate electrocardiogram (ECG) will not be necessary for subjects in Part B (Section 6.9.1), based on data already collected.
- Added a section for suspected unexpected serious adverse reactions (new Section 8.3), to inform sites, some of which may be new, of recording and reporting of these events.
- Added a section for management of irAEs (Section 9.1.1), as additional guidance for the treatment of irAEs, particularly with immunomodulatory agents such as steroids.
- Updated American Society of Clinical Oncology (ASCO) guidelines for use of granulocyte colony-stimulating factors (Section 10.6.1).
- Clarified that premedication for IMC-CS4, such as antihistamines or steroids for the prophylaxis of hypersensitivity, is not recommended prior to the first infusion of IMC-CS4 (Section 10.6.5).
- Revised statistical language (Sections 12.1, 12.3, and 12.6), to include the standard statistical language for protocols.
- Added details regarding pharmacodynamic assessments (Section 12.7.2).
- Revised authorship criteria (Section 13.11) according to current International Committee of Medical Journal Editors (ICMJE) requirements.

The changes above were also made in the Synopsis, as needed.

In addition, minor revisions were made for clarity or consistency within the document or with Lilly style, or to correct grammar, redundancy, or typographical errors; these minor revisions do not affect the planned conduct of the study or the planned analyses of data.

Revised Protocol Sections

Note: All deletions have been identified by strikethroughs.

All additions have been identified by the use of underscore.

Clinical Trial Protocol

IMCL CP24-1001

I5F-IE-JSCA

Sponsor: ~~ImClone LLC, a wholly-owned subsidiary of~~ Eli Lilly and Company
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Protocol Amendment Version ~~6~~7.0: Electronically signed and approved by ~~ImClone LLC, a wholly-owned subsidiary of~~ Eli Lilly and Company~~,~~ on date provided below.

~~Confidentiality Statement~~

Confidential Information

SYNOPSIS

Sponsor:

~~ImClone LLC, a wholly-owned subsidiary of~~ Eli Lilly and Company

Secondary Objectives:

The secondary objectives of this study are:

- Part A only: To define the recommended Phase 2 dose (RP2D~~);~~) using weight-based dosing;
- Part B only: To define the RP2D using non-weight-based dosing;
- To characterize the pharmacodynamic profile of IMC-CS4 on circulating levels of CSF-1; and
- To assess the development of antibodies against IMC-CS4 (immunogenicity).

Study Design:

This open-label, dose-escalation, Phase 1 study will enroll (that is, assign to a dose cohort) approximately ~~47 subjects; the~~72 subjects to 2 parts – Parts A and B. Part A consisted of dose escalation of IMC-CS4 using weight-based dosing; Part B will consist of dose escalation of IMC-CS4 using non-weight-based dosing. The actual enrollment will depend on the number of dose-limiting toxicities (DLTs) observed and the resultant size of each cohort.

Dose cohorts, including dose and dosing schedule, are summarized in the table below. For each cohort, one cycle is 6 weeks. In each cohort, subjects will receive IMC-CS4 by intravenous (I.V.) infusion (with an observation period for weekly [qw] and every-2-week [q2w] cohorts in Cycle 1 only, as described in the following table).

Dose Cohort Assignment

Cohort	Dose Level ~~(mg/kg)~~	Dosing Schedule[a]	Cycle 1 Observation Period[b]	Number of Infusions
Part A (weight-based dosing)				
1	2.5 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
2	0.3 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
3	0.6 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
4	1.25 mg/kg	q2w	3 weeks (Weeks 4-6)	Cycle 1: 2 Subsequent cycles: 3
5	1.25 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
Part B (non-weight-based dosing)				
6a	100 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
~~6~~6b[c,d]	~~2.5~~100 mg	~~q2w~~qw on Weeks 1, 2, 4, and 5	~~3 weeks~~None (Weeks ~~4~~ 3 and 6 are rest)	Cycle 1: ~~2~~4 Subsequent cycles: ~~3~~4
6c[c]	75 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
7a	150 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
~~7~~7b[c,d]	~~2.5~~[e]150 mg	qw on Weeks 1, 2, 4, and 5	None (Weeks 3 and 6 are rest)	Cycle 1: 4 Subsequent cycles: ~~4~~[d]4
7c[c]	125 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6

8a	200 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
~~8~~[e] 8b[c,d]	~~3.75~~[e] 200 mg	qw on Weeks 1, 2, 4, and 5	None (Weeks 3 and 6 are rest)	Cycle 1: 4 Subsequent cycles: ~~4~~[d] 4
8c[c]	175 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6

Abbreviations: aEC = approving Ethics Committee~~; CRP = clinical research physician~~; DLT = dose-limiting toxicity; IRB = Institutional Review Board; PK = pharmacokinetic(s); qw = weekly; q2w = every 2 weeks.

a – At the highest dose level where major toxicity is observed and that requires a longer recovery period between infusions, a change in the periodicity of dosing (that is, other dosing schedules based on safety and PK considerations) will be agreed upon with the Investigator and communicated to IRBs/aECs.

b – Observation following the fourth infusion in Cohorts 1, 2, 3, and 5 (qw dosing) and the second infusion in ~~Cohorts~~ Cohort 4 ~~and 6~~ (q2w dosing) in Cycle 1 only. No Cycle 1 observation period for Cohorts 6a, 6c, 7a, 7c, 8a, or 8c. Weeks 3 and 6 of all cycles are rest weeks in Cohorts ~~7~~6b, 7b, and ~~8~~8b (qw dosing on Weeks 1, 2, 4, and 5).

~~c – In case of unacceptable toxicity in Cohorts 7 or 8 (qw dosing on Weeks 1, 2, 4, and 5), the following reduced doses will be explored, beginning no sooner than Cycle 2: Cohort 7 dose will be reduced to 2.5 mg/kg q2w; Cohort 8 dose will be reduced to 2.5 mg/kg qw on Weeks 1, 2, 4, and 5. In the event that 2 DLTs are observed in 6 subjects in Cohort 7, the next cohort will receive doses of 2.2 mg/kg qw on Weeks 1, 2, 4, and 5, which is an intermediate dose between that of Cohorts 6 and 7.~~

c – Concurrently enroll to Cohorts 6b/7b/8b and 6c/7c/8c, should ≥2 subjects in Cohort 6a/7a/8a experience DLT events.

d – For all cycles: Infusions on Weeks 1, 2, 4, and 5, and rest on Weeks 3 and 6.

~~e – The dose level for cohorts beyond Cohort 8 will be agreed among the investigators and the ImClone CRP at the safety review meeting following Cohort 8. Further dose escalations beyond Cohort 8 may occur by following the same dosing schedule (qw on Weeks 1, 2, 4, and 5) but increasing the dose level by 1.25 mg/kg until a DLT has occurred, unless otherwise agreed among the investigators and the ImClone CRP.~~

Following the first cycle of therapy (Cycle 1), subjects may continue to receive IMC-CS4 at the same dose and schedule until there is unequivocal evidence of disease progression or other withdrawal criteria are met. Radiographically confirmed disease progression (that is, numerical disease progression, per Response Evaluation Criteria in Solid Tumors [RECIST]) only is not sufficient to discontinue treatment (refer to "Duration of Treatment" section in this Synopsis for further details). Radiographic assessment of tumor response will be performed at the end of the initial cycle (that is, prior to administration of any study therapy in Cycle 2) and the end of every subsequent cycle; radiographic assessment should be performed prior to the start of a cycle so that results are available before the subject receives a new cycle of treatment. However, if a DLT is observed in Cycle 1~~, and~~ in a subject who is benefitting from treatment, Cycle 2 dosing ~~is~~ may be initiated within 4 weeks of Cycle 1, Day 1, with Sponsor approval; in this case, no radiographic disease assessment is required prior to dosing in Cycle 2.

Each cohort will initially enroll at least 3 subjects.

For all cohorts, all subjects who complete the first treatment cycle (that is, receive all scheduled treatments for Cycle 1 and complete the observation period, as needed) or discontinue therapy due to a DLT will be considered evaluable subjects and will be included in the DLT analyses. Subjects who do not complete Cycle 1 for reasons other than a DLT will be replaced for the analysis until the cohort includes 3 evaluable subjects (or 6 evaluable subjects in case of one DLT in the first 3 subjects); however, if benefitting from treatment (that is, no disease progression or other withdrawal criteria), any subject in Cohort 3 and beyond who experiences a DLT may continue to receive IMC-CS4 upon agreement of the Sponsor and according to the dose reduction guidelines for this study.

If the first 3 evaluable subjects in a cohort complete Cycle 1 of therapy with no DLT, dose escalation to the next cohort may proceed. If 1 of the first 3 evaluable subjects in a cohort experiences a DLT, enrollment will proceed until there are at least 6 evaluable subjects in that cohort. If no additional subject experiences a DLT, dose escalation may proceed. If 2 or more subjects experience a DLT in a cohort (whether in the initial 3-subject cohort or following expansion to 6 subjects), dose escalation will not occur and the recommended Phase 2 dose (RP2D) will be determined according to the instructions that

follow.

Each subsequent cohort will be opened upon completion of the previous cohort. A safety review meeting will be held prior to each dose escalation.

The provisional RP2D will be defined as the dose level at which pharmacodynamic effects are observed in the absence of clinically relevant toxic effects (that is, measurable pharmacodynamic effects with no DLT in the first 3 subjects or ≤1 DLT in the first 6 subjects enrolled at that dose level). ~~When~~After discussion with the ~~RP2D is identified, at least 6~~ Investigator, the Sponsor may choose to enroll additional subjects ~~will be enrolled to ensure a total of at least 9 evaluable (in terms of PK analysis) subjects treated~~ at the RP2D.

~~Consideration will be given to enrollment of up to 12 subjects into 1 or 2 additional cohorts~~ below ~~the RP2D rather than at the RP2D, if appropriate based on PK, pharmacodynamic, and/or safety findings from this study.~~

A DLT is defined as any IMC-CS4-related adverse event (AE) that occurs during Cycle 1~~, as follows~~ and does not improve to Grade ≤2 (unless stated otherwise), despite medical management , including steroids (if applicable) within 7 days of documented occurrence. The following are considered DLTs:

- Grade 4 neutropenia lasting ≥7 days;
- Grade 3 or 4 neutropenia complicated by fever ≥38.0°C or infection;
- Grade 4 thrombocytopenia;
- Grade 3 thrombocytopenia complicated by hemorrhage;
- Grade 3 or 4 anemia;
- ~~Grade ≥3~~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), aspartate aminotransferase (AST~~)~~), and alanine aminotransferase (ALT~~) elevation (exceptions may be made for transient [that is, lasting <7 days] Grade 3 elevations of AST/ALT~~), without evidence of hepatic injury
    - Transient Grade ≥2 bilirubin elevation in the presence of known liver metastases ~~and without evidence of other hepatic injury, if agreed by the Investigator and ImClone clinical research physician [CRP])~~;lasting ≤7 days
- ~~Grade ≥2 AST/ALT elevation and Grade ≥2 bilirubin elevation (exceptions may be made for transient [that is, lasting <7 days] elevations of ALT/AST and bilirubin in the presence of known liver metastases without evidence of other hepatic injury, if agreed by the Investigator and ImClone CRP); and/or~~
- ~~Grade 3 or 4 nonhematologic toxicity (excluding fatigue or anorexia lasting <7 days, or Grade 3 nausea and/or vomiting that persists for <2 days following appropriate supportive care).~~
    - Laboratory abnormalities that are reversible to Grade ≤2 or baseline levels within 7 days after initial documentation or that are deemed not clinically significant
    - Grade 3 elevation of CK **WITHOUT** elevation in serum and urine myoglobin is **NOT** considered a DLT.

Throughout this protocol, "days" refers to calendar days, unless otherwise indicated.

Study Population:

It is anticipated that approximately ~~47~~ 72 subjects will be enrolled in approximately ~~3~~ 6 study sites in the United States.

Inclusion/Exclusion Criteria:

Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study:

1. The subject has a histologic or cytologic confirmation of advanced solid tumors that are refractory to standard therapy or for which no standard therapy is available.
2. The subject has measurable or nonmeasurable disease according to the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1).
3. The subject has resolution to Grade ≤1 by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03, of all clinically significant toxic effects of prior chemotherapy, surgery, radiotherapy, or hormonal therapy (with the exception of alopecia).
4. The subject has an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-2.
5. The subject has adequate hematologic function, as defined by:
   Absolute neutrophil count (ANC) ≥1500/μL;
   Hemoglobin ≥9 g/dL (5.58 mmol/L); and
   Platelets ≥100,000/μL.
6. The subject has adequate hepatic function, as defined by:
   Bilirubin ≤1.5 times the upper limit of normal (× ULN); and
   AST and ALT ≤2.5 × ULN (or ≤5 × ULN in the presence of known liver metastases).
7. The subject has adequate renal function as defined by creatinine clearance ≥50 mL/min measured either by 24-hour urine collection or calculated using the Cockcroft-Gault formula.
8. The subject must have adequate coagulation function as defined by:
   International Normalized Ratio (INR) ≤1.5; and
   Prothrombin time (PT) and partial thromboplastin time (PTT) or activated PTT ≤1.5 × ULN.
9. The subject has CK ≤ ULN.
10. The subject has a life expectancy >3 months.
11. The subject is 18 years of age or older.
12. The subject (women of childbearing potential [WOCBP] or fertile men with partners of childbearing potential) agrees to use adequate contraception during the study period and for 12 weeks after the last dose of study therapy.
13. The subject has provided signed informed consent.
14. The subject is accessible for treatment and follow-up~~, including one pretreatment and one posttreatment tumor biopsy procedure~~; subjects enrolled in this trial must be treated at the study center.
15. The subject must undergo mandatory biopsies, including one pretreatment and one posttreatment tumor biopsy procedure.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. The subject has experienced acute pathologic fracture~~,~~ or spinal cord compression~~, or clinically significant hypercalcemia~~ within 28 days prior to first dose of study therapy.
2. The subject has a known hypersensitivity to monoclonal antibodies or to agents of similar biologic composition as IMC-CS4.

3. The subject has received treatment with any monoclonal antibodies within ~~6~~4 weeks prior to first dose of study therapy.
4. The subject has undergone a major surgical procedure~~, radiation therapy~~, open biopsy, radiofrequency ablation, or has experienced a significant traumatic injury within 28 days prior to enrollment.
5. The subject has a history of another primary cancer, with the exception of: a) curatively resected non-melanomatous skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid tumor treated with curative intent, no known active disease present, and no treatment administered during the last 3 years prior to study entry.
6. The subject is receiving concurrent treatment with other anticancer therapy, including other chemotherapy, immunotherapy, ~~radiotherapy, -~~chemoembolization, targeted therapy, or any investigational agent within 4 weeks prior to study entry~~.~~, or radiotherapy within 2 weeks prior to study entry. An exception is that subjects with metastatic breast or prostate cancer who have been on a stable dose (≥28 days) of an approved hormonal agent will not be excluded (ie, they will be eligible). Subjects with breast cancer may also continue with concurrent human epidermal growth factor receptor 2 (HER2)-directed therapy.
~~7. The subject has received treatment with agents specifically targeting the CSF-1 or CSF-1R including (but not limited to) imatinib, nilotinib, and sunitinib.~~
~~8.~~7. The subject has known muscle damage due to a primary, traumatic, or other muscle disease.
~~9.~~8. The subject is known to be human immunodeficiency virus (HIV) seropositive.
~~10.~~9. The subject has a known and uncontrolled infection ~~(presumed or documented) with progression after appropriate therapy for greater than one month~~.
~~11.~~10. The subject is known to have active tuberculosis, leishmaniasis, or listeriosis.
~~12.~~11. The subject has a history of and/or current: symptomatic coronary artery disease, confirmed left ventricular ejection fraction (LVEF) ≤50% or any cardiac insufficiency > New York Heart Association (NYHA) class II,* uncontrolled hypertension, or serious cardiac arrhythmia (well-controlled atrial fibrillation is permitted).
~~13.~~12. Subjects with known history or clinical or laboratory evidence of liver disease. Notably, subjects with any of the following liver function abnormalities will be excluded:

a Cirrhosis with evidence of portal hypertension or bridging fibrosis
b Alcoholic hepatitis
c Esophageal varices
d A history of bleeding esophageal varices
e Hepatic encephalopathy
f Ascites related to portal hypertension
g Chronic viral hepatitis with total serum bilirubin >3 mg/dL

~~14.~~13. The subject has active bleeding.
~~15.~~14. The subject has leukemia or lymphoma.
~~16.~~15. The subject has a known psychiatric illness/social situation (including alcohol and/or drug dependency) that would, in the Investigator's opinion, limit compliance with study requirements.
~~17.~~16. The subject has known or suspected primary brain or leptomeningeal tumors or metastases (subjects with a history of brain metastases must have received definitive surgery or radiotherapy, be clinically stable, and may not be taking steroids; subjects receiving anticonvulsants are eligible).
~~18.~~17. The subject is pregnant (confirmed by serum beta human chorionic gonadotropin [β-hCG] test performed within 7 days prior to first dose of study therapy) or breastfeeding.
~~19.~~18. The subject has received a solid organ transplant.
~~20.~~19. The subject has any other serious uncontrolled medical disorders, which, in the opinion of the Investigator, would compromise the subject's safety or the ability of the subject to participate in the study.

*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.

Efficacy Assessments:

Radiographic assessment of disease response and tumor assessments, according to RECIST 1.1, will be performed at baseline and at the end of every cycle. Radiographic assessment should be performed prior to the start of a cycle so that results are available before the subject receives a new cycle of treatment. However, if a ~~subject experiences a~~ DLT is observed in Cycle 1~~, and the subject's~~ in a subject who is benefitting from treatment, Cycle 2 dosing ~~is~~may be initiated within 4 weeks of Cycle 1, Day 1, with Sponsor approval; in this case, no radiographic disease assessment is required prior to dosing in Cycle 2.

Tissue Assessments:

To assess the pharmacodynamic effect of IMC-CS4 administration on tumor-associated myeloid cells, including macrophages, all subjects enrolled in Cohort 2 and beyond will undergo tumor biopsies before study enrollment~~ (unless medically contraindicated and if acceptable archived tumor material is available). The~~. For these cohorts, investigators will carry out a tumor (core needle or excisional) biopsy (attempt to obtain at least 3 cores) before starting the treatment and at the end of Cycle 1 (to be done in the week prior to Cycle 2, at the same time as tumor evaluation), if the subject's condition allows it. If~~ the subject's condition allows it~~ an enrolled subject undergoes a pretreatment tumor biopsy but is unable to tolerate a posttreatment tumor biopsy, then a skin punch biopsy will be acceptable. At the time of disease progression, the Investigator will also perform a tumor biopsy if ~~disease progression is diagnosed. If a tumor core biopsy is not possible, the Investigator may consult~~the subject consents to it and if the ~~ImClone CRP to evaluate the possibility of performing a tumor fine needle aspiration (FNA).~~subject's condition allows it.

Statistical Methods:

~~Overall response rate (number of subjects who achieve a best response of complete response [CR] or partial response [PR] during therapy, divided by the total number of subjects treated) and disease control rate (number of subjects who achieve a best response of CR or PR or stable disease [SD] during therapy, divided by the total number of subjects treated) will be presented for each cohort of subjects.~~Tumor response data will be summarized, if appropriate.

Version History:

Version 6.0: 31 March 2014

LIST OF ABBREVIATIONS AND DEFINITIONS

~~CRP~~CRS	clinical research ~~physician~~scientist
GGT	gamma glutamyl transferase
HER2	human epidermal growth factor receptor 2
irAE	immune-related adverse event
LFT	liver function test
MTD	maximum tolerated dose
~~q4w~~	~~every 4 weeks~~
SUSAR	suspected unexpected serious adverse reaction

1.4.1 Rationale for Starting Dose

The optimal dose and regimen of IMC-CS4 in humans are not known. The proposed starting dose and regimen of IMC-CS4 ~~is~~was 2.5 mg/kg administered qw by I.V. infusion. This starting dose ~~is~~was based on the following rationale:

1.4.2 Clinical Experience from Cohort 1

IMC-CS4 was administered to 6 subjects at the starting dose of 2.5 mg/kg qw. Two of the first 3 subjects experienced Grade 2 creatine kinase (CK) serum level elevations, associated ~~to~~ with elevated levels of AST (Grade 1-2), LDH, and CSF-1. A muscle biopsy was performed, independently of the protocol, in one of the subjects with elevated CK values and did not reveal any signs of rhabdomyolysis, nor of muscle damage of inflammatory or non-inflammatory origin. However, because of the serum enzyme elevation and subjects' general conditions, Cycle 1 was not completed as per protocol in 2 of the 3 subjects.

1.4.3 Clinical Experience from ~~Cohort~~Cohorts 2 ~~and Beyond~~through 5

This section describes the clinical experience after the revised dose-escalation scheme was implemented in Protocol Amendment Version 3.0, specifically, the clinical observations for Cohorts 2, 3, 4, and ~~4. (Note that Cohort 4 is still ongoing.) To date, no~~5. No DLTs were observed in Cohorts 2 and 3. The clinical data generated for subjects treated in Cohorts 2 and 3 indicate that IMC-CS4 is safe and well tolerated when administered as 4 qw doses (0.3 or 0.6 mg/kg) followed by 2 weeks of recovery.

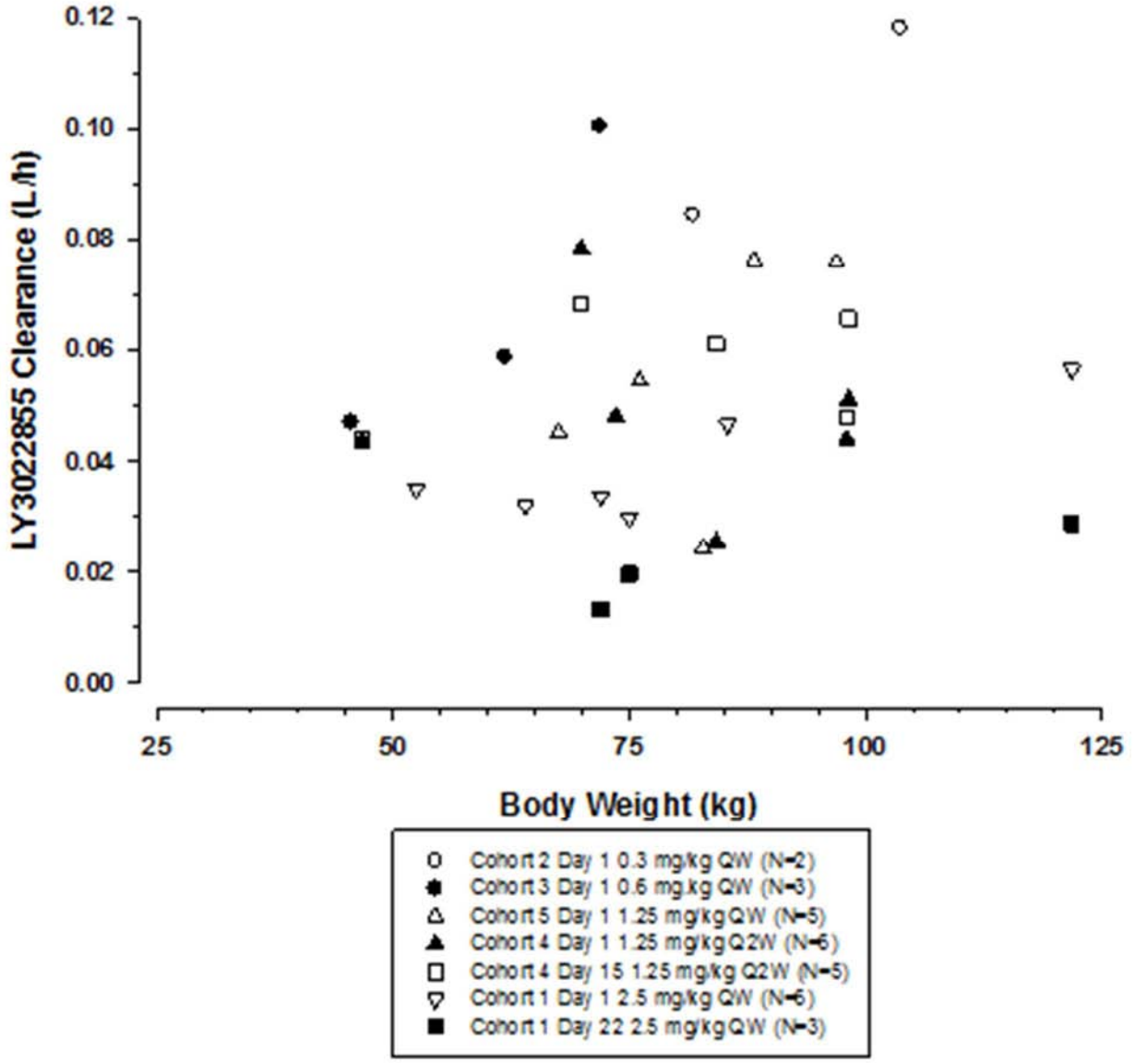
In Cohort 4~~,~~ (1.25 mg/kg q2w), one subject with a history of cardiac dysfunction developed a Grade 3 left ventricular systolic dysfunction (verbatim) after one dose of IMC-CS4; the event was considered by the Investigator to be related to IMC-CS4. Because DLT could not be ruled out for this event, 2 additional subjects ~~are to be enrolled into Cohort 4. Following completion of Cycle 1 by these 2 additional subjects, a safety review is to be conducted to determine whether IMC-CS4 is safe and well tolerated when administered as 2 biweekly doses (1.25 mg/kg) followed by 3 weeks of recovery.~~were enrolled into Cohort 4 and completed protocol-defined therapy without experiencing DLT events.

In Cohort 5 (1.25 mg/kg qw), 2 subjects experienced DLT events: 1 subject was diagnosed with rhabdomyolysis complicated by acute renal failure following 1 dose of IMC-CS4, and the second

subject was diagnosed with pancreatitis after receiving 3 doses of IMC-CS4. The subject diagnosed with pancreatitis slowly developed symptoms in conjunction with rising amylase and lipase levels during the course of treatment; these signs and symptoms, which were consistent with pancreatitis, resolved upon discontinuation of IMC-CS4 and initiation of systemic steroids. As a result of these 2 DLT events, the RP2D was determined to be 1.25 mg/kg every 2 weeks.

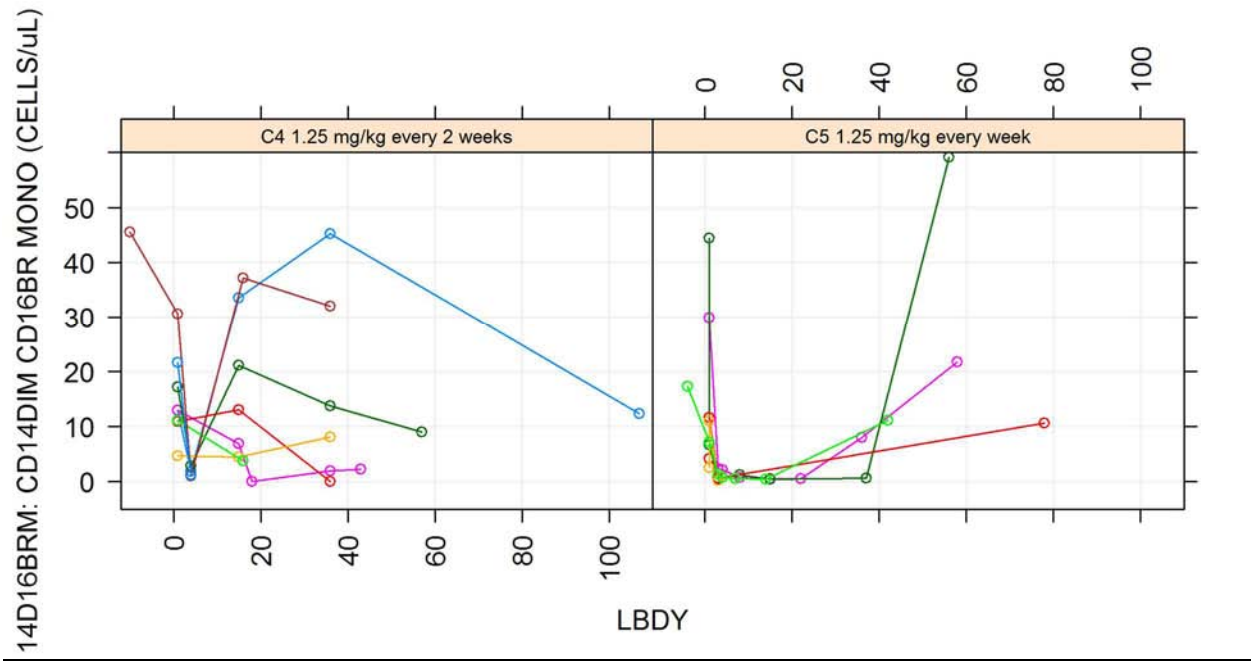
1.4.4 Exploring Non-Weight-Based Dosing (Cohorts 6a through 8c)

Exploratory graphical analysis of the pharmacokinetics of IMC-CS4 in Cohorts 1 to 5 indicates no clear relationship between body weight and drug clearance (Figure 1). Furthermore, weekly dosing results in sustained elevation of CSF-1, an indicator of target engagement, for the duration of the dosing period (Figure 2). In contrast, dosing every 2 weeks allows CSF-1 levels to return to baseline, indicating reduced target engagement with a more intermittent dosing schedule. Therefore, additional cohorts are being added in this protocol amendment, Version 7.0, to evaluate safety, pharmacokinetics, and pharmacodynamics of non-weight-based dosing of IMC-CS4 administered on a weekly schedule. As was done for weight-based dosing cohorts, doses for non-weight-based dosing cohorts will be escalated to identify RP2D. To accommodate these new non-weight-based dosing cohorts, the definition of DLT has been revised and an algorithm added to initiate steroid therapy early during the course of an immune-related adverse event (irAE) (refer to Section 9.1.1 for additional details).



Abbreviations: QW = weekly; Q2W = every 2 weeks.

Figure 1. Reported body weight versus LY3022855 drug clearance (as determined using non-compartmental analysis) for eligible subject data from Study JSCA (IMCL CP24-1001.)



Profile plot of CD14DIM CD16BR MONO (CELLS/uL)
Program Location: F:/lillyce/prd/ly3022855/i5f_ie_jsca/misc1/programs_nonsdd/CS4_jsca_CD14dimCD16br_C4-C5.r
Data Location: F:/lillyce/prd/ly3022855/i5f_ie_jsca/misc1/data/shared/custom/dm.csv
Data Location: F:/lillyce/prd/ly3022855/i5f_ie_jsca/misc1/data/shared/custom/lb.csv
Output Location: F:/lillyce/prd/ly3022855/i5f_ie_jsca/misc1/programs_nonsdd/tfl_output/CS4_JSCA_CD14dimCD16br_C4-C5.rtf

Figure 2. Profile review of $CD14^{DIM}$ $CD16^{BR}$ MONO (cells/µL).

~~Additional cohorts are being added in this protocol amendment, Version 6.0, to permit further dose escalation beyond the previously planned cohorts. Newly added Cohorts 7 and 8 will provide for the following doses: 2.5 mg/kg in Cohort 7 and 3.75 mg/kg in Cohort 8. In these new cohorts, study drug will be administered qw on Weeks 1, 2, 4, and 5 of every 6-week cycle, with Weeks 3 and 6 as rest weeks. This dosing regimen was selected to correspond to other standard-of-care anticancer regimens. Further dose escalations beyond Cohort 8 may occur by following the same dosing schedule (qw on Weeks 1, 2, 4, and 5) but increasing the dose level by 1.25 mg/kg until a DLT has occurred (that is, dose escalation will occur only if the criteria described in Section are met), unless otherwise agreed among the investigators and the ImClone clinical research physician (CRP).~~

1.5 Human Experience

NOTE:

Protocol Amendment Version 7.0 describes additional cohorts for non-weight-based dosing of IMC-CS4, which will be referred to as Part B of the study. Cohorts described in the protocol prior to Protocol Amendment Version 7.0 (that is, for weight-based dosing of IMC-CS4) will now be referred to as Part A of the study. Refer to Section 4.1 for details of the dose assignments for Parts A and B.

Throughout the protocol, information relevant only to Part A (weight-based dosing) or only to Part B (non-weight-based dosing) is indicated as such. Any information not indicated as "Part A only" or "Part B only" is relevant to both parts.

2.2 Secondary Objectives

The secondary objectives of this study are:

- Part A only – To define the recommended Phase 2 dose (RP2D) using weight-based dosing;
- Part B only – To define the RP2D using non-weight-based dosing;
- To characterize the pharmacodynamic profile of IMC-CS4 on circulating levels of CSF-1; and
- To assess the development of antibodies against IMC-CS4 (immunogenicity).

3.1 Study Population

Subjects will be recruited from a population of cancer subjects treated at the investigational centers. A record of the most recent pretreatment evaluations will be reviewed to determine the eligibility of a subject for this study. ~~It is anticipated that approximately 47 subjects will be enrolled (that is, assigned to a dose cohort) in approximately 3 study sites in the United States.~~

3.2 Inclusion Criteria

14. The subject is accessible for treatment and follow-up; subjects enrolled in this trial must be treated at the study center.
15. The subject must undergo mandatory biopsies, including one pretreatment and one posttreatment tumor biopsy procedure (refer to tumor biopsy Section 7.2.1.1~~); subjects enrolled in this trial must be treated at the study center.~~).

3.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. The subject has experienced acute pathologic fracture~~,~~ or spinal cord compression~~, or clinically significant hypercalcemia~~ within 28 days prior to first dose of study therapy.
2. The subject has a known hypersensitivity to monoclonal antibodies or to agents of similar biologic composition as IMC-CS4.
3. The subject has received treatment with any monoclonal antibodies within ~~6~~4 weeks prior to first dose of study therapy.
4. The subject has undergone a major surgical procedure~~, radiation therapy~~, open biopsy, radiofrequency ablation, or has experienced a significant traumatic injury within 28 days prior to enrollment.
5. The subject has a history of another primary cancer, with the exception of a) curatively resected non-melanomatous skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid tumor treated with curative intent, no known active disease present, and no treatment administered during the last 3 years prior to study entry.
6. The subject is receiving concurrent treatment with other anticancer therapy, including other chemotherapy, immunotherapy, ~~radiotherapy, c~~hemoembolization, targeted therapy, or any investigational agent within 4 weeks prior to study entry, or radiotherapy within 2 weeks prior to study entry. An exception is that subjects with metastatic breast or prostate cancer who have been on a stable dose (≥28 days) of an approved hormonal agent will not be excluded (ie, they will be eligible). Subjects with breast cancer may also continue with concurrent human epidermal growth factor receptor 2 (HER2)-directed therapy.
~~7. The subject has received treatment with agents specifically targeting the CSF-1 or CSF-1R including (but not limited to) imatinib, nilotinib, and sunitinib.~~
~~8.~~7. The subject has known muscle damage due to a primary, traumatic, or other muscle disease.
~~9.~~8. The subject is known to be human immunodeficiency virus (HIV) seropositive.
~~10.~~9. The subject has a known and uncontrolled infection~~ (presumed or documented) with progression after appropriate therapy for greater than one month~~.
~~11.~~10. The subject is known to have active tuberculosis, leishmaniasis, or listeriosis.
~~12.~~11. The subject has a history of and/or current: symptomatic coronary artery disease, confirmed left ventricular ejection fraction (LVEF) ≤50% or any cardiac insufficiency > New York Heart Association (NYHA) class II,* uncontrolled hypertension, or serious cardiac arrhythmia (well-controlled atrial fibrillation is permitted).
~~13.~~12. Subjects with known history, or clinical or laboratory evidence of, liver disease. Notably, subjects with any of the following liver function abnormalities will be excluded:
   a Cirrhosis with evidence of portal hypertension or bridging fibrosis
   b Alcoholic hepatitis
   c Esophageal varices
   d A history of bleeding esophageal varices
   e Hepatic encephalopathy
   f Ascites related to portal hypertension
   g Chronic viral hepatitis with total serum bilirubin >3 mg/dL.
~~14.~~13. The subject has active bleeding.
~~15.~~14. The subject has leukemia or lymphoma.
~~16.~~15. The subject has a known psychiatric illness/social situation (including alcohol and/or drug dependency) that, in the Investigator's opinion, would limit compliance with study requirements.

~~17.~~16. The subject has known or suspected primary brain or leptomeningeal tumors or metastases (subjects with a history of brain metastases must have received definitive surgery or radiotherapy, be clinically stable, and may not be taking steroids; subjects receiving anticonvulsants are eligible).
~~18.~~17. The subject is pregnant (confirmed by serum beta human chorionic gonadotropin [β-hCG] test performed within 7 days prior to first dose of study therapy) or breastfeeding.
~~19.~~18. The subject has received a solid organ transplant.
~~20.~~19. The subject has any other serious uncontrolled medical disorders that, in the opinion of the Investigator, would compromise the subject's safety or the ability of the subject to participate in the study.

3.4 Subject Enrollment

Individuals who do not meet the criteria for participation in this study (screen failure) within 14 days after study entry may be rescreened once. Sites are responsible for determining if the subject must sign a new ICF, based on regulatory and institutional or central IRB/aEC guidelines. ~~The subject should meet all eligibility criteria before~~All subjects who have signed an informed consent form will be assigned a study identification (ID) number ~~is assigned~~.

4.1 Overall Study Design and Plan

This open-label, dose-escalation, Phase 1 study will enroll ~~approximately 47 subjects~~ a total of approximately 72 subjects to 2 parts - Parts A and B, in approximately 6 study sites in the United States. Part A consists of dose escalation of IMC-CS4 using weight-based dosing (Part A enrollment is planned to be discontinued as of 30 September 2015); Part B will consist of dose escalation of IMC-CS4 using non-weight-based dosing; the actual enrollment will depend on the number of DLTs observed and the resultant size of each cohort.

~~In addition, the cohort identified as the RP2D~~ Throughout this protocol, any information not indicated as "Part A only" or "Part B only" is relevant to both parts. In Part A, additional subjects were enrolled to the maximum tolerated dose (MTD) of 1.25 mg/kg q2w, in order to help establish the safety profile of IMC-CS4. In Part B, the cohort associated with the dose identified as the MTD may be expanded (up to a maximum of 12 evaluable subjects) in order to help establish the safety profile of IMC-CS4 ~~at an expected biologically effective dose. Alternately, consideration will be given to enrollment of up to 12 subjects into 1 or 2 additional cohorts~~ below ~~the RP2D rather than at the RP2D, if appropriate based on PK, pharmacodynamic, and/or safety findings from this study.~~ . Enrollment to the MTD expansion cohort may cease if

the Sponsor (after conferring with the investigators) deems the toxicity profile precludes further enrollment. Refer also to Section 4.1.2.

Dose cohorts, including dose and dosing schedule, are summarized in Table 1. For each cohort, one cycle is 6 weeks. In each cohort, subjects will receive IMC-CS4 by I.V. infusion (with an observation period, in Part A only, for weekly ([qw)] and every-2-week ([q2w)] cohorts, in Cycle 1 only, as described in Table 1). Beginning with Protocol Amendment Version 7.0, enrollment to Part B of the study will start with Cohort 6a, then escalate to Cohorts 7a and 8a. In the event 2 or more subjects on Cohort 6a experience a DLT event, concurrent enrollment of 3 to 6 subjects to each of Cohorts 6b and 6c will start and further dose escalation (that is, to Cohort 7a) will cease. Likewise, the same algorithm will apply for Cohorts 7a and 8a if enrollment to those cohorts occurs. Subjects will be assigned to "b" and "c" cohorts by the Sponsor. Note that there will be no Cycle 1 observation period for Part B cohorts. No intra-subject dose-escalation is permitted for any subject. Dose escalation may be reduced or ceased at any time based on safety and PK behavior.

Table 1. Dose Cohort Assignment

Cohort	Dose Level ~~(mg/kg)~~	Dosing Schedule[a]	Cycle 1 Observation Period[b]	Number of Infusions
Part A (weight-based dosing)				
1	2.5 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
2	0.3 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
3	0.6 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
4	1.25 mg/kg	q2w	3 weeks (Weeks 4-6)	Cycle 1: 2 Subsequent cycles: 3
5	1.25 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
Part B (non-weight-based dosing)				
6a	100 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
~~6~~6b[c,d]	~~2.5~~100 mg	~~q2w~~qw on Weeks 1, 2, 4, and 5	~~3 weeks~~None (Weeks ~~4~~ 3 and 6 are rest)	Cycle 1: ~~2~~4 Subsequent cycles: ~~3~~4
6c[c]	75 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
7a	150 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
~~7~~7b[c,d]	~~2.5~~[e]150 mg	qw on Weeks 1, 2, 4, and 5	None (Weeks 3 and 6 are rest)	Cycle 1: 4 Subsequent cycles: ~~4~~[d]4
7c[c]	125 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
8a	200 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
~~8~~[e]8b[c,d]	~~3.75~~[e]200 mg	qw on Weeks 1, 2, 4, and 5	None (Weeks 3 and 6 are rest)	Cycle 1: 4 Subsequent cycles: ~~4~~[d]4
8c[c]	175 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6

Abbreviations: aEC = approving Ethics Committee~~; CRP = clinical research physician~~; DLT = dose-limiting toxicity; IRB = Institutional Review Board; PK = pharmacokinetic(s); qw = weekly; q2w = every 2 weeks.

a – At the highest dose level where major toxicity is observed and that requires a longer recovery period between infusions, a change in the periodicity of dosing (that is, other dosing schedules based on safety and PK considerations) will be agreed upon with the Investigator and communicated to IRBs/aECs.

b – Observation following the fourth infusion in Cohorts 1, 2, 3, and 5 (qw dosing) and the second infusion in ~~Cohorts~~Cohort 4 ~~and 6~~ (q2w dosing) in Cycle 1 only. No Cycle 1 observation period for Cohorts 6a, 6c, 7a, 7c, 8a, or 8c. Weeks 3 and 6 of all cycles are rest weeks in Cohorts ~~7~~6b, 7b, and ~~8~~8b (qw dosing on Weeks 1, 2, 4, and 5).

~~c – In case of unacceptable toxicity in Cohorts 7 or 8 (qw dosing on Weeks 1, 2, 4, and 5), the following reduced doses will be explored, beginning no sooner than Cycle 2: Cohort 7 dose will be reduced to 2.5 mg/kg q2w; Cohort 8 dose will be reduced to 2.5 mg/kg qw on Weeks 1, 2, 4, and 5. In the event that 2 DLTs are observed in 6 subjects in Cohort 7, the next cohort will receive doses of 2.2 mg/kg qw on Weeks 1, 2, 4, and 5, which is an intermediate dose between that of Cohorts 6 and 7.~~

c – Concurrently enroll to Cohorts 6b/7b/8b and 6c/7c/8c, should ≥2 subjects in Cohort 6a/7a/8a experience DLT events.

d – For all cycles: Infusions on Weeks 1, 2, 4, and 5, and rest on Weeks 3 and 6.

~~e – The dose level for cohorts beyond Cohort 8 will be agreed among the investigators and the ImClone CRP at the safety review meeting following Cohort 8. Further dose escalations beyond Cohort 8 may occur by following the same dosing schedule (qw on Weeks 1, 2, 4, and 5) but increasing the dose level by 1.25 mg/kg until a DLT has occurred, unless otherwise agreed among the~~

~~investigators and the ImClone CRP.~~

It is recognized that in the course of clinical cancer care, it is not always possible to schedule therapeutic infusions at precise intervals (because of holidays, travel difficulties, or other circumstances). Accordingly, infusions administered within 2 days (~~qw~~all cohorts other than q2w dosing) or 3 days (q2w dosing) before or after the planned infusion time point will be considered acceptable. Deviations beyond this window are not permitted in Cycle 1 and will be allowed thereafter only if medically indicated or if the subject cannot be treated on the scheduled day.

Following the first cycle of therapy (Cycle 1), subjects should continue to receive IMC-CS4 at the same dose and schedule until there is unequivocal evidence of disease progression (per immune-related response criteria [Wolchok et al. 2009]) or other withdrawal criteria are met. Radiographically confirmed disease progression (that is, numerical disease progression, per RECIST) only is not sufficient to discontinue treatment.* Radiographic assessment of tumor response will be performed at the end of the initial 6-week cycle and at the end of every subsequent cycle; radiographic assessment should be performed prior to the start of a cycle so that results are available before the subject receives a new cycle of treatment. However, if a DLT is observed in Cycle 1~~, and~~ in a subject who is benefitting from treatment, Cycle 2 dosing ~~is~~may be initiated within 4 weeks of Cycle 1, Day 1, with Sponsor approval; in this case, no radiographic disease assessment is required prior to dosing in Cycle 2.

*Note: Subjects with disease progression (per RECIST) but without clinical deterioration at Week 6 (the first response assessment) may continue to receive IMC-CS4, at the discretion of the Investigator; study treatment will be discontinued if, at the next disease assessment (performed at least 4 weeks later), disease progression is unequivocal (that is, radiographically confirmed disease progression alone is sufficient). On the other hand, subjects with disease progression (per RECIST) and with clinical deterioration (unequivocal) at Week 6 (the first response assessment) will be discontinued from study treatment.

The treatment schedule, radiographic tumor assessment schedule, and observation period for each dosing schedule are summarized in Table 2, Table 3, Table 4, and Table 5.

Table 2. Treatment Schedule (Part A - Weekly Dosing – Cohorts 1, 2, 3, and 5)

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
	Cycle 1						Cycle 2						Cycle 3						Cycle 4					
Tx[a]	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
O.P.[b]					X	X																		
Tumor eval[c]	X[d]					X						X						X						X

Abbreviations: eval = evaluation; O.P. = observation period; Tx = treatment.

a – Administer IMC-CS4; b – Observation period; c – Radiographic assessment of tumor status; d – Baseline assessment, within 28 days prior to the first dose of study therapy; subsequent assessment should be performed in the week prior to the onset of the new cycle.

Table 3. Treatment Schedule (Part A - Every-2-Week Dosing – ~~Cohorts~~Cohort 4 ~~and 6~~)

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
	Cycle 1						Cycle 2						Cycle 3						Cycle 4					
Tx[a]	X		X				X		X		X		X		X		X		X		X		X	
O.P.[b]				X	X	X																		
Tumor eval[c]	X[d]					X						X						X						X

Abbreviations: eval = evaluation; O.P. = observation period; Tx = treatment.

a – Administer IMC-CS4; b – Observation period; c – Radiographic assessment of tumor status; d – Baseline assessment, within 28 days prior to the first dose of study therapy; subsequent assessment should be performed in the week prior to the onset of the new cycle.

Table 4. Treatment Schedule (Part B - Weekly Dosing ~~on Weeks 1, 2, 4, and 5 –~~ Cohorts ~~7~~6a, 6c, 7a, 7c, 8a, and ~~8~~8c)

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
	Cycle 1						Cycle 2						Cycle 3						Cycle 4					
Tx[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
O.P.[b]																								
Tumor eval[c]	X[d]					X						X						X						X

Abbreviations: eval = evaluation; O.P. = observation period; Tx = treatment.

a – Administer IMC-CS4; b – Observation period; c – Radiographic assessment of tumor status; d – Baseline assessment, within 28 days prior to the first dose of study therapy; subsequent assessment should be performed in the week prior to the onset of the new cycle.

Table 5. Treatment Schedule (Part B - Weekly Dosing on Weeks 1, 2, 4, and 5 – Cohorts 6b, 7b, and 8b)

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
	Cycle 1						Cycle 2						Cycle 3						Cycle 4					
Tx[a]	X	X		X	X		X	X		X	X		X	X		X	X		X	X		X	X	
O.P.[b]																								
Tumor eval[c]	X[d]					X						X						X						X

Abbreviations: eval = evaluation; O.P. = observation period; Tx = treatment.

a – Administer IMC-CS4; b – Observation period; c – Radiographic assessment of tumor status; d – Baseline assessment, within 28 days prior to the first dose of study therapy; subsequent assessment to be performed in the week prior to the onset of the new cycle.

4.1.1 Cohort Enrollment and Dose Escalation

For all cohorts, all subjects who complete the first treatment cycle (that is, receive all scheduled treatments for Cycle 1 and complete the observation period, as needed) or discontinue therapy due to a DLT will be considered evaluable subjects and will be included in the DLT analyses. Subjects who do not complete Cycle 1 for reasons other than a DLT will be replaced for the analysis until the cohort includes 3 evaluable subjects (or 6 evaluable subjects in case of one DLT in the first 3 subjects); however, if benefitting from treatment (that is, no disease progression or other withdrawal criteria), any subject in Cohort 3 and beyond who experiences a DLT may continue to receive IMC-CS4 upon agreement of the Sponsor and according to the dose reduction guidelines for this study. Refer to Section 10.1 for details of general dose modifications for IMC-CS4.

In all cases, dose escalation will occur only if the criteria described in this section (Section 4.1.1) are met. Each subsequent cohort will be opened upon completion of the previous cohort. A safety review meeting will be held prior to each dose escalation.

4.1.2 Determination of the Recommended Dose for Phase 2

The provisional RP2D will be defined as the dose level at which pharmacodynamic effects are observed in the absence of clinically relevant toxic effects (that is, measurable pharmacodynamic effects with no DLT in the first 3 subjects or ≤1 DLT in the first 6 subjects enrolled at that dose level). ~~When the RP2D is identified, at least 6 additional subjects will be enrolled to ensure a total of at least 9 evaluable (in terms of PK analysis) subjects treated at the RP2D to further characterize the toxicity, PK, and/or pharmacodynamics of IMC-CS4. Consideration will be given to enrollment of up to 12 subjects into 1 or 2 additional cohorts below the RP2D rather~~

~~than at the RP2D, if appropriate based on PK, pharmacodynamic, and/or safety findings from this study~~After discussion with the Investigator, the Sponsor may choose to enroll additional subjects at or below the RP2D.

4.1.4 Dose-Limiting Toxicity Definition

A DLT is defined as any IMC-CS4-related AE that occurs during Cycle 1~~, as follows~~ and does not improve to Grade ≤2 (unless stated otherwise), despite medical management, including steroids (if applicable) within 7 days of documented occurrence. The following are considered DLTs:

- Grade 4 neutropenia lasting ≥7 days;
- Grade 3 or 4 neutropenia complicated by fever ≥38.0°C or infection;
- Grade 4 thrombocytopenia;
- Grade 3 thrombocytopenia complicated by hemorrhage;
- Grade 3 or 4 anemia;
- Grade ≥3 ~~AST/ALT elevation (exceptions may~~or 4 nonhematologic toxicity. Exceptions maybe be made for ~~transient [that is, lasting <7 days]~~ the following, if agreed upon by the Sponsor AND the Investigator:
    - Grade ~~3 elevations of AST/ALT~~ ≥3 liver function test (LFT) abnormality, such as alkaline phosphatase, gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), and alanine aminotransferase ALT, without evidence of hepatic injury
    - Transient Grade ≥2 bilirubin elevation in the presence of known liver metastases ~~and without evidence of other hepatic injury, if agreed by the Investigator and ImClone CRP);~~lasting ≤7 days
- ~~Grade ≥2 AST/ALT elevation and Grade ≥2 bilirubin elevation (exceptions may be made for transient [that is, lasting < 7 days] elevations of AST/ALT and bilirubin in the presence of known liver metastases without evidence of other hepatic injury, if agreed by the Investigator and ImClone CRP); and/or~~
- ~~Grade 3 or 4 nonhematologic toxicity (excluding fatigue or anorexia lasting <7 days, or Grade 3 nausea and/or vomiting that persists for <2 days following appropriate supportive care).~~
    - Laboratory abnormalities that are reversible to Grade ≤2 or baseline levels within 7 days after initial documentation or that are deemed not clinically significant
    - Grade 3 elevation of CK WITHOUT elevation in serum and urine myoglobin is NOT considered a DLT.

4.4 ~~Extension~~ Continued Access Period

All subjects remaining on study treatment without disease progression or unacceptable toxicity following the final analysis for RP2D will be able to enter the ~~extension~~ continued access period

of the study. The ~~extension~~ continued access period begins after study completion and ends at the end of trial. During the ~~extension~~ continued access period, subjects 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 ~~extension~~ continued access period includes a Follow-up visit. The Follow-up visit begins 1 day after the subject and the Investigator agree that the subject will no longer continue treatment in the ~~extension~~ continued access period and lasts approximately 30 days. If it is deemed to be in the best interest of the subject 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.

Subjects must sign a new ICF before entering the ~~extension~~ continued access period. The Sponsor will notify investigators when the ~~extension~~ continued access period begins.

During the ~~extension~~ continued access period, all AEs, SAEs, study drug dosing, and dose reduction of treatment will be collected on the eCRF.

5.1.1.1 Part A Only

The dose of IMC-CS4 is based on the subject's body weight in kilograms. Subjects recruited in Cohort 1 have received IMC-CS4 infusions over a period of 90 minutes. Because of a change in the dosing scheme in Protocol Amendment 3.0, subjects in Cohorts 2 through ~~6 will receive~~5 received IMC-CS4 I.V. via infusion over a period of 30 minutes. ~~Subjects in Cohorts 7 and 8 will receive IMC-CS4 I.V. via infusion over a period of 90 minutes.~~ Subjects in the RP2D expansion cohort will receive IMC-CS4 I.V. via infusion over a period of 90 minutes for the first infusion, 60 minutes for the second infusion, and 30 minutes for the remaining infusions. The infusion rate should not exceed 25 mg/minute.

The first dose of IMC-CS4 is dependent upon the subject's baseline body weight in kilograms. Subsequent doses of IMC-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 subjects 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 ~~ImClone~~Sponsor CRP or designee should be consulted regarding optimal assessment of dry weight).

5.1.1.2 Part B Only

The dose of IMC-CS4 is non-weight based. Subjects will receive IMC-CS4 I.V. via infusion over a period of 30 minutes. The infusion rate should not exceed 25 mg/minute.

5.1.1.3 Both Parts A and B

~~5.1.1.1 Monitoring~~

6.2 Medical History

Concomitant medication assessment – To be performed and documented as outlined in Section 7 (Study Activities).

6.3 Physical Examination

Complete physical examination – Evaluation by body system and height (at pretreatment only).

Weight measurement ~~– Performed qw.~~

ECOG performance status– According to the ECOG PS criteria.

~~Concomitant medication assessment – To be performed and documented qw.~~

6.5 Clinical Laboratory Tests

Serum chemistry profile – Includes sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, glucose, total protein, albumin, AST, ALT, AP, total bilirubin, LDH, CK, lipase, amylase, calcium, magnesium, and phosphorus~~, and troponin T~~. Serum myoglobin levels will be analyzed in case of CK elevation (for CK increases $\geq 2.5 \times$ ULN).

Troponin (I or T or institutional standard) - Results are not needed prior to dosing, except for the Cycle 1, Day 1 dose.

Hepatic monitoring – The following selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with subjects in consultation with the ~~ImClone~~Sponsor CRP:

6.6 Efficacy Assessments

- Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the chest, abdomen, pelvis, and (if applicable) brain. CT or MRI of the neck should be performed, if clinically indicated. It is recommended that CT imaging of the abdomen/pelvis be performed with I.V. contrast, whenever possible. For subjects with known serious allergic reactions to CT contrast material, a CT of the chest without contrast and contrast-enhanced MRI of the abdomen/pelvis or a CT of the abdomen/pelvis with oral contrast should be performed, at the discretion of the Investigator.
- Chest x-rays are not permitted for tumor response assessment in this trial.
- Bone scans should be performed at baseline~~.~~ as clinically indicated. Routine bone scans during treatment must be performed only in the setting of bone-only disease (no lymph node, visceral, skin, or subcutaneous metastases), or as deemed appropriate by the Investigator. In the event that a positron emission tomography (PET) scan is performed within 28 (calendar) days prior to first dose of study therapy that is negative for bone disease, then no baseline bone scan is required.
- Imaging methods must be employed consistently during the course of each subject's evaluation during the study (that is, subjects who have MRI as baseline examination continue to have MRI assessments as a means of determining response/progression).

6.7 Tissue Sampling

To assess the pharmacodynamic effect of IMC-CS4 administration on tumor-associated macrophages, all subjects enrolled in Cohort 2 and beyond will undergo tumor biopsies before study enrollment ~~(unless medically contraindicated and if acceptable archived tumor material is available)~~ and as specified in Table 6~~.~~

~~The~~. For these cohorts, investigators will carry out a tumor (core needle or excisional) biopsy (attempt to obtain at least 3 cores) before starting the treatment and at the end of Cycle 1 (to be done in the week prior to Cycle 2, at the same time as tumor evaluation), if the subject's condition allows it. If an enrolled subject undergoes a pretreatment tumor biopsy but is unable to tolerate a posttreatment tumor biopsy, then a skin punch biopsy will be acceptable.

At the time of disease progression, the Investigator will also perform a tumor biopsy if the subject consents to it and if the subject's condition allows it.

Previously archived tumor tissue from the primary tumor (paraffin block [whole or partial block] or 20 unstained slides), if available, will be collected (if possible) prior to receiving the first dose of study therapy ~~if a tumor core biopsy cannot be performed before treatment, either because of the tumor location or because the subject's condition does not permit it (that is, medically contraindicated). If the subject's condition allows it, the Investigator will also perform a tumor biopsy if disease progression is diagnosed. If a tumor core biopsy is not possible, the Investigator may consult the ImClone CRP to evaluate the possibility of performing a tumor fine-needle aspiration (FNA)~~.

~~Tissue will~~ Previously archived and/or biopsied tissue may be used for analysis that may include, but would not be limited to ~~immunohistochemistry for CD68 and CD163 and for potential pharmacogenomics analysis of,~~ factors related to the CSF ~~1 pathways and analysis of macrophage-specific markers.~~1R pathway, macrophages, and immune microenvironment. All tissue samples will be kept by the Sponsor for a ~~total~~ maximum of 15 years after the main study is completed; then all samples will be destroyed.

6.8.1 Pharmacokinetics

The analytical methods used to determine serum drug concentration will ~~conform to the May 2001 United States Food and Drug Administration (FDA) *Guidance for Industry: Bioanalytical Method Validation* (FDA 2001).~~be validated at a laboratory determined by the sponsor. Serum concentrations of IMC-CS4 will be determined using an enzyme-linked immunosorbent assay.

6.8.4 Other Analyses

Refer to Section 6.5 for details of blood samples drawn for other analyses, including flow-cytometric analysis of peripheral leukocytes; isoenzymes of LDH, CK, and AP; troponin (I or T~~;~~); and bone metabolism markers CTX-I and P1NP. These samples will be separate from those used for PK/immunogenicity and pharmacodynamic analyses, and drawn according to the schedule described in Sections 7.2.2.2, 7.2.2.3, 7.2.2.4, and 7.2.2.5.

6.9.1 Triplicate ECG (Part A Only)

Triplicate ECG consisting of 3 individual ECGs performed consecutively within a period of approximately 4 minutes will be obtained at the time points specified in Section 7.2.3.1 from ~~the 6~~ additional subjects enrolled at the RP2D.

6.10 Multigated Acquisition Scan or Echocardiogram

A multigated acquisition (MUGA) scan or an echocardiogram will be performed for all subjects during pretreatment evaluations (within 28 [calendar] days prior to first dose of study therapy), as an eligibility assessment of LVEF. Refer to exclusion criterion #~~12~~11 (Section 3.3) for subject eligibility regarding LVEF.

6.11.1 Tumor Tissue Submission

If a core biopsy, surgical biopsy, or resection is performed in the course of the study as routine clinical care, the Sponsor requests a tissue block or unstained slides for analysis of potentially relevant surrogate biomarkers. Tissue will be kept with the intention to perform tests as new techniques, research tools, and biomarkers become available. All tissue samples will be kept by the Sponsor for a ~~total~~ maximum of 15 years after the main study is completed, then all samples will be destroyed.

7.1 Pretreatment Evaluations

- Blood sample for troponin (I or T) assessment (prior to the first infusion of Cycle 1 so that results are obtained before dosing);
- Bone scan, as clinically indicated (within 28 days prior to the first dose of study therapy; not required if PET is performed within 28 days prior to the first dose of study therapy that is negative for bone disease); and
- Tumor (core needle or excisional) biopsy (mandatory) (within 7 days prior to the first dose of study therapy) for subjects in Cohort 2 and beyond ~~(unless medically contraindicated and if acceptable archived tumor material is available).~~.

7.2 Treatment Period

A series of clinical tests and procedures will be performed at specified intervals throughout the study (see also Section 7.6). If, at any time during the study, tumor tissue is obtained as routine clinical care or through a biopsy, fine-needle aspiration (FNA), or resection, the Sponsor requests a portion of the sample for exploratory analyses.

IMC-CS4 is administered I.V. as shown in Section 4.1, Table 2, Table 3, Table 4, and Table 5. An observation period will occur, as needed, in Cycle 1 of Part A only, as described in Section 4.1. Radiographic assessment of tumor response will be performed at the end of every treatment cycle (prior to the first dose of study therapy in the subsequent cycle, approximately every 6 weeks assuming no treatment delays); radiographic assessment should be performed prior to the start of a cycle so that results are available before the subject receives a new cycle of treatment. However, if a ~~subject experiences a~~ DLT is observed in Cycle 1~~, and the subject's~~ in a subject who is benefitting from treatment, Cycle 2 dosing ~~is~~ may be initiated within 4 weeks of Cycle 1, Day 1, with Sponsor approval; in this case, no radiographic disease assessment is required prior to dosing in Cycle 2. Routine bone scans during treatment must be performed only in the setting of bone-only disease (no lymph node, visceral, skin, or subcutaneous metastases), or as deemed appropriate by the Investigator.

7.2.1 Regular Assessments

Beginning with Week 1, Day 1, the following evaluations will be performed every week (±2 days for subjects in the qw cohorts and Cohorts ~~7~~ 6b, 7b, and 8b and ±3 days for subjects in the q2w cohorts) for the first 12 weeks on therapy (this includes nontreatment weeks for subjects enrolled in the q2w cohorts and Cohorts ~~4 and 6, as well as Cohorts 7~~6b, 7b, and 8b), unless otherwise indicated:

- ECOG PS assessment;
- Vital sign measurements (vital signs to be checked and recorded prior to each infusion of IMC-CS4, midway through each infusion, at the end of each infusion, and every 15 minutes for the first hour following each infusion, including Week 1, Day 1 [also to be checked and recorded at nontreatment visits during Cycle 1]);
- Weight measurement;
- Toxicity/AE evaluations;
- Concomitant medication assessment;
- Hematology profile (evaluations performed within 7 days prior to the first dose do not need to be repeated at Week 1, Day 1);
- Serum chemistry profile (evaluations performed within 7 days prior to the first dose do not need to be repeated at Week 1, Day 1);
- C-reactive protein assessment;
- Tumor biopsy – At the end of Cycle 1, if the subject's condition allows it, a (mandatory) (core needle or excisional) biopsy of the tumor will be performed, regardless of whether the tumor progressed, stabilized, or regressed (refer to Section 7.2.1.1 for the timing of non-mandatory tumor biopsies);

- Blood samples for PK, immunogenicity, and pharmacodynamic analyses, per Section 7.7 (Table 7, Table 8, and Table 9); and
- Blood samples for the following assessments, per Section 7.7 (Table 7, Table 8, and Table 9): flow cytometry of peripheral leukocytes; isoenzymes of LDH, CK, and AP; troponin (I or T); and bone metabolism markers CTX-I and P1NP.

After study Week 12 (that is, after Cycle 2), ECOG PS assessment, vital sign measurements, weight measurement, toxicity/AE evaluations, and concomitant medication assessment will continue to be performed every week, while C-reactive protein assessment will be performed q2w. After Week 12, hematology and serum chemistry will be performed: q2w for ~~cohorts up to and including~~ Cohorts 1, 2, 3, 4, 5, 6a, 6c, 7a, 7c, 8a, 8c, and every 3 weeks (q3w) for Cohorts ~~7~~ 6b, 7b, and 8b (such that these hematology and serum chemistry assessments are done on rest Weeks 3 and 6).

7.2.1.1 Tumor Biopsy

Tumor (core needle or excisional) biopsy will be performed at the following time points:

Weekly Cohorts and Cohorts ~~7~~ 6b, 7b, and 8b

Mandatory (unless medically contraindicated)

- Prior to the first IMC-CS4 infusion of Cycle 1 (≤7 days) ~~(unless medically contraindicated and if acceptable archived tumor material is available)~~
- At the end of Cycle 1, if the subject's condition allows it, a (core needle or excisional) biopsy of the tumor will be performed, regardless of whether the tumor progressed, stabilized, or regressed.

Non-mandatory

- In cases of tumor progression, if the subject's condition allows it, a (core needle or excisional) biopsy will be performed.

Every-2-Week Cohorts

Mandatory (unless medically contraindicated)

- Prior to the first IMC-CS4 infusion of Cycle 1 (≤7 days)
- At the end of Cycle 1, if the subject's condition allows it, a (core needle or excisional) biopsy of the tumor will be performed, regardless of whether the tumor progressed, stabilized, or regressed.

Non-mandatory

- ~~Prior to the third IMC-CS4 infusion of Cycle 1, if the subject's condition allows it~~
  In cases of tumor progression, if the subject's condition allows it, a (core needle or excisional) biopsy will be performed.

~~Every-2-Week Cohorts~~

~~**Mandatory** (unless medically contraindicated)~~

- ~~Prior to the first IMC-CS4 infusion of Cycle 1 (≤7 days) (unless medically contraindicated and if acceptable archived tumor material is available)~~
- ~~At the end of Cycle 1, if the subject's condition allows it, a core biopsy of the tumor will be performed, regardless of whether the tumor progressed, stabilized, or regressed.~~

~~**Non-mandatory**~~

- ~~Prior to the second IMC-CS4 infusion of Cycle 1, if the subject's condition allows it~~
- ~~In cases of tumor progression, if the subject's condition allows it, a core biopsy will be performed.~~

7.2.2.2 Flow Cytometry Analysis

Weekly Cohorts and Cohorts ~~7~~ 6b, 7b, and 8b

- Prior to the first IMC-CS4 infusion of Cycle 1 (≤7 days)
- 1 day (approximately 24 hours) after the first IMC-CS4 infusion in Cycle 1
- 2 days (approximately 48 hours) after the first IMC-CS4 infusion in Cycle 1
- 3 days (approximately 72 hours) after the first IMC-CS4 infusion in Cycle 1
- Immediately prior to the second IMC-CS4 infusion of Cycle 1
- Immediately prior to the third IMC-CS4 infusion of Cycle 1
- Immediately prior to the fourth IMC-CS4 infusion of Cycle 1
- Cohorts ~~7~~ 6b, 7b, and 8b only: 1 day after the first IMC-CS4 infusion in Cycle 3 (approximately 24 hours)
- Immediately prior to the second IMC-CS4 infusion of Cycle 3.

7.2.2.3 LDH, CK, and AP Isoenzymes

Weekly Cohorts and Cohorts 6b, 7b, and 8b

- Prior to the first IMC-CS4 infusion of Cycle 1 (≤7 days)
- Prior to the second IMC-CS4 infusion of Cycle 1 (≤3 days)
- Prior to the third IMC-CS4 infusion of Cycle 1 (≤3 days)

- On Week 1 of Cycle 2; collected only if serum enzymes are ≥2.5 × ULN at Week 5 of Cycle 1
- Cohorts ~~7~~ 6b, 7b, and 8b only: Prior to the second IMC-CS4 infusion of Cycle 3 (≤3 days); collected only if serum enzymes are ≥2.5 × ULN at Week 5 of Cycle 1.

7.2.2.4 Troponin ~~T~~

Serum levels of troponin (I or T) will be assessed at the following time points:

Weekly Cohorts and Cohorts ~~7~~ 6b, 7b, and 8b

- Prior to the first IMC-CS4 infusion of Cycle 1 (sample to be collected prior to the first infusion of Cycle 1 so that results are obtained before dosing)
- Prior to the second IMC-CS4 infusion of Cycle 1 (≤3 days)
- Prior to the third IMC-CS4 infusion of Cycle 1 (≤3 days)
- On Week 1 of Cycle 2; collected only if serum CK levels are ≥2.5 × ULN at Week 5 of Cycle 1
- Cohorts ~~7~~ 6b, 7b, and 8b only: Prior to the second IMC-CS4 infusion of Cycle 3 (≤3 days); collected only if serum CK levels are ≥2.5 × ULN at Week 5 of Cycle 1
- When deemed appropriate by the Investigator.

In all cohorts, blood samples for troponin ~~T~~ analysis will be collected at the end of therapy and at the 30-Day Follow-up visit only if CK ≥2.5 × ULN at Week 5 of Cycle 1.

With the exception of the first IMC-CS4 infusion of Cycle 1, IMC-CS4 may be administered as planned while troponin ~~T~~ results are pending, provided no cardiac symptoms have been revealed upon ECG or physical examination. For the first IMC-CS4 infusion of Cycle 1 (all cohorts), troponin ~~T~~ results should be obtained before dosing.

7.2.2.5 Bone Metabolism Markers CTX-I and P1NP

Weekly Cohorts and Cohorts ~~7~~ 6b, 7b, and 8b

- Prior to the first IMC-CS4 infusion of Cycle 1 (≤7 days)
- Prior to the second IMC-CS4 infusion of Cycle 1 (≤3 days)
- Prior to the fourth IMC-CS4 infusion of Cycle 1 (≤3 days)
- Prior to the second IMC-CS4 infusion of Cycle 3 (≤3 days).

7.2.3.1 Triplicate ECG Schedule (Part A Only)

As described in Section 4.1.2, ~~6~~ additional subjects ~~will~~ may be enrolled at the RP2D ~~for each dosing schedule~~. These ~~6~~ subjects only will undergo triplicate ECG testing (see Section 6.9.1) at each of the following time points:

- Prior to the first infusion of Cycle 1 and 1 hour (±30 minutes) following the completion of the first infusion of Cycle 1
- Prior to the last infusion of Cycle 1 and 1 hour (±30 minutes) following the completion of the last infusion of Cycle 1 (qw cohorts ~~and Cohorts 7 and 8 only~~)
- Prior to the last infusion of Cycle 3 and 1 hour (±30 minutes) following the completion of the last infusion of Cycle 3 (q2w cohorts only)
- Prior to the last infusion of all subsequent cycles and 1 hour (±30 minutes) following the completion of the last infusion of all subsequent cycles.

7.3 End-of-Therapy Evaluations

End-of-therapy evaluations will be assessed on subjects who are no longer receiving study therapy. The end-of-therapy evaluations will include:

- ECG (triplicate ECG for ~~the 6 additional subjects in whichever cohort is expanded to 12 subjects; refer also to~~ Part A only, as described in Sections 6.9.1 and 7.2.3.1);
- ECOG PS assessment;
- Physical examination;
- Vital signs (including temperature, pulse rate, respiration rate, and blood pressure);
- Weight measurement;
- Toxicity/AE evaluations;
- Concomitant medication assessment;
- Hematology profile;
- Serum chemistry profile;
- C-reactive protein assessment;
- Troponin (I or T) analysis and isoenzyme assessment of LDH, CK, and AP only if serum enzymes are ≥2.5 × ULN at Week 5 of Cycle 1; and
- Urinalysis.

In cases of tumor progression, if the subject's condition allows it, a (core needle or excisional) biopsy of the tumor will be performed. For subjects who discontinue study therapy for any reason other than PD, every effort will be made to obtain radiographic tumor assessments at 6 and 12 weeks following the first dose of study therapy and/or until radiographic documentation of PD.

7.4 30-Day Follow-up Evaluations

- Troponin (I or T) analysis and isoenzyme assessment of LDH, CK, and AP only if serum enzymes are ≥2.5 × ULN at Week 5 of Cycle 1;

7.6 Study Events Table

Table 6. Flow Chart for Protocol

Procedures	Pretreatment (Prior to first dose)			Treatment Cycles[a]					End of Therapy	30-Day Follow-up	Extended Follow-up
	Within 28 Days	Within 14 Days	Within 7 Days	Every Week[b]	Every 2 Weeks	Every 3 Weeks	Every 6 Weeks	Every 12 Weeks			
Eligibility Assessments											
Informed consent		X[c]		N/A							
Medical history		X		N/A							
β-hCG Pregnancy test			X[d]					X[d]		X[d]	
ECG		X		X[e]					X		
MUGA/echocardiogram	X										
Triplicate ECG (Part A only)				X[e,f]					X[f]		
ECOG PS assessment		X		X					X	X	
Safety Assessments											
Physical examination		X[g]			X[h]		X[h]		X	X	
Vital signs		X[i]		X[i]					X[i]	X	
Weight measurement		X		X					X	X	
Toxicity/AE assessment		X[j]		X					X	X	X[k]
Concomitant medication assessment		X[l]		X					X	X	
Laboratory Tests											
Hematology profile		X		X[m,n]	X[m]	X[m]			X	X	
Coagulation profile		X					X[o]				
Serum chemistry profile		X		X[m,n]	X[m]	X[m]			X	X	
C-reactive protein assessment		X		X[m,n]	X[m]				X	X	

Table 6~~5~~. Flow Chart for Protocol

Procedures	Pretreatment (Prior to first dose)			Treatment Cycles[a]					End of Therapy	30-Day Follow-up	Extended Follow-up
	Within 28 Days	Within 14 Days	Within 7 Days	Every Week[b]	Every 2 Weeks	Every 3 Weeks	Every 6 Weeks	Every 12 Weeks			
Urinalysis		X					X[o]		X		
Blood Sampling											
All blood sampling	Refer to Table 7 (qw cohorts), Table 8 (q2w cohorts), and Table 9 (Cohorts 6b, 7b, and 8b).										
Efficacy Assessments											
Imaging studies (CT/MRI)	X						X[p]				
Bone scan	X[q]			X[r]							
Tumor assessments	X						X[p]				
Tumor (core needle or excisional) biopsy			X				X[s]		X[t]		
Tumor tissue submission				X[u]							
Study Therapy Administration											
Administer IMC-CS4	N/A			Refer to Table 2 (Part A - qw cohorts), Table 3 (q2w cohorts), Table 4 (Part B – qw cohorts), and Table 5 (Cohorts 6b, 7b, and 8b)~~,~~.					N/A		

Abbreviations: β-hCG = beta human chorionic gonadotropin; AE = adverse event; CK = creatine kinase; CT/MRI = computed tomography (scan)/magnetic resonance imaging; DLT = dose-limiting toxicity; ECOG PS = Eastern Cooperative Oncology Group performance status; ECG = electrocardiogram; ~~FNA = fine-needle aspiration;~~ MUGA = multigated acquisition; N/A = not applicable; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PET = positron emission tomography; PK = pharmacokinetic(s); qw = weekly; q2w = every 2 weeks; q3w = every 3 weeks; RP2D = recommended Phase 2 dose; ULN = upper limit of normal; WOCBP = women of childbearing potential.

a Visit windows will coincide with the study therapy administration windows; that is, ±2 days for subjects in the qw cohorts and Cohorts 6b, 7b, and 8b, and ±3 days for subjects in the q2w cohorts.

b Evaluations performed as part of the pretreatment assessment do not need to be repeated on Day 1 of Week 1 unless required in the opinion of the Investigator.

c Written permission will be given by each subject prior to undergoing any protocol-specific pretreatment evaluations and prior to receiving treatment.

d At baseline, serum pregnancy test is required for WOCBP. Thereafter, including at Week 13 (that is, 12 weeks after the first dose), every 12 weeks (or according to local regulations, whichever is more frequent), and at the 30-Day Follow-up visit, a serum or urine pregnancy test may be performed.

e ECG assessment will be performed at the following time points: Prior to the first infusion of Cycle 1 and 1 hour (±30 minutes) following the completion of the first infusion of Cycle 1; prior to the last infusion of Cycle 1 and 1 hour (±30 minutes) following the completion of the last infusion of Cycle 1; prior to the last infusion of all subsequent cycles and 1 hour (±30 minutes) following the completion of the last infusion of all subsequent cycles; and when deemed appropriate by the Investigator. 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.

Table 6~~5~~. Flow Chart for Protocol

f For ~~6~~ additional subjects enrolled ~~either: (1)~~ at the RP2D of Part A only; ~~or (2) into a cohort below the RP2D rather than at the RP2D, if appropriate based on PK and/or safety findings from this study. T~~they will undergo triplicate (instead of single) ECG testing, according to the following schedule: Prior to the first infusion of Cycle 1 and 1 hour (±30 minutes) following the completion of the first infusion of Cycle 1; prior to the last infusion of Cycle 1 and 1 hour (±30 minutes) following the completion of the last infusion of Cycle 1 (qw cohorts ~~and Cohorts 7 and 8 only~~); prior to the last infusion of Cycle 3 and 1 hour (±30 minutes) following the completion of the last infusion of Cycle 3 (q2w cohorts only); and prior to the last infusion of all subsequent cycles and 1 hour (±30 minutes) following the completion of the last infusion of all subsequent cycles.

g The complete physical examination includes height (at baseline only).

h Every 2 weeks for the first 12 weeks of the study, and every 6 weeks thereafter.

i Vital signs include temperature, pulse rate, respiration rate, and blood pressure. Vital signs will be checked and recorded prior to each infusion of IMC-CS4, midway through each infusion, at the end of each infusion, and every 15 minutes for the first hour following each infusion, including Week 1, Day 1 (also to be checked and recorded at nontreatment visits during Cycle 1).

j Any preexisting toxicity should be documented, recorded, and graded (NCI-CTCAE, Version 4.0 grade) as a part of the pretreatment medical history.

k All SAEs and 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.

l Including those medications taken within 30 days prior to the first dose of study therapy.

m Every week for the first 12 weeks on therapy. After Week 12, C-reactive protein assessment will be performed q2w; hematology and serum chemistry will be performed q2w for C~~e~~ohorts 1, 2, 3, 4, 5, 6a, 6c, 7a, 7c, 8a, and 8c~~up to and including Cohort 6~~ and q3w for Cohorts 6b, 7b, and 8b (that is, on rest Weeks 3 and 6).

n Hematology and serum chemistry evaluations performed within 7 days prior to the first dose do not need to be repeated at Week 1, Day 1.

o Coagulation profile and urinalysis will be performed at the beginning of each cycle (that is, approximately every 6 weeks following the first dose of study therapy).

p Radiographic assessment of tumor response should be performed prior to the start of a cycle so that results are available before the subject receives a new cycle of treatment. However, if a DLT is observed in Cycle 1 in a subject who is benefitting from treatment, ~~and~~ Cycle 2 dosing ~~is~~ may be initiated within 4 weeks of Cycle 1, Day 1, with Sponsor approval; in this case, no radiographic disease assessment is required prior to dosing in Cycle 2.

q Not required if PET is performed within 28 days prior to the first dose of study therapy that is negative for bone disease.

r Bone scan at baseline, as clinically indicated. Routine bone scans during treatment must be performed only in the setting of bone-only disease (no lymph node, visceral, skin, or subcutaneous metastases), or as deemed appropriate by the Investigator.

s At the end of Cycle 1, if the subject's condition allows it, a biopsy of the tumor will be performed, regardless of whether the tumor progressed, stabilized, or regressed. If the subjects's condition does not safely permit a tumor biopsy, then a skin biopsy may be submitted.~~A non-mandatory biopsy may be performed, if the subject's condition allows it: prior to the third IMC-CS4 infusion of Cycle 1 (for qw cohorts and Cohorts 7 and 8) or prior to the second IMC-CS4 infusion of Cycle 1 (for q2w cohorts).~~

t In cases of disease progression, if the subject's condition allows it, a tumor biopsy will be performed. ~~If a tumor core biopsy is not possible, the investigators may consult the ImClone CRP to evaluate the possibility of performing a tumor FNA.~~

u 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. Subjects must consent to these optional procedures.

7.7 Pharmacokinetic and Other Sampling

Table 7, Table 8, and Table 9 summarize PK and other sampling scheduled to occur as part of Study IMCL CP24-1001.

Table 7. Blood Collection Schedule (Parts A and B - Weekly Cohorts 1, 2, 3, 5, 6a, 6c, 7a, 7c, 8a, and 8c)

Blood Collection Time Point[a]	Analyses						
	PK[b]	IGx[b]	PD	FC	Iso	TropT	Bone
Pretreatment							
Prior to the first infusion	X[c]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Cycle 1 (Week 1)							
Immediately after the end of the first infusion of Cycle 1	X						
1 hr after the end of the first infusion	X		X				
2 hr after the end of the first infusion	X		X				
4 hr after the end of the first infusion	X		X				
24 hr (Day 2) after the end of the first infusion	X		X	X			
48 hr (Day 3) after the end of the first infusion	X		X	X			
72 hr (Day 4) after the end of the first infusion	X		X	X			
168 hr (Day 8) after the end of the first infusion immediately (unless otherwise footnoted) prior the second infusion of Cycle 1	X	X	X	X	X[e]	X[e]	X[e]
Cycle 1 (Week 3)							
Immediately (unless otherwise footnoted) prior to the third infusion of Cycle 1				X	X[e]	X[e]	
Cycle 1 (Week 4)							
Immediately (unless otherwise footnoted) prior to the fourth infusion of Cycle 1	X	X	X	X			X[e]
Cycle 2 (Week 1)							
Prior to the first infusion of Cycle 2					X[f]	X[g]	
Cycle 2 (Week 6)							
Immediately prior to the sixth infusion of Cycle 2	X		X				
Cycle 3 (Week 1)							
Immediately prior to the first infusion of Cycle 3	X	X	X				
Immediately after the end of the first infusion	X						
1 hr after the end of the first infusion	X		X				
2 hr after the end of the first infusion	X						
4 hr after the end of the first infusion	X		X				
24 hr (Day 2) after the end of the first infusion	X						
48 hr (Day 3) after the end of the first infusion	X						
96 hr (Day 5) after the end of the first infusion	X						
168 hr (Day 8) after the end of the first infusion, immediately (unless otherwise footnoted) prior to the second infusion of Cycle 3	X		X	X			X[e]
Cycle 3 (Week 4)							
Immediately prior to the fourth infusion of Cycle 3	X	X	X				
Cycles 4-6[i-h]							
Prior to the last infusion of each cycle	X		X				

Table is continued on the next page.

Table 7~~6~~. Blood Collection Schedule (Parts A and B - Weekly Cohorts 1, 2, 3, 5, 6a, 6c, 7a, 7c, 8a, and 8c)

Blood Collection Time Point[a]	Analyses						
	PK[b]	IGx[b]	PD	FC	Iso	Trop~~T~~	Bone
Cycle 5							
Immediately prior to the first infusion of Cycle 5 (6 months after the first infusion of Cycle 1)		X					
End of Therapy							
At the End-of-Therapy visit					X[f]	X[g]	
Follow-up							
30-Day Follow-up visit~~[i]~~[i]	X	X	X	X	X[f]	X[g]	

Abbreviations: Bone = assessment of bone metabolism markers (CTX-I and P1NP); CK = creatine kinase; CTX-I = C-terminal cross-linking telopeptide of type I collagen; ECG = electrocardiogram; FC = flow cytometry analysis; IGx = immunogenicity; Iso = isoenzyme analysis; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamic markers; PK = pharmacokinetic(s); Trop~~T~~ = troponin (I or T) assessment; ULN = upper limit of normal.

a It is understood that it may not be feasible to collect samples at precise intervals following the end of the infusions. Every attempt should be made to collect each of these samples as close to the time point as possible. The date and time of all PK samplings must be clearly and accurately recorded.

b PK samples will be collected from all subjects. The date and time of all samplings must be clearly and accurately recorded. The blood samples collected for PK will also be used for immunogenicity analyses. For each specified time point, 1 tube ~~(approximately 7.5 mL/tube)~~ of blood is required to be drawn for any combination of PK or immunogenicity analyses. As an example, if the timing of a PK sample should coincide with that of an immunogenicity sample, the same sample will suffice for these studies and the same total amount of blood (1 tube, approximately 7.5 mL/tube) will be collected.

c Pretreatment sampling should be collected on the day of and immediately prior to the first infusion.

d IGx, PD, FC, isoenzyme analysis, and bone metabolism markers: Sample to be collected ≤7 days prior to the first infusion of Cycle 1. Troponin (I or T) analysis: Sample to be collected prior to the first infusion of Cycle 1 so that results are obtained before dosing.

e Sample to be collected at any time ≤3 days prior to the infusion. IMC-CS4 may be administered as planned while troponin (I or T) results are pending, provided no cardiac symptoms have been revealed upon ECG or physical examination.

f Analysis to be performed only if serum enzymes are ≥2.5 × ULN at Week 5 of Cycle 1.

g Analysis to be performed only if serum CK levels are ≥2.5 × ULN at Week 5 of Cycle 1. IMC-CS4 may be administered as planned while troponin (I or T) results are pending, provided no cardiac symptoms have been revealed upon ECG or physical examination.

h For subjects who proceed to Cycles ~~2~~4 to 6, blood samples will be collected prior to the last infusion of each cycle. In the event that a subject does not proceed to these cycles, these samples will not be collected.

i A sample will be collected 30 days after last dose of investigational agent, regardless of duration of therapy.

Note: If at any time a subject experiences an infusion-related reaction to 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.

Table 8. Blood Collection Schedule (Part A - Every-2-Week Cohorts 4)

Blood Collection Time Point[a]	Analyses						
	PK[b]	IGx[b]	PD	FC	Iso	Trop~~T~~	Bone
Pretreatment							
Prior to the first infusion	X[c]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Cycle 1 (Week 1)							
Immediately after the end of the first infusion of Cycle 1	X						
1 hr after the end of the first infusion	X		X				
2 hr after the end of the first infusion	X		X				
4 hr after the end of the first infusion	X		X				
24 hr (Day 2) after the end of the first infusion	X		X				
72 hr (Day 4) after the end of the first infusion	X		X	X			
168 hr (Day 8) after the end of the first infusion	X		X				
336 hr (Day 15) after the end of the first infusion, immediately (unless otherwise footnoted) prior to the second infusion of Cycle 1	X	X		X	X[e]	X[e]	X[e]
Cycle 1 (Week 3)							
Immediately after the end of the second infusion of Cycle 1	X						
1 hr after the end of the second infusion	X		X				
2 hr after the end of the second infusion	X		X				
4 hr after the end of the second infusion	X		X				
24 hr (Day 2) after the end of the second infusion	X		X				
72 hr (Day 4) after the end of the second infusion	X		X				
168 hr (Day 8) after the end of the second infusion	X		X				
336 hr (Day 15) after the end of the second infusion (Week 5)	X		X				
504 hr (Day 22) after the end of the second infusion (Week 6) of Cycle 1	X		X				
Cycle 2 (Week 1)[h]							
Prior to the first infusion of Cycle 2					X[f]	X[g]	
Cycle 2 (Week 5)[h]							
Immediately prior to the third infusion of Cycle 2	X		X				
Cycle 3 (Week 1)[h]							
Immediately prior to the first infusion of Cycle 3	X	X	X				
Immediately after the end of the first infusion	X						
1 hr after the end of the first infusion	X		X				
2 hr after the end of the first infusion	X						
4 hr after the end of the first infusion	X		X				
24 hr (Day 2) after the end of the first infusion	X						
72 hr (Day 4) after the end of the first infusion	X						
168 hr (Day 8) after the end of the first infusion	X						
336 hr (Day 15) after the end of the first infusion, immediately prior to the second infusion of Cycle 3	X		X	X			
Cycle 3 (Week 5)[h]							
Immediately prior to the third infusion of Cycle 3	X	X	X				
Cycles 4-6[h]							
Prior to the last infusion of each cycle	X		X				

Table is continued on the next page.

Table 8~~7~~. Blood Collection Schedule (Part A - Every-2-Week Cohorts~~s~~ 4)

Blood Collection Time Point[a]	Analyses						
	PK[b]	IGx[b]	PD	FC	Iso	Trop~~I~~	Bone
Cycle 5							
Immediately prior to the first infusion of Cycle 5 (6 months after the first infusion of Cycle 1)		X					
End of Therapy							
At the End-of-Therapy visit					X[f]	X[g]	
Follow-up							
30-Day Follow-up visit[i]	X	X	X	X	X[f]	X[g]	

Abbreviations: Bone = assessment of bone metabolism markers (CTX-I and P1NP); CK = creatine kinase; CTX-I = C-terminal cross-linking telopeptide of type I collagen; ECG = electrocardiogram; FC = flow cytometry analysis; IGx = immunogenicity; Iso = isoenzyme analysis; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamic markers; PK = pharmacokinetic(s); Trop~~I~~ = troponin (I or T) assessment; ULN = upper limit of normal.

a It is understood that it may not be feasible to collect samples at precise intervals following the end of the infusions. Every attempt should be made to collect each of these samples as close to the time point as possible. The date and time of all PK samplings must be clearly and accurately recorded.

b PK samples will be collected from all subjects. The date and time of all samplings must be clearly and accurately recorded. The blood samples collected for PK will also be used for immunogenicity analyses. For each specified time point, 1 tube ~~(approximately 7.5 mL/tube)~~ of blood is required to be drawn for any combination of PK or immunogenicity analyses. As an example, if the timing of a PK sample should coincide with that of an immunogenicity sample, the same sample will suffice for these studies and the same total amount of blood (1 tube, approximately 7.5 mL/tube) will be collected.

c Pretreatment sampling should be collected on the day of and immediately prior to the first infusion.

d IGx, PD, FC, isoenzyme analysis, and bone metabolism markers: Sample to be collected ≤7 days prior to the first infusion of Cycle 1. Troponin (I or T) analysis: Sample to be collected prior to the first infusion of Cycle 1 so that results are obtained before dosing.

e Sample to be collected at any time ≤3 days prior to the second infusion of Cycle 1. IMC-CS4 may be administered as planned while troponin (I or T) results are pending, provided no cardiac symptoms have been revealed upon ECG or physical examination.

f Analysis to be performed only if serum enzymes are ≥2.5 × ULN at Week 5 of Cycle 1.

g Analysis to be performed only if serum CK levels are ≥2.5 × ULN at Week 5 of Cycle 1. IMC-CS4 may be administered as planned while troponin (I or T) results are pending, provided no cardiac symptoms have been revealed upon ECG or physical examination.

h For subjects who proceed to Cycles 2 to 6, blood samples will be collected as shown in this table. In the event that a subject does not proceed to these cycles, these samples will not be collected.

i A sample will be collected 30 days after last dose of investigational agent, regardless of duration of therapy.

Note: If at any time a subject experiences an infusion-related reaction to 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.

Table 9. Blood Collection Schedule (Part B - Cohorts 6b, 7b, and 8b)

Blood Collection Time Point[a]	Analyses						
	PK[b]	IGx[b]	PD	FC	Iso	TropT	Bone
Pretreatment							
Prior to the first infusion	X[c]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Cycle 1 (Week 1)							
Immediately after the end of the first infusion of Cycle 1	X						
1 hr after the end of the first infusion	X		X				
2 hr after the end of the first infusion	X		X				
4 hr after the end of the first infusion	X		X				
24 hr (Day 2) after the end of the first infusion	X		X	X			
48 hr (Day 3) after the end of the first infusion	X		X	X			
72 hr (Day 4) after the end of the first infusion	X		X	X			
168 hr (Day 8) after the end of the first infusion immediately (unless otherwise footnoted) prior the second infusion of Cycle 1	X	X	X	X	X[e]	X[e]	X[e]
Cycle 1 (Week 2)							
1 hr after the end of the second infusion of Cycle 1	X						
2 hr after the end of the second infusion	X						
4 hr after the end of the second infusion	X						
24 hr (Day 2) after the end of the second infusion	X						
48 hr (Day 3) after the end of the second infusion	X						
72 hr (Day 4) after the end of the second infusion	X						
168 hr (Day 8) after the end of the second infusion of Cycle 1	X						
Cycle 1 (Week 4)							
Immediately (unless otherwise footnoted) prior to the third infusion of Cycle 1			X	X	X[e]	X[e]	
Cycle 1 (Week 5)							
Immediately (unless otherwise footnoted) prior to the fourth infusion of Cycle 1	X	X	X	X			X[e]
Cycle 2 (Week 1)							
Prior to the first infusion of Cycle 2					X[g]	X[h]	
Cycle 2 (Week 4)							
Immediately prior to the third infusion of Cycle 2	X						
Cycle 3 (Week 1)							
Immediately prior to the first infusion of Cycle 3	X	X	X				
Immediately after the end of the first infusion	X						
1 hr after the end of the first infusion	X		X				
2 hr after the end of the first infusion	X		X				
4 hr after the end of the first infusion	X		X				
24 hr (Day 2) after the end of the first infusion	X		X	X			
48 hr (Day 3) after the end of the first infusion	X		X				
72 hr (Day 4) after the end of the first infusion	X		X				
168 hr (Day 8) after the end of the first infusion immediately (unless otherwise footnoted) prior to the second infusion of Cycle 3	X		X	X	X[f]	X[g]	X[e]

Table is continued on the next page.

Table 98. Blood Collection Schedule (Part B - Cohorts 6b, 7b, and 8b)

Blood Collection Time Point[a]	Analyses						
	PK[b]	IGx[b]	PD	FC	Iso	Trop~~T~~	Bone
Cycle 3 (Week 2)							
1 hr after the end of the second infusion of Cycle 3	X						
2 hr after the end of the second infusion	X						
4 hr after the end of the second infusion	X						
24 hr (Day 2) after the end of the second infusion	X						
48 hr (Day 3) after the end of the second infusion	X						
72 hr (Day 4) after the end of the second infusion	X						
168 hr (Day 8) after the end of the second infusion	X						
Cycle 3 (Week 4)							
Immediately prior to the third infusion of Cycle 3	X	X					
Cycles 4-6[h]							
Prior to the last infusion of each cycle	X	X	X				
Cycle 5							
Immediately prior to the first infusion of Cycle 5 (6 months after the first infusion of Cycle 1)		X					
End of Therapy							
At the End-of-Therapy visit					X[f]	X[g]	
Follow-up							
30-Day Follow-up visit[i]	X	X	X	X	X[f]	X[g]	

Abbreviations: Bone = assessment of bone metabolism markers (CTX-I and P1NP); CK = creatine kinase; CTX-I = C-terminal cross-linking telopeptide of type I collagen; ECG = electrocardiogram; FC = flow cytometry analysis; IGx = immunogenicity; Iso = isoenzyme analysis; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamic markers; PK = pharmacokinetic(s); Trop~~T~~ = troponin (I or T) assessment; ULN = upper limit of normal.

a It is understood that it may not be feasible to collect samples at precise intervals following the end of the infusions. Every attempt should be made to collect each of these samples as close to the time point as possible. The date and time of all PK samplings must be clearly and accurately recorded.

b PK samples will be collected from all subjects. The date and time of all samplings must be clearly and accurately recorded. The blood samples collected for PK will also be used for immunogenicity analyses. For each specified time point, 1 tube (approximately 7.5 mL/tube) of blood is required to be drawn for any combination of PK or immunogenicity analyses. As an example, if the timing of a PK sample should coincide with that of an immunogenicity sample, the same sample will suffice for these studies and the same total amount of blood (1 tube, approximately 7.5 mL/tube) will be collected.

c Pretreatment sampling should be collected on the day of and immediately prior to the first infusion.

d IGx, PD, FC, isoenzyme analysis, and bone metabolism markers: Sample to be collected ≤7 days prior to the first infusion of Cycle 1. Troponin (I or T) analysis: Sample to be collected prior to the first infusion of Cycle 1 so that results are obtained before dosing.

e Sample to be collected at any time ≤3 days prior to the infusion. IMC-CS4 may be administered as planned while troponin (I or T) results are pending, provided no cardiac symptoms have been revealed upon ECG or physical examination.

f Analysis to be performed only if serum enzymes are ≥2.5 × ULN at Week 5 of previous ~~C~~cycle ~~1~~.

g Analysis to be performed only if serum CK levels are ≥2.5 × ULN at Week 5 of previous ~~C~~cycle ~~1~~. IMC-CS4 may be administered as planned while troponin (I or T) results are pending, provided no cardiac symptoms have been revealed upon ECG or physical examination.

h For subjects who proceed to Cycles 4~~2~~ to 6, blood samples will be collected prior to the last infusion of each cycle. In the event that a subject does not proceed to these cycles, these samples will not be collected.

i A sample will be collected 30 days after last dose of investigational agent, regardless of duration of therapy.

Note: If at any time a subject experiences an infusion-related reaction to 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.

8.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are not listed in the Development Core Safety Information (DCSI) or 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.

~~8.3~~ 8.4 Safety Monitoring

The ~~ImClone~~ Sponsor CRP or designee will monitor safety data throughout the course of the study.

The ~~ImClone~~ Sponsor CRP or designee will review SAEs within time frames mandated by company procedures. The ~~ImClone~~ Sponsor CRP or designee, will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist (CRS), and periodically review trends and laboratory analytes.

If a subject experiences elevated ALT ≥5 × ULN and elevated total bilirubin ≥2 × ULN, clinical and laboratory monitoring should be initiated by the Investigator. For subjects 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 subject safety and comply with regulatory guidance, the Investigator is to consult with the ~~ImClone~~ Sponsor CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. Refer to Section 6.5 for a list of the hepatic monitoring tests to be performed.

~~8.4~~ 8.5 Complaint Handling

9 Treatment-Related Adverse Events

Subjects will be closely monitored for treatment-related AEs, especially infusion-related reactions, immune-related adverse events (irAE), periorbital edema, and signs indicative of

hepatic impairment, leukocyte alterations, and inflammation. Subjects will be evaluated for AEs at each visit and will be instructed to call their study physician to report any AEs between visits.

Adverse event collection will include verbatim term, onset and resolution dates, action taken, outcome, severity (NCI-CTCAE, Version 4.0 grade), relationship to the study therapy, and, if the event is serious, a clear indication of the seriousness.

9.1 IMC-CS4

9.1.1 Immune-Related Adverse Events

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 irAE occurring following infusion of investigational therapy, investigators are encouraged to refer to Table 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. Table 10 is a guideline for the management of irAEs; local standards may supersede recommendations when deemed appropriate by the Investigator.

Table 10. 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.
			Symptomatic	Continue drug. Administer thyroid replacement.
	Hypotension, altered mental status, headache, fatigue		Endocrine issues aside from thyroid (for example, hypophysitis)	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.
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		Permanently discontinue drug. Administer steroids (1-2 mg/kg/d prednisone), except if the possibility of perforation exists. If >3 days' duration despite steroids, also administer nonsteroidal immunosuppressive.
	Pancreatitis	1-2		Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Can resume drug during taper.
		≥3		Permanently discontinue drug.

Table 10. 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	
Hepatobiliary	Transaminitis, elevated bilirubin		**Subjects with baseline AST or ALT ≤2.5 × ULN:** AST or ALT >5 × ULN but ≤7.5 × ULN and total bilirubin ≤ULN	Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Resume drug when AST or ALT ≤5 × ULN.
			Subjects with baseline AST or ALT >2.5 × ULN and ≤5 × ULN: AST or ALT >7.5 × but ≤10 × ULN and total bilirubin ≤ ULN	Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Resume drug when AST or ALT ≤7.5 × ULN.
			Subjects with baseline AST or ALT ≤2.5 × ULN: AST or ALT >7.5 × ULN or total bilirubin > 3× ULN	Permanently discontinue drug. Administer steroids (1-2 mg/kg/d prednisone).
			Subjects with baseline AST or ALT >2.5 × ULN and ≤5 × ULN: AST or ALT >10 × ULN or total bilirubin >3× ULN	Permanently discontinue drug. Administer steroids (1-2 mg/kg/d prednisone).
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.
Respiratory	Dyspnea, hypoxia, pneumonitis	1		Consider to withhold drug. Resume drug when stable.
		2	~~mild to~~ 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).

Table 10. 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	
Renal and urinary	Elevated creatinine, decreased urine output, blood in urine, edema	1	≤1.5 × baseline	Continue drug.
		2-3	>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.
		4	>6 × ULN	Permanently discontinue drug. Administer steroids (1-2 mg/kg/d prednisone).
Skin	Rash, pruritus		≤50% skin affected	Withhold drug. 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 regarding steroids: Steroids should be tapered over 1 month after symptoms have resolved; if withheld drug may be resumed (that is, not permanently discontinued), it can be resumed only after taper has begun. Other steroid options (besides those shown in this table) may be administered at equivalent doses. For severe adverse events, administration of I.V. steroids is recommended. In the case of adrenal crisis, mineralocorticoid should be administered in addition to steroids.

~~9.1.1~~ 9.1.2 IMC-CS4 Infusion-Related Reactions

In the setting of symptoms occurring during or following infusion of investigational therapy, ~~I~~investigators are encouraged to use the AE term "infusion-related reaction" and any additional terms (including those not listed here) that best describe the event.

Consistent with usual medical practice, selected parenteral medications may be utilized for Grade 2 allergic/hypersensitivity reaction as detailed below. The Sponsor~~ImClone~~ CRP should be contacted immediately if questions arise concerning the grade of the reaction. The following are treatment guidelines for IMC-CS4 infusion-related reactions:

10.1.1 During Cycle 1

No IMC-CS4 dose reductions ~~are~~ were permitted for any subject (in Cohort 1 or 2) following a DLT. If a subject (in Cohort 1 or 2) experienced~~s~~ a DLT during Cycle 1, IMC-CS4 was ~~must be~~ permanently discontinued.

If benefitting from treatment (that is, no disease progression or other withdrawal criteria), any subject in Cohort 3 and beyond who experiences a DLT may continue to receive IMC-CS4 upon agreement of the Sponsor and according to the dose reduction guidelines for this study (Table 12).

In the setting of non-life-threatening reversible Grade ≤3 IMC-CS4-related toxicities in Cycle 1 that do not meet the definition of a DLT, IMC-CS4 may be held (if appropriate, in the opinion of the Investigator and upon agreement with the Sponsor) for a maximum of 3 weeks, until resolution to baseline or improvement to Grade ≤~~<~~2. Upon resolution to baseline or improvement to Grade ≤~~<~~2, IMC-CS4 may be administered at a reduced dose (according to Table 12) beginning with Cycle 2, if appropriate, in the opinion of the Investigator and upon agreement with the Sponsor (no dose reductions are permitted during Cycle 1 [for subjects in Cohort 1 or 2]; subjects [in Cohort 1 or 2] who would require dose reductions during Cycle 1 must be discontinued). If toxicity does not resolve to baseline or improve to Grade ≤~~<~~2 within 3 weeks following the last administered dose, IMC-CS4 should be permanently discontinued.

10.1.2 After Cycle 1

Dose reductions, if required during Cycle 2 or after, in the context of IMC-CS4-related toxicity, may be implemented according to the guidelines in Table 12. Any individual subject (including those experiencing an event that occurred after the DLT assessment period that otherwise would have been considered a DLT) may be dose reduced a maximum of 2 times during the course of the study (except as noted in Table 12; for example, subjects in Cohort 3 are only permitted to have one dose reduction). Once a subject 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 subject experiencing toxicity that would necessitate more than 2 dose reductions must discontinue treatment. Dose reductions must be confirmed by the Sponsor.

Any subject who experiences a Grade 4 toxicity after Cycle 1 may continue to receive study treatment only if agreed upon by the Investigator and the ~~ImClone~~ Sponsor CRP and according to the dose reduction guidelines for this study (Table 12).

Table 12. General Dose Reduction Guidelines

Cohort	Starting Dose Level and Schedule	First Reduction	Second Reduction
Part A Only			
1	2.5 mg/kg (qw)	Discontinue	Discontinue
2	0.3 mg/kg (qw)	Discontinue	Discontinue
3	0.6 mg/kg (qw)	0.3 mg/kg (qw)	Discontinue
4	1.25 mg/kg (q2w)	0.6 mg/kg (qw)	0.3 mg/kg (qw)
5	1.25 mg/kg (qw)	1.25 mg/kg (q2w)	0.6 mg/kg (qw)
Part B Only			
6a	~~2.5~~ 100 mg~~/kg~~ (q~~2~~w)	~~1.25~~ 75 mg~~/kg~~ (qw)	~~1.25~~ 50 mg~~/kg~~ (q~~2~~w)
6b	100 mg (Weeks 1, 2, 4, and 5)	75 mg (Weeks 1, 2, 4, and 5)	50 mg (Weeks 1, 2, 4, and 5)
6c	75 mg (qw)	50 mg (qw)	40 mg (qw)
7a	~~2.5~~ 150 mg~~/kg~~ (~~Weeks 1, 2, 4, and 5~~qw)	~~2.5~~ 125 mg~~/kg~~ (q~~2~~w)	~~1.25~~ 100 mg~~/kg~~ (qw)
7b	150 mg (Weeks 1, 2, 4, and 5)	125 mg (Weeks 1, 2, 4, and 5)	100 mg (Weeks 1, 2, 4, and 5)
7c	125 mg (qw)	100 mg (qw)	75 mg (qw)
8a	~~3.75~~ 200 mg~~/kg~~ (~~Weeks 1, 2, 4, and 5~~qw)	~~2.5~~ 175 mg~~/kg~~ (~~Weeks 1, 2, 4, and 5~~qw)	~~2.5~~ 150 mg~~/kg~~ (q~~2~~w)
8b	200 mg (Weeks 1, 2, 4, and 5)	175 mg (Weeks 1, 2, 4, and 5)	150 mg (Weeks 1, 2, 4, and 5)
8c	175 mg (qw)	150 mg (qw)	125 mg (qw)

Abbreviations: qw = weekly; q2w = every 2 weeks.

10.6.1 Granulocyte Colony-Stimulating Factors

Although neutropenia is not an expected side effect of IMC-CS4, the use of granulocyte colony-stimulating factors (G-CSFs) is permitted during investigational therapy, based on American Society of Clinical Oncology (ASCO) guidelines (Smith et al. ~~2006~~2015). G-CSF or similar agents are strongly recommended following Grade 3 or 4 neutropenia lasting more than 5 days duration or following any incidence of febrile neutropenia ~~(ANC <1000/µL with temperature ≥38.5°C, which would constitute a DLT in the present study [see Section 4.1.4])~~.

10.6.5 Premedication for IMC-CS4

Premedication such as antihistamines or steroids for the prophylaxis of hypersensitivity is not recommended to be administered prior to the first infusion of IMC-CS4 administration. Premedication must be implemented in the setting of a prior Grade 1-2 IMC-CS4-related infusion-related reaction and is detailed in Section 9.1.2.

11 Criteria for Tumor Response Evaluation

Study evaluations will take place in accordance with the flow chart in Section 7.6.

Subjects will be evaluated for response according to RECIST 1.1 guidelines (Eisenhauer et al. 2009). Radiographic assessment of tumor response will be performed at the end of the initial 6-week cycle, and the end of every subsequent cycle. However, if a DLT is observed in Cycle 1 in a subject who is benefitting from treatment, ~~and~~ Cycle 2 dosing ~~is~~ may be initiated within 4 weeks of Cycle 1, Day 1, with Sponsor approval; in this case, no radiographic disease assessment is required prior to dosing in Cycle 2.

12.1 General Considerations

Statistical analysis of this study will be the responsibility of the Sponsor.

The interpretation of the study results will be the responsibility of the investigators with the Lilly CRP or CRS, pharmacokineticist, and statistician. The CRP or CRS and statistician will also be responsible for the appropriate conduct of an internal review for both the final study report and any study-related material to be authorized by Lilly for publication.

The analyses for this study will be descriptive, except for possible exploratory analyses as deemed appropriate. Data analyses will be provided by dose levels and for all subjects

combined, wherever appropriate. For continuous variables, summary statistics will include number of subjects (N), mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using N, frequency, and percentages. Missing data will not be imputed. Exploratory analyses of the data that are not described in the protocol will be conducted as deemed appropriate. A detailed description of data analyses will be provided in a separate statistical analysis plan document for this study.

This is a Phase 1 study with an open-label, dose-escalation design. Subjects will be enrolled into cohorts sequentially without randomization to dose level. During dose escalation, the total sample size per cohort will be guided by the standard oncology 3+3 method and determined by the occurrences of DLTs for the treated subjects. The total sample size for Parts A and B is estimated to be approximately 72 treated subjects. In Part A, the sample size is estimated to be approximately 30 subjects. In Part B, the sample size is estimated to be approximately 9 to 42 subjects.

12.3 Subject Disposition

Additional summary of subject participation flow will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements. A participant flow will describe how many enrolled subjects completed the study, and for those who did not, the frequency of each reason for not completing.

12.6 Analyses of Antitumor Response

Radiographic assessment of tumor response will be performed at the end of the initial 6-week cycle and the end of every subsequent cycle. However, if a DLT is observed in Cycle 1 in a subject who is benefitting from treatment, ~~and~~ Cycle 2 dosing ~~is~~ may be initiated within 4 weeks of Cycle 1, Day 1, with Sponsor approval; in this case, no radiographic disease assessment is required prior to dosing in Cycle 2. ~~Overall response rate (number of subjects who achieve a best response of CR or PR during therapy divided by the total number of subjects treated) and disease control rate (number of subjects who achieve a best response of CR or PR or SD during therapy divided by the total number of subjects treated) will be presented for each cohort of subjects.~~ Tumor response data will be summarized, if appropriate.

12.7.2 Pharmacodynamic Assessments

Pharmacodynamic analyses will be descriptive, and correlations to safety and/or efficacy will be performed as appropriate. Those biomarkers collected from different types of tissues or assays will be analyzed separately. Whether a subject is available or willing to provide tissue samples may be considered as a potential confounding variable for exploratory pharmacodynamic analysis.

12.8 Data Safety Monitoring Plan

In order to track and clearly document/record the occurrence of DLTs and identify the decisions made regarding dose escalation, the study investigators, the ~~ImClone~~ Sponsor CRP, and other members of the study team, as appropriate, will meet at specific times throughout this clinical study to review subject safety data. They will make the determination regarding dose escalation based upon their review of the safety/tolerability data and upon availability the PK data from the previous cohorts. At a minimum, they will meet:

- If there are 2 subjects with DLTs within a single cohort during the DLT assessment period;
- At the completion of each dose cohort, in order to determine if dose escalation will proceed (as described in Section 4.1). This review will include safety data collected to date, across all dose cohorts;
- After the RP2D is determined, to determine whether dose escalation should proceed; and
- At least quarterly.

The aforementioned team will determine if the number of subjects experiencing DLTs, as well as any events that occurred after the DLT assessment period that otherwise would have been considered DLTs, exceeds that expected with IMC-CS4 and recommend action, if necessary. The recommended actions may include protocol modification, termination, or additional safety review at specified time points. The ~~ImClone~~ Sponsor CRP may perform additional periodic reviews of relevant safety data (such as a review of Council for International Organizations of Medical Sciences [CIOMS] reports); these evaluations will be documented according to the trial-level safety review plan (a separate, study-specific document that will further detail the process).

13.1 Organizational Structure of the Study

The study sponsor, ~~ImClone LLC, a wholly-owned subsidiary of~~ Eli Lilly and Company, may delegate certain tasks to designees, including a contract research organization or other third-party vendor.

13.4 Compliance with the Protocol and Protocol Revisions

The Investigator must comply with all requirements of the protocol. If a situation occurs that requires a temporary departure from the protocol, the Investigator or other physician in attendance must contact the ~~ImClone~~ Sponsor CRP as soon as possible to discuss the situation and agree on an appropriate course of action. The Investigator will describe the departure from the protocol and the circumstances requiring it on the applicable subjects' eCRFs and will notify the IRB/aEC as appropriate.

13.11 Publication and Disclosure Policy

Lilly's authorship criteria are based on the International Committee of Medical Journal Editors (ICMJE) *Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals* (www.ICMJE.org, updated August 2013):

1. Substantial contributions to conception and design of the work, or the acquisition, analysis, or interpretation of data for the work
2. Drafting the article or revising it critically for important intellectual content
3. Final approval of the version to be published
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

NOTE: Authors must meet conditions 1, 2, 3, and 4.

~~The Sponsor's authorship criteria are based on the International Committee of Medical Journal Editors (ICMJE) *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (ICMJE 2010):~~

~~Substantial contributions to conception and design, or to acquisition of data, or to analysis and interpretation of data;~~

~~Drafting the article or revising it critically for important intellectual content;~~

~~Final approval of the version to be published.~~

~~Note: Authors must meet conditions 1, 2, and 3.~~

14 References

~~[FDA] United States Food and Drug Administration. *Guidance for Industry: Bioanalytical Methods Validation*. May 2001. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf. Accessed August 28, 2013.~~

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Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, Goldberg JM, Khatcheressian JL, Leighl NB, Perkins CL, Somlo G, Wade JL, Wozniak AJ, Armitage JO. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015 Jul 13. pii: JCO.2015.62.3488. [Epub ahead of print].

SYNOPSIS

Sponsor:

Eli Lilly and Company

Name of Finished Product:

IMC-CS4 (LY3022855)

Name of Active Ingredient:

IMC-CS4, a recombinant human immunoglobulin G, subclass 1 (IgG1) monoclonal antibody targeted to the colony-stimulating factor-1 receptor (CSF-1R).

Study Title:

Phase 1 Study of IMC-CS4, a Monoclonal Antibody Targeted to the CSF-1 Receptor (CSF-1R) in Subjects With Advanced Solid Tumors Refractory to Standard Therapy or for Which No Standard Therapy Is Available

Study Number:

IMCL CP24-1001 (I5F-IE-JSCA)

Study Phase:

Phase 1

Primary Objectives:

The primary objectives of this study are to establish the safety profile and characterize the pharmacokinetic (PK) profile of IMC-CS4 in the treatment of subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy is available.

Secondary Objectives:

The secondary objectives of this study are:

- Part A only: To define the recommended Phase 2 dose (RP2D) using weight-based dosing;
- Part B only: To define the RP2D using non-weight-based dosing;
- To characterize the pharmacodynamic profile of IMC-CS4 on circulating levels of CSF-1; and
- To assess the development of antibodies against IMC-CS4 (immunogenicity).

Exploratory Objectives:

The exploratory objectives of this study are:

- To assess pharmacodynamic response markers including, but not limited to, interleukin-34 (IL-34) and MCP-1;
- To assess the impact of IMC-CS4 monotherapy on lactate dehydrogenase (LDH), creatine kinase (CK), and alkaline phosphatase (AP) isoenzymes;
- To assess the pharmacodynamic impact of IMC-CS4 on selected cellular and molecular markers to establish a potential correlation with safety and antitumor activity;
- To assess the pharmacodynamic impact of IMC-CS4 on various components of the monocyte-macrophage system in hematologic or tissue specimens;
- To assess the impact of IMC-CS4 monotherapy on bone metabolism; and
- To assess the antitumor activity of IMC-CS4 as monotherapy in the treatment of advanced solid tumors.

Study Design:

This open-label, dose-escalation, Phase 1 study will enroll (that is, assign to a dose cohort) approximately 72 subjects to 2 parts – Parts A and B. Part A consisted of dose escalation of IMC-CS4 using weight-based dosing; Part B will consist of dose escalation of IMC-CS4 using non-weight-based dosing. The actual enrollment will depend on the number of dose-limiting toxicities (DLTs) observed and the resultant size of each cohort.

Dose cohorts, including dose and dosing schedule, are summarized in the table below. For each cohort, one cycle is 6 weeks. In each cohort, subjects will receive IMC-CS4 by intravenous (I.V.) infusion (with an observation period for weekly [qw] and every-2-week [q2w] cohorts in Cycle 1 only, as described in the following table).

Dose Cohort Assignment

Cohort	Dose Level	Dosing Schedule[a]	Cycle 1 Observation Period[b]	Number of Infusions
Part A (weight-based dosing)				
1	2.5 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
2	0.3 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
3	0.6 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
4	1.25 mg/kg	q2w	3 weeks (Weeks 4-6)	Cycle 1: 2 Subsequent cycles: 3
5	1.25 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
Part B (non-weight-based dosing)				
6a	100 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
6b[c,d]	100 mg	qw on Weeks 1, 2, 4, and 5	None (Weeks 3 and 6 are rest)	Cycle 1: 4 Subsequent cycles: 4
6c[c]	75 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
7a	150 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
7b[c,d]	150 mg	qw on Weeks 1, 2, 4, and 5	None (Weeks 3 and 6 are rest)	Cycle 1: 4 Subsequent cycles: 4
7c[c]	125 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
8a	200 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
8b[c,d]	200 mg	qw on Weeks 1, 2, 4, and 5	None (Weeks 3 and 6 are rest)	Cycle 1: 4 Subsequent cycles: 4
8c[c]	175 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6

Abbreviations: aEC = approving Ethics Committee; DLT = dose-limiting toxicity; IRB = Institutional Review Board; PK = pharmacokinetic(s); qw = weekly; q2w = every 2 weeks.

a – At the highest dose level where major toxicity is observed and that requires a longer recovery period between infusions, a change in the periodicity of dosing (that is, other dosing schedules based on safety and PK considerations) will be agreed upon with the Investigator and communicated to IRBs/aECs.

b – Observation following the fourth infusion in Cohorts 1, 2, 3, and 5 (qw dosing) and the second infusion in Cohort 4 (q2w dosing) in Cycle 1 only. No Cycle 1 observation period for Cohorts 6a, 6c, 7a, 7c, 8a, or 8c. Weeks 3 and 6 of all cycles are rest weeks in Cohorts 6b, 7b, and 8b (qw dosing on Weeks 1, 2, 4, and 5).

c – Concurrently enroll to Cohorts 6b/7b/8b and 6c/7c/8c, should ≥2 subjects in Cohort 6a/7a/8a experience DLT events.

d – For all cycles: Infusions on Weeks 1, 2, 4, and 5, and rest on Weeks 3 and 6.

Following the first cycle of therapy (Cycle 1), subjects may continue to receive IMC-CS4 at the same dose and schedule until there is unequivocal evidence of disease progression or other withdrawal criteria are met. Radiographically confirmed disease progression (that is, numerical disease progression, per Response Evaluation Criteria in Solid Tumors [RECIST]) only is not sufficient to discontinue treatment (refer to "Duration of Treatment" section in this Synopsis for further details). Radiographic assessment of tumor response will be performed at the end of the initial cycle (that is, prior to administration of any study therapy in Cycle 2) and the end of every subsequent cycle; radiographic assessment should be performed prior to the start of a cycle so that results are available before the subject receives a new cycle of treatment. However, if a DLT is observed in Cycle 1 in a subject who is benefitting from treatment, Cycle 2 dosing may be initiated within 4 weeks of Cycle 1, Day 1, with Sponsor approval; in this case, no radiographic disease assessment is required prior to dosing in Cycle 2.

Each cohort will initially enroll at least 3 subjects.

For all cohorts, all subjects who complete the first treatment cycle (that is, receive all scheduled treatments for Cycle 1 and complete the observation period, as needed) or discontinue therapy due to a DLT will be considered evaluable subjects and will be included in the DLT analyses. Subjects who do not complete Cycle 1 for reasons other than a DLT will be replaced for the analysis until the cohort includes 3 evaluable subjects (or 6 evaluable subjects in case of one DLT in the first 3 subjects); however, if benefitting from treatment (that is, no disease progression or other withdrawal criteria), any subject in Cohort 3 and beyond who experiences a DLT may continue to receive IMC-CS4 upon agreement of the Sponsor and according to the dose reduction guidelines for this study.

If the first 3 evaluable subjects in a cohort complete Cycle 1 of therapy with no DLT, dose escalation to the next cohort may proceed. If 1 of the first 3 evaluable subjects in a cohort experiences a DLT, enrollment will proceed until there are at least 6 evaluable subjects in that cohort. If no additional subject experiences a DLT, dose escalation may proceed. If 2 or more subjects experience a DLT in a cohort (whether in the initial 3-subject cohort or following expansion to 6 subjects), dose escalation will not occur and the recommended Phase 2 dose (RP2D) will be determined according to the instructions that follow.

Each subsequent cohort will be opened upon completion of the previous cohort. A safety review meeting will be held prior to each dose escalation.

The provisional RP2D will be defined as the dose level at which pharmacodynamic effects are observed in the absence of clinically relevant toxic effects (that is, measurable pharmacodynamic effects with no DLT in the first 3 subjects or ≤1 DLT in the first 6 subjects enrolled at that dose level). After discussion with the Investigator, the Sponsor may choose to enroll additional subjects at the RP2D.

A DLT is defined as any IMC-CS4-related adverse event (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. The following are considered DLTs:

- Grade 4 neutropenia lasting ≥7 days;
- Grade 3 or 4 neutropenia complicated by fever ≥38.0°C or infection;
- Grade 4 thrombocytopenia;
- Grade 3 thrombocytopenia complicated by hemorrhage;
- Grade 3 or 4 anemia;

- 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), aspartate aminotransferase (AST), and alanine aminotransferase (ALT), without evidence of hepatic injury
  - Transient Grade ≥2 bilirubin elevation in the presence of known liver metastases lasting ≤7 days
  - Laboratory abnormalities that are reversible to Grade ≤2 or baseline levels within 7 days after initial documentation or that are deemed not clinically significant
  - Grade 3 elevation of CK **WITHOUT** elevation in serum and urine myoglobin is **NOT** considered a DLT.

Throughout this protocol, "days" refers to calendar days, unless otherwise indicated.

Study Population:

It is anticipated that approximately 72 subjects will be enrolled in approximately 6 study sites in the United States.

Inclusion/Exclusion Criteria:

Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study:

1. The subject has a histologic or cytologic confirmation of advanced solid tumors that are refractory to standard therapy or for which no standard therapy is available.
2. The subject has measurable or nonmeasurable disease according to the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1).
3. The subject has resolution to Grade ≤1 by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03, of all clinically significant toxic effects of prior chemotherapy, surgery, radiotherapy, or hormonal therapy (with the exception of alopecia).
4. The subject has an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-2.
5. The subject has adequate hematologic function, as defined by:
   - Absolute neutrophil count (ANC) ≥1500/μL;
   - Hemoglobin ≥9 g/dL (5.58 mmol/L); and
   - Platelets ≥100,000/μL.
6. The subject has adequate hepatic function, as defined by:
   - Bilirubin ≤1.5 times the upper limit of normal (× ULN); and
   - AST and ALT ≤2.5 × ULN (or ≤5 × ULN in the presence of known liver metastases).
7. The subject has adequate renal function as defined by creatinine clearance ≥50 mL/min measured either by 24-hour urine collection or calculated using the Cockcroft-Gault formula.
8. The subject must have adequate coagulation function as defined by:
   - International Normalized Ratio (INR) ≤1.5; and
   - Prothrombin time (PT) and partial thromboplastin time (PTT) or activated PTT ≤1.5 × ULN.
9. The subject has CK ≤ ULN.
10. The subject has a life expectancy >3 months.
11. The subject is 18 years of age or older.
12. The subject (women of childbearing potential [WOCBP] or fertile men with partners of childbearing potential) agrees to use adequate contraception during the study period and for 12 weeks after the last dose of study therapy.
13. The subject has provided signed informed consent.

14. The subject is accessible for treatment and follow-up; subjects enrolled in this trial must be treated at the study center.
15. The subject must undergo mandatory biopsies, including one pretreatment and one posttreatment tumor biopsy procedure.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. The subject has experienced acute pathologic fracture or spinal cord compression within 28 days prior to first dose of study therapy.
2. The subject has a known hypersensitivity to monoclonal antibodies or to agents of similar biologic composition as IMC-CS4.
3. The subject has received treatment with any monoclonal antibodies within 4 weeks prior to first dose of study therapy.
4. The subject has undergone a major surgical procedure, open biopsy, radiofrequency ablation, or has experienced a significant traumatic injury within 28 days prior to enrollment.
5. The subject has a history of another primary cancer, with the exception of: a) curatively resected non-melanomatous skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid tumor treated with curative intent, no known active disease present, and no treatment administered during the last 3 years prior to study entry.
6. The subject is receiving concurrent treatment with other anticancer therapy, including other chemotherapy, immunotherapy, chemoembolization, targeted therapy, or any investigational agent within 4 weeks prior to study entry, or radiotherapy within 2 weeks prior to study entry. An exception is that subjects with metastatic breast or prostate cancer who have been on a stable dose (≥28 days) of an approved hormonal agent will not be excluded (ie, they will be eligible). Subjects with breast cancer may also continue with concurrent human epidermal growth factor receptor 2 (HER2)-directed therapy.
7. The subject has known muscle damage due to a primary, traumatic, or other muscle disease.
8. The subject is known to be human immunodeficiency virus (HIV) seropositive.
9. The subject has a known and uncontrolled infection.
10. The subject is known to have active tuberculosis, leishmaniasis, or listeriosis.
11. The subject has a history of and/or current: symptomatic coronary artery disease, confirmed left ventricular ejection fraction (LVEF) ≤50% or any cardiac insufficiency > New York Heart Association (NYHA) class II,* uncontrolled hypertension, or serious cardiac arrhythmia (well-controlled atrial fibrillation is permitted).
12. Subjects with known history or clinical or laboratory evidence of liver disease. Notably, subjects with any of the following liver function abnormalities will be excluded:
    a Cirrhosis with evidence of portal hypertension or bridging fibrosis
    b Alcoholic hepatitis
    c Esophageal varices
    d A history of bleeding esophageal varices
    e Hepatic encephalopathy
    f Ascites related to portal hypertension
    g Chronic viral hepatitis with total serum bilirubin >3 mg/dL
13. The subject has active bleeding.
14. The subject has leukemia or lymphoma.
15. The subject has a known psychiatric illness/social situation (including alcohol and/or drug dependency) that would, in the Investigator's opinion, limit compliance with study requirements.
16. The subject has known or suspected primary brain or leptomeningeal tumors or metastases

(subjects with a history of brain metastases must have received definitive surgery or radiotherapy, be clinically stable, and may not be taking steroids; subjects receiving anticonvulsants are eligible).

17. The subject is pregnant (confirmed by serum beta human chorionic gonadotropin [β-hCG] test performed within 7 days prior to first dose of study therapy) or breastfeeding.
18. The subject has received a solid organ transplant.
19. The subject has any other serious uncontrolled medical disorders, which, in the opinion of the Investigator, would compromise the subject's safety or the ability of the subject to participate in the study.

*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.

Test Product, Dose, and Mode of Administration:

IMC-CS4 drug product (DP) is a sterile, preservative-free injection for I.V. use of IMC-CS4 drug substance (DS) formulated in a histidine buffer at a concentration of 5 mg/mL (100 mg/20-mL vial), administered as a weekly (qw) or every-2-week (q2w) I.V. infusion at the dose specified for each cohort. IMC-CS4 will be infused over a period of 30 minutes at infusion rates that will not exceed 25 mg/minute.

Reference Therapy, Dose, and Mode of Administration:

Not applicable.

Duration of Treatment:

All subjects should continue to receive treatment until there is unequivocal evidence of progressive disease (PD) (per immune-related response criteria), toxicity requiring cessation, protocol noncompliance (in the opinion of the Investigator or Sponsor), withdrawal of consent by the subject, or until other withdrawal criteria are met. Radiographically confirmed disease progression (that is, numerical disease progression, per RECIST) only is not sufficient to discontinue treatment. Subjects with disease progression (per RECIST) but without clinical deterioration at Week 6 (the first response assessment) may continue to receive IMC-CS4, at the discretion of the Investigator; study treatment will be discontinued if, at the next disease assessment (performed at least 4 weeks later), disease progression is unequivocal (that is, radiographically confirmed disease progression alone is sufficient). On the other hand, subjects with disease progression (per RECIST) and with clinical deterioration (unequivocal) at Week 6 (the first response assessment) will be discontinued from study treatment.

Safety Assessments:

The safety and tolerability of study drug will be assessed based on reported AEs (including any DLTs), serious adverse events (SAEs), and laboratory tests. Adverse events will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary and graded using NCI-CTCAE, Version 4.0. Clinical laboratory values will be classified using NCI-CTCAE, Version 4.0 criteria.

Efficacy Assessments:

Radiographic assessment of disease response and tumor assessments, according to RECIST 1.1, will be performed at baseline and at the end of every cycle. Radiographic assessment should be performed prior to the start of a cycle so that results are available before the subject receives a new cycle of treatment. However, if a DLT is observed in Cycle 1 in a subject who is benefitting from treatment, Cycle 2 dosing may be initiated within 4 weeks of Cycle 1, Day 1, with Sponsor approval; in this case, no radiographic disease assessment is required prior to dosing in Cycle 2.

Pharmacokinetic Assessments:

Pharmacokinetic assessments will be performed in order to assess the levels of IMC-CS4 in serum. Parameters to be reported may include, but not be limited to, maximum serum concentration (C_{max}),

trough serum concentration (C_{min}), area under the serum concentration versus time curve (AUC), half-life ($t_{1/2}$), clearance (Cl), and volume at steady state (V_{ss}) of IMC-CS4.

Pharmacodynamic Assessments:

Blood and tissue samples will be taken. Pharmacodynamic analyses may include, but are not limited to, the following parameters:

- Levels of potential circulating and tissue pharmacodynamic markers, including but not limited to, CSF-1, IL-34, MCP-1, and macrophage-specific markers (for example, CD68 and CD163);
- Characterization of blood monocyte subsets by flow cytometry (CD14, CD16, and HLA/DR); and
- Serum markers of bone metabolism (C-terminal cross-linking telopeptide of type I collagen [CTX-I] and procollagen type 1 N-terminal propeptide [P1NP]).

Immunogenicity Assessments:

Blood samples for the assessment of antibodies against IMC-CS4 will be collected for all study subjects at specified time points throughout the study.

Other Serum Assessments:

Blood samples may also be drawn for analyses of LDH, CK, and AP isoenzymes.

Tissue Assessments:

To assess the pharmacodynamic effect of IMC-CS4 administration on tumor-associated myeloid cells, including macrophages, all subjects enrolled in Cohort 2 and beyond will undergo tumor biopsies before study enrollment. For these cohorts, investigators will carry out a tumor (core needle or excisional) biopsy (attempt to obtain at least 3 cores) before starting the treatment and at the end of Cycle 1 (to be done in the week prior to Cycle 2, at the same time as tumor evaluation), if the subject's condition allows it. If an enrolled subject undergoes a pretreatment tumor biopsy but is unable to tolerate a posttreatment tumor biopsy, then a skin punch biopsy will be acceptable. At the time of disease progression, the Investigator will also perform a tumor biopsy if the subject consents to it and if the subject's condition allows it.

Statistical Methods:

All enrolled subjects who received at least one dose of IMC-CS4 will be included in the safety population. Subjects who complete the initial cycle of therapy or experience a DLT will be included in the DLT population. The DLT population will be used for the determination of the RP2D, including evaluation of DLTs. All other variables (including demographic and baseline subject characteristics, efficacy and safety variables) will be analyzed using the safety population.

Demographic and baseline subject characteristics will be summarized using descriptive statistics.

The number of subjects who experience any DLT will be presented based on all DLT-evaluable subjects (DLT population).

Adverse events will be summarized by MedDRA System Organ Class and Preferred Term, classified from verbatim terms. The incidence and percentage of subjects with at least one occurrence of a Preferred Term will be included, according to the most severe NCI-CTCAE, Version 4.0 grade. Causality (relationship to study drug) will be summarized separately. Duration of AE will be determined and included in listings along with action taken and outcome.

Laboratory results will be classified according to NCI-CTCAE, Version 4.0. Laboratory results not corresponding to an NCI-CTCAE, Version 4.0 term will not be graded. Laboratory toxicity shifts from baseline to worst grade will be provided. The results from physical examination, vital sign measurement, and other assessments will be tabulated.

Tumor response data will be summarized, if appropriate.

Version History:

Date of Original Approved Protocol: 14 December 2010

Version 2.0: 01 March 2011

Version 3.0: 28 March 2012

Version 4.0: 08 January 2013

Version 5.0: 02 May 2013

Version 6.0: 31 March 2014

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LIST OF IN-TEXT FIGURES

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LIST OF ABBREVIATIONS AND DEFINITIONS

ADA	anti-drug antibody
AE	adverse event: Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An 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.
aEC	approving Ethics Committee
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AP	alkaline phosphatase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the serum concentration versus time curve
β-hCG	beta human chorionic gonadotropin
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
Cl	clearance
C_{max}	maximum serum concentration
C_{min}	trough serum concentration
collection database	A computer database where clinical trial data are entered and validated.
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.
CR	complete response
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-1	colony-stimulating factor-1
CSF-1R	colony-stimulating factor-1 receptor (also known as CSF-1 receptor)
CT	computed tomography (scan)
CTX-I	C-terminal cross-linking telopeptide of type I collagen
DLT	dose-limiting toxicity
DP	drug product
DS	drug substance
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EDC	electronic data capture
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last subject.
enroll	Subjects who are enrolled in the trial are those who have been assigned to a dose cohort.
enter	Subjects who are entered in the trial are those who have signed the informed consent form directly or through their legally acceptable representatives.
FDA	United States Food and Drug Administration

FDG	fluorodeoxyglucose
FITC	fluorescein isothiocyanate
FNA	fine-needle aspiration
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma glutamyl transferase
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	identification
IgG1	immunoglobulin G, subclass 1
IL-34	interleukin-34
INR	International Normalized Ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
I.V.	intravenous(ly)
K_d	dissociation constant
LDH	lactate dehydrogenase
LFT	liver function test
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
LVEF	left ventricular ejection fraction
MedDRA®	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition (scan)
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	non-evaluable
NK	natural killer
NOAEL	no-observed-adverse-effect level
NYHA	New York Heart Association
P1NP	procollagen type 1 N-terminal propeptide
PD	progressive disease; also, pharmacodynamic markers (in tables only)
PET	positron emission tomography
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QTc	corrected QT (interval)
qw	weekly
q2w	every 2 weeks
q3w	every 3 weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
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.
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.
screen failure	A subject who does not meet one or more criteria required for participation in a trial.
SD	stable disease
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TK	toxicokinetic(s)
TNM	tumor, nodes, and metastases
TRAP-5b	tartrate-resistant acid phosphatase 5b
ULN	upper limit of normal
V_d	volume of distribution
V_{ss}	volume at steady state
WOCBP	women of childbearing potential

1 INTRODUCTION

1.1 The CSF-1 Receptor and the Treatment of Cancer

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 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; Lin et al. 2006). In addition to the effects of CSF-1R on macrophages, there are reports of CSF-1R expression on cancer cells, particularly leukemias of myeloid origin, which proliferate in response to CSF-1 (Dubreuil et al. 1988; Tang et al. 1992; Kacinski 1995). Furthermore, CSF-1 and CSF-1R are required for osteoclast formation and activity in bone metastases, osteoclasts being a major component leading to bone erosion and pain in cancer patients (Ross 2006). Inhibition of CSF-1R signaling results in lessening of osteolytic bone destruction in mouse models of bone metastasis (Ohno et al. 2006; Manthey et al. 2009). While CSF-1R levels are infrequently increased in tumors compared to 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 (Lawicki et al. 2006; Mroczko et al. 2007; Zhu et al. 2008). These data suggest that targeting CSF-1R has potential to limit cancer progression.

1.2 IMC-CS4

IMC-CS4 is a recombinant human monoclonal antibody of the immunoglobulin G, subclass 1 (IgG1) targeting CSF-1R. CCI [redacted] IMC-CS4 was selected for having high affinity binding to CSF-1R and its ability to block the binding of

CSF-1 and IL-34 to CSF-1R. The IMC-CS4 heavy and light chain antibody genes were then engineered into a suitable vector for expression in Chinese hamster ovary cells. Subcloning techniques were utilized to generate a stable clone expressing high levels of IMC-CS4 for manufacturing purposes.

1.3 Nonclinical Studies

Detailed results from all relevant studies conducted to assess the nonclinical pharmacology, pharmacokinetics (PK), and toxicology of IMC-CS4 are provided in the current Investigator's Brochure (IB).

IMC-CS4 prevents the ligands CSF-1 and IL-34 from binding to CSF-1R with CCI [redacted] respectively, 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]

Because IMC-CS4 does not recognize the mouse CSF-1R, the use of a mouse surrogate antibody, CS7, was required to target macrophages in proof of principle preclinical pharmacology studies. The effects of CS7 in several tumor models of breast, prostate, and endometrial cancer established in mice with human and murine tumor cells were evaluated. CS7 was efficacious in decreasing tumor size in 3 xenograft breast cancer models and 2 syngeneic mammary cancer models in mice. Additionally, CS7 inhibited tumor growth in a prostate and endometrial tumor model. Utilizing data from testing CS7 in a panel of models, antitumor efficacy was found to be significantly better against tumors established with cell lines that produce CSF-1. CS7 effectively depleted tumor macrophages in all tumor models evaluated. However, CS7 was particularly efficacious in those models in which tumor cells expressed high levels of CSF-1. These data suggest that tumors secreting CSF-1 may be most responsive to therapy with IMC-CS4. In line with the potential utility of IMC-CS4 as a combination therapy, CS7 increased the antitumor effects of targeted agents such as trastuzumab, doxorubicin, paclitaxel, and docetaxel in preclinical models. In addition to antitumor effects, antibodies to CSF-1R decrease osteolytic activity by osteoclasts in the bone. In a bone metastasis model where breast cancer cells were injected into the mouse tibia, treatment with CS7 not only decreased tumor burden but also minimized bone erosion.

As stated above, the antitumor effects of IMC-CS4 mediated by targeting macrophages could not be evaluated in murine models. However, CCI [redacted]

1.3.1 Pharmacokinetics

IMC-CS4 was administered to mice at 20 mg/kg and to cynomolgus monkeys at dose levels that ranged from 10 to 180 mg/kg. The PK of IMC-CS4 in cynomolgus monkeys were characterized by a relatively long serum half-life ($t_{1/2}$) after single (183-275 hours) or multiple doses (158-470 hours), which were substantially longer than observed in CD-1 mice (110 hours). Accumulation (approximately 2-fold) of IMC-CS4 was evident after repeated once weekly (qw) dosing, suggesting that accumulation may similarly occur in humans depending on the frequency of dosing. The estimated CCI [redacted] In the cynomolgus monkey studies, 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 IMC-CS4, suggesting that CSF-1 is a pharmacodynamic marker of IMC-CS4 exposure. However, in contrast to the IMC-CS4 levels, CSF-1 levels did not increase proportionally to the increase in IMC-CS4 dose. The concentration of CSF-1 reached apparent maximal levels in all dose groups after the first dose, typically between 24 and 168 hours following administration of IMC-CS4. This observation suggests that the CCI [redacted]

In the repeat-dose cynomolgus monkey toxicity study, CCI [redacted] ADA in the other animals did not appear to impact the IMC-CS4 concentrations.

1.3.2 Target IMC-CS4 Blood Level for Nonclinical Efficacy

One of the main pharmacological effects of 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 IMC-CS4 does not bind to murine CSF-1R, a surrogate antibody, CS7, was developed and utilized in order to examine pharmacokinetic/pharmacodynamic (PK/PD) relationships. The binding affinity of CS7 to murine CSF-1R (K_d = 0.13nM) is 6-fold greater than that of 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 (CCI [redacted]), monocyte differentiation (CCI [redacted]), and inhibition of monocyte proliferation (CCI [redacted]). Therefore, CS7 and 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 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. IMC-CS4 was evaluated in the leukemia model established following 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 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. Because the clinical investigation is conducted in solid tumors, this concentration was initially regarded as a conservative target concentration for efficacy.

1.3.3 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 IMC-CS4. The nonclinical safety assessment of IMC-CS4 was conducted in cynomolgus monkeys, which was considered a relevant model for the nonclinical safety evaluation of 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 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 IMC-CS4 by I.V. infusion, the intended clinical method of administration, using the most aggressive dosing schedule (qw) in the planned clinical investigations of IMC-CS4. The pivotal study included evaluations of relevant safety pharmacology parameters. Because of an anticipated effect of 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 $CD68^+$ macrophages in liver and spleen was 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 IMC-CS4 have not been conducted.

1.3.3.1 Tissue Cross Reactivity

A comprehensive tissue cross-reactivity study was conducted in cryosections of normal human and cynomolgus monkey tissues using a fluorescein isothiocyanate (FITC)-labeled form of IMC-CS4, designated IMC-CS4-FITC, applied to cryosections of normal human and cynomolgus monkey tissues at 2 concentrations (5 µg/mL and 0.5 µg/mL).

The tissue binding and distribution profile of IMC-CS4-FITC staining observed in the human and cynomolgus monkey tissue panels was generally consistent with reported sites of CSF-1R expression, and no important, unexpected (that is, off-target) binding was observed. CCI

[redacted]

Although CSF-1R is expressed mainly by cells of myeloid and mononuclear phagocytic lineage (for example, macrophages and monocytes, and glomerular mesangial cells), expression has also been reported in the trophoblasts (Mori et al. 1990; Pampfer et al. 1992; Jokhi et al. 1993; Watanabe et al. 2001; Hume 2006; Guo and Cantley 2010).

1.3.3.2 Single-Dose Toxicity

Single-dose I.V. administration of 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). Sustained, dose-proportional exposure to IMC-CS4 was generally observed throughout a 14-day observation period at all dose levels following administration with no apparent sex differences. A relatively long $t_{1/2}$ was observed for IMC-CS4, ranging from approximately 183 to 275 hours.

The key toxicological findings after a single administration of IMC-CS4 were elevations in serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and lactate dehydrogenase (LDH) on Days 2, 7 and 15 after dosing. Elevations in ALT were

generally minimal at the lowest dose level (10 mg/kg), whereas generally minimal to moderate elevations were observed in ALT at 40 and 140 mg/kg and in AST and LDH across all dose groups. The elevations in ALT, AST, and LDH observed on Day 7 declined towards baseline levels in most animals by the end of the observation period, suggesting reversibility of these effects. No histological changes in the liver were noted to correlate with the increases in ALT, AST, and LDH, nor were any changes noted in liver functional parameters (that is, alkaline phosphatase [AP], bilirubin, coagulation). Therefore, based on the small magnitude of the elevations, and the absence of histological or functional changes, the increases in ALT, AST, and LDH were not considered adverse.

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

The no-observed-adverse-effect level (NOAEL) in this study was considered to be the highest dose tested of 140 mg/kg. This dose corresponded to Day 1 mean C_{168hr} of 1097 µg/mL, mean maximum serum concentration (C_{max}) of 4010 µg/mL, and mean area under the serum concentration versus time curve $(AUC)_{0\text{-}168hr}$ of 303127 µg•hr/mL for males and females.

1.3.3.3 Repeat-Dose Toxicity

In the pivotal repeat-dose toxicity, TK, and immunogenicity study of IMC-CS4, doses of 0, 20, 60, and 180 mg/kg/dose IMC-CS4 were administered by I.V. infusion qw 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, 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 $CD68^+$ cells in liver and spleen was also conducted.

Intravenous infusion of IMC-CS4 was generally well tolerated at all dose levels. Sustained, dose-proportional to slightly-greater-than-dose-proportional increases in exposure to IMC-CS4 were generally observed, and no sex differences in exposure were apparent. Moderate accumulation (approximately 2-fold) of IMC-CS4 occurred after repeated administration. CCI [redacted]

As noted in the single-dose exploratory study, CCI [redacted]

The key toxicological findings attributed to 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 IMC-CS4, possibly due to elevations in circulating CSF-1 levels noted during the study.

Elevations in ALT after the last dosing of 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 to baseline. No histological changes in the liver were noted to correlate with the transaminases increases, nor

were any changes in liver functional parameters (that is, AP, bilirubin, 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. Similar elevations in serum enzyme levels have also been observed when treating with other pharmacological agents targeting CSF-1R (MacDonald et al. 2010) or CSF-1 (Radi et al. 2011).

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 IMC-CS4 treated groups. Variability in NK cell numbers in the peripheral blood of animals in all dose groups (including control) precluded any definitive relationship with 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 A:G 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 the small magnitude of changes.

Anatomic pathology changes attributed to the administration of 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 60 mg/kg male), bone marrow lymphoid aggregates (one male, one female at 180 mg/kg), and Kupffer cell hypertrophy/hyperplasia (primarily minimal, all male dose groups, one 60 mg/kg female). 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. [redacted] CCI [redacted] These changes were not considered adverse because of the small magnitude of changes.

Slight to moderate periorbital swelling was observed primarily during the recovery phase in all IMC-CS4-treated groups. 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 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 IMC-CS4. These clinical signs were not considered adverse based on their limited impact to the overall health of the animal.

Based on the absence of any definitive IMC-CS4-related adverse findings, the NOAEL for IMC-CS4 administered via 15-minute I.V. infusion qw on 4 occasions was considered to be 180 mg/kg/dose (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).

1.4 Dose Rationale

1.4.1 Rationale for Starting Dose

The optimal dose and regimen of IMC-CS4 in humans are not known. The proposed starting dose and regimen of IMC-CS4 was 2.5 mg/kg administered qw by I.V. infusion. This starting dose was based on the following rationale:

- IMC-CS4 was well tolerated in cynomolgus monkeys when administered qw at 20, 60, or 180 mg/kg by I.V. infusion for 4 weeks. The key toxicological findings included periorbital swelling, increased serum transaminases, and immunomodulatory effects on monocytes, neutrophils, spleen, Kupffer cells, and bone marrow. As none of the observed effects were considered adverse, the NOAEL was identified as 180 mg/kg.
- Most antibodies and other large proteins scale best between species when doses are compared directly in mg/kg (FDA 2005). Given the similar binding affinities of IMC-CS4 to human and monkey CSF-1R, this approach predicts that 20 mg/kg in humans will have similar findings as in the monkey at the same dose, and that a dose equal to one-eighth of this (2.5 mg/kg), would be an acceptable and safe starting dose for this first-in-human study in oncologic indications. This starting dose is 72-fold lower than the NOAEL (180 mg/kg).
- A noncompartmental PK analysis of IMC-CS4 in cynomolgus monkeys of serum sampled following the fourth infusion, where the drug is at or approaching steady state, indicated a mean (sex-combined) elimination half-life of 158, 243, and 470 hours (approximately 7 to 20 days) for the 20, 60, and 180 mg/kg doses, respectively, and is supportive of a dosing interval of equal to or greater than qw.
- The target serum trough concentration for IMC-CS4 based on antitumor activity of the surrogate antibody CS7 in a murine model of breast cancer is approximately 425 µg/mL.

To further support identification of the appropriate IMC-CS4 dose and regimen to attain these serum concentrations, simulations based on the mathematical modeling of serum concentration data of IMC-CS4 derived from the cynomolgus monkey PK study were used. A one-compartment model best fit the data. The simulations were based on the following assumptions:

1. The one-compartmental model was applicable to the simulated doses.
2. PK parameters obtained from the 20-mg/kg dose monkey PK study and elimination half-life values were applicable to human PK dosing and regimens.
3. IMC-CS4 drug levels following the fourth infusion were at or near steady state.
4. No inter-subject or intra-subject variability was accounted for.

The simulations suggest that doses of 20 mg/kg IMC-CS4 every week achieve target minimum trough levels of 480 µg/mL IMC-CS4, which approximates the trough level associated with antitumor activity in nonclinical tumor xenograft models (425 µg/mL).

Based on the above, subjects in the first cohort were administered a dose of 2.5 mg/kg qw.

1.4.2 Clinical Experience from Cohort 1

IMC-CS4 was administered to 6 subjects at the starting dose of 2.5 mg/kg qw. Two of the first 3 subjects experienced Grade 2 creatine kinase (CK) serum level elevations, associated with elevated levels of AST (Grade 1-2), LDH, and CSF-1. A muscle biopsy was performed, independently of the protocol, in one of the subjects with elevated CK values and did not reveal any signs of rhabdomyolysis, nor of muscle damage of inflammatory or non-inflammatory origin. However, because of the serum enzyme elevation and subjects' general conditions, Cycle 1 was not completed as per protocol in 2 of the 3 subjects.

Therefore, 3 additional subjects were ultimately recruited (a total of 3 of 6 subjects completed Cycle 1). These subjects also exhibited elevated levels of CK, AST, and LDH, in agreement with data obtained in various experimental models of CSF-1R blockade (Mori et al. 1990) and with nonclinical observations (in cynomolgus monkeys). In one subject, the serum levels of CK and AST reached Grade 3; however, this event was not classified as a dose-limiting toxicity (DLT) because of the lack of clinical signs and symptoms of organ toxicity upon comprehensive clinical evaluation of the subject. Enzyme levels decreased upon discontinuation of IMC-CS4, indicating that this effect was temporary and reversible.

Overall, in the cohort of 6 subjects treated with IMC-CS4 administered at an I.V. dose of 2.5 mg/kg every week, the following laboratory findings were consistently reported:

- Elevation of CK ranging from Grade 1-3;
- Elevation of AST ranging from Grade 1-3, in the absence of a significant increase in ALT (except in 1 of 6 subjects) and an increase in bilirubin;
- Elevated levels of LDH ranging from 3- to 7-fold above the upper limit of normal (ULN);
- Elevation of CSF-1 levels above normal values.

The concomitant elevation in CSF-1 serum levels and the increase in the serum levels of CK, LDH, and AST suggest pharmacodynamic activity of IMC-CS4. Since preclinical studies with IMC-CS4 in monkeys demonstrated a dose-response correlation between the dose of IMC-CS4 and the increase in serum enzyme levels, a dose escalation was considered likely to result in a DLT. Therefore, it was considered medically prudent not to dose escalate further as initially planned.

In order to better characterize the IMC-CS4 dose-response effect on the monocyte / macrophage system and on various serologic and hematologic parameters, the dosing scheme and schedule was amended in Protocol Amendment Version 3.0 to reflect dose reductions and prolonged administration intervals as follows: Under Version 2.0 of the protocol, dose escalation was to begin at 2.5 mg/kg in Cohort 1 and proceed to 5, 10, 20, and 30 mg/kg (all qw) in Cohorts 2 to 5, respectively. Following completion of Cohort 1 (2.5 mg/kg), the dose-escalation scheme was revised to 0.3 mg/kg qw in Cohort 2, 0.6 mg/kg qw in Cohort 3, 1.25 mg/kg every 2 weeks (q2w) in Cohort 4, 1.25 mg/kg qw in Cohort 5, and 2.5 mg/kg q2w in Cohort 6 (a newly added cohort). The addition of q2w dosing was deemed reasonable based on the relatively long half-life observed in cynomolgus monkeys.

Further rationale for the revised dose-escalation scheme was as follows. The second cohort started at approximately an 8-fold lower dose level (0.3 mg/kg administered qw) than the study starting dose (2.5 mg/kg qw in Cohort 1). Additionally, certain doses (1.25 and 2.5 mg/kg) were to be administered on both qw and q2w regimens to facilitate PK/PD characterization. Upon completion of all 6 planned cohorts, the PK/PD and safety profiles were to be evaluated to assess if further dose escalation and/or regimens were warranted to determine the recommended Phase 2 dose (RP2D).

1.4.3 Clinical Experience from Cohorts 2 through 5

This section describes the clinical experience after the revised dose-escalation scheme was implemented in Protocol Amendment Version 3.0, specifically, the clinical observations for Cohorts 2, 3, 4, and 5. No DLTs were observed in Cohorts 2 and 3. The clinical data generated for subjects treated in Cohorts 2 and 3 indicate that IMC-CS4 is safe and well tolerated when administered as 4 qw doses (0.3 or 0.6 mg/kg) followed by 2 weeks of recovery.

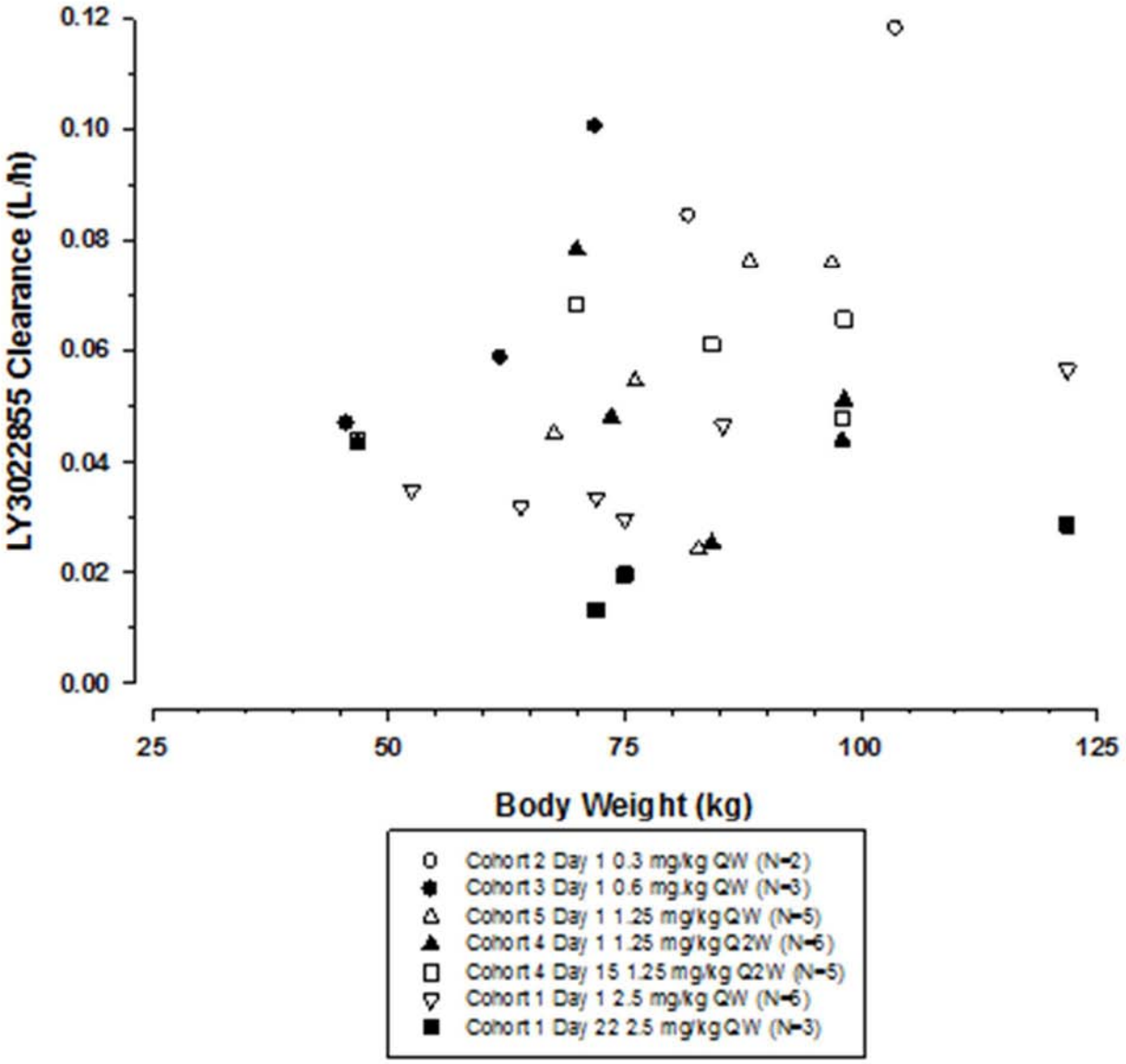
In Cohort 4 (1.25 mg/kg q2w), one subject with a history of cardiac dysfunction developed a Grade 3 left ventricular systolic dysfunction (verbatim) after one dose of IMC-CS4; the event was considered by the Investigator to be related to IMC-CS4. Because DLT could not be ruled out for this event, 2 additional subjects were enrolled into Cohort 4 and completed protocol-defined therapy without experiencing DLT events.

In Cohort 5 (1.25 mg/kg qw), 2 subjects experienced DLT events: 1 subject was diagnosed with rhabdomyolysis complicated by acute renal failure following 1 dose of IMC-CS4, and the second subject was diagnosed with pancreatitis after receiving 3 doses of IMC-CS4. The subject diagnosed with pancreatitis slowly developed symptoms in conjunction with rising amylase and lipase levels during the course of treatment; these signs and symptoms, which were consistent with pancreatitis, resolved upon discontinuation of IMC-CS4 and initiation of systemic steroids. As a result of these 2 DLT events, the RP2D was determined to be 1.25 mg/kg every 2 weeks.

1.4.4 Exploring Non-Weight-Based Dosing (Cohorts 6a through 8c)

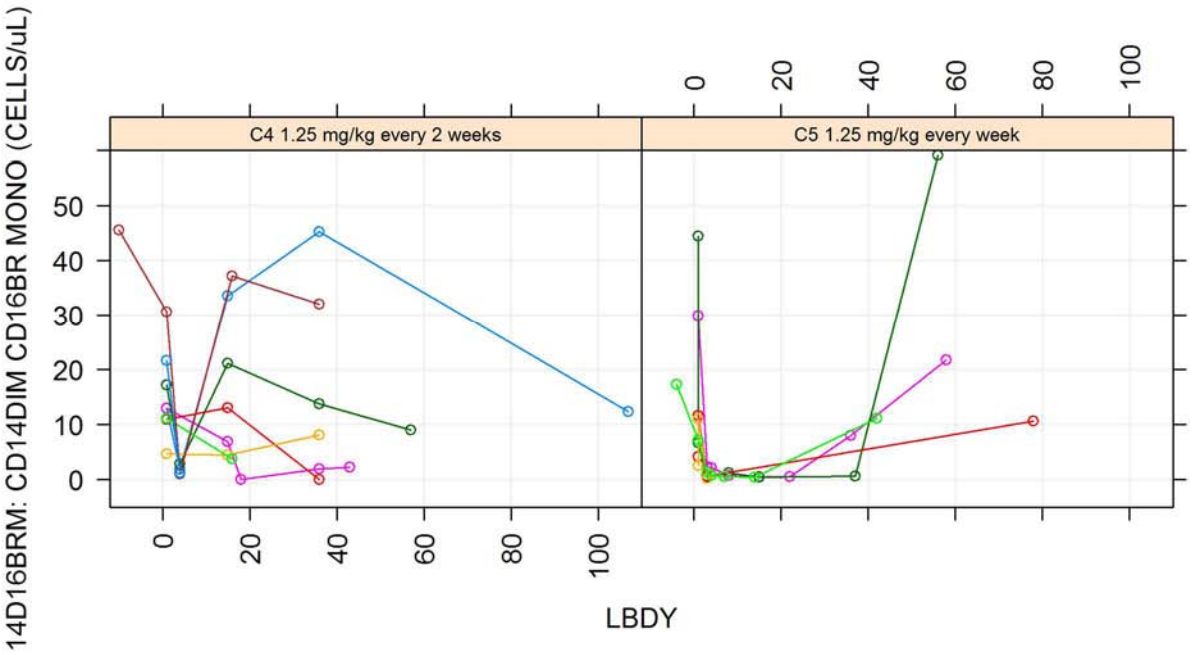
Exploratory graphical analysis of the pharmacokinetics of IMC-CS4 in Cohorts 1 to 5 indicates no clear relationship between body weight and drug clearance (Figure 1). Furthermore, weekly dosing results in sustained elevation of CSF-1, an indicator of target engagement, for the duration of the dosing period (Figure 2). In contrast, dosing every 2 weeks allows CSF-1 levels to return to baseline, indicating reduced target engagement with a more intermittent dosing schedule. Therefore, additional cohorts are being added in this protocol amendment, Version 7.0, to evaluate safety, pharmacokinetics, and pharmacodynamics of non-weight-based dosing of IMC-CS4 administered on a weekly schedule. As was done for weight-based dosing cohorts, doses for non-weight-based dosing cohorts will be escalated to identify RP2D. To accommodate these new non-weight-based dosing cohorts, the definition of DLT has been

revised and an algorithm added to initiate steroid therapy early during the course of an immune-related adverse event (irAE) (refer to Section 9.1.1 for additional details).



Abbreviations: QW = weekly; Q2W = every 2 weeks.

Figure 1. **Reported body weight versus LY3022855 drug clearance (as determined using non-compartmental analysis) for eligible subject data from Study JSCA (IMCL CP24-1001.)**



Profile plot of CD14DIM CD16BR MONO (CELLS/uL)
Program Location: F:/lillyce/prd/ly3022855/i5f_ie_jsca/misc1/programs_nonsdd/CS4_jsca_CD14dimCD16br_C4-C5.r
Data Location: F:/lillyce/prd/ly3022855/i5f_ie_jsca/misc1/data/shared/custom/dm.csv
Data Location: F:/lillyce/prd/ly3022855/i5f_ie_jsca/misc1/data/shared/custom/lb.csv
Output Location: F:/lillyce/prd/ly3022855/i5f_ie_jsca/misc1/programs_nonsdd/tfl_output/CS4_JSCA_CD14dimCD16br_C4-C5.rtf

Figure 2. Profile review of $CD14^{DIM}$ $CD16^{BR}$ MONO (cells/µL).

1.5 Human Experience

This is the first study of IMC-CS4 in humans. Limited data are available from this study to date, and are described in Sections 1.4.2 and 1.4.3.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (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 serious adverse events (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.

NOTE:

Protocol Amendment Version 7.0 describes additional cohorts for non-weight-based dosing of IMC-CS4, which will be referred to as Part B of the study. Cohorts described in the protocol prior to Protocol Amendment Version 7.0 (that is, for weight-based dosing of IMC-CS4) will now be referred to as Part A of the study. Refer to Section 4.1 for details of the dose assignments for Parts A and B.

Throughout the protocol, information relevant only to Part A (weight-based dosing) or only to Part B (non-weight-based dosing) is indicated as such. Any information not indicated as "Part A only" or "Part B only" is relevant to both parts.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are to establish the safety profile and characterize the pharmacokinetic (PK) profile of IMC-CS4 in the treatment of subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy is available.

2.2 Secondary Objectives

The secondary objectives of this study are:

- Part A only – To define the recommended Phase 2 dose (RP2D) using weight-based dosing;
- Part B only – To define the RP2D using non-weight-based dosing;
- To characterize the pharmacodynamic profile of IMC-CS4 on circulating levels of CSF-1; and
- To assess the development of antibodies against IMC-CS4 (immunogenicity).

2.3 Exploratory Objectives

The exploratory objectives of this study are:

- To assess pharmacodynamic response markers including, but not limited to, interleukin-34 (IL-34) and MCP-1;
  - To assess the impact of IMC-CS4 monotherapy on LDH, CK, and AP isoenzymes;
  - To assess the pharmacodynamic impact of IMC-CS4 on selected cellular and molecular markers to establish a potential correlation with safety and antitumor activity;
  - To assess the pharmacodynamic impact of IMC-CS4 on various components of the monocyte-macrophage system in hematologic or tissue specimens;
  - To assess the impact of IMC-CS4 monotherapy on bone metabolism; and
  - To assess the antitumor activity of IMC-CS4 as monotherapy in the treatment of advanced solid tumors.

3 STUDY POPULATION SELECTION

3.1 Study Population

Subjects will be recruited from a population of cancer subjects treated at the investigational centers. A record of the most recent pretreatment evaluations will be reviewed to determine the eligibility of a subject for this study.

3.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study:

1. The subject has a histologic or cytologic confirmation of advanced solid tumors that are refractory to standard therapy or for which no standard therapy is available.
2. The subject has measurable or nonmeasurable disease according to the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1; see Section 11).
3. The subject has resolution to Grade ≤1 by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03, of all clinically significant toxic effects of prior chemotherapy, surgery, radiotherapy, or hormonal therapy (with the exception of alopecia).
4. The subject has an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-2.
5. The subject has adequate hematologic function, as defined by:
   - Absolute neutrophil count (ANC) ≥1500/μL;
   - Hemoglobin ≥9 g/dL (5.58 mmol/L); and
   - Platelets ≥100,000/μL.
6. The subject has adequate hepatic function, as defined by:
   - Bilirubin ≤1.5 times the upper limit of normal (× ULN); and
   - AST and ALT ≤2.5 × ULN (≤5 × ULN in the presence of known liver metastases).
7. The subject has adequate renal function as defined by creatinine clearance ≥50 mL/min measured either by 24-hour urine collection or calculated using the Cockcroft-Gault formula.
8. The subject must have adequate coagulation function as defined by:
   - International Normalized Ratio (INR) ≤1.5; and
   - Prothrombin time (PT) and partial thromboplastin time (PTT) or activated PTT ≤1.5 × ULN.
9. The subject has CK ≤ ULN.
10. The subject has a life expectancy >3 months.
11. The subject is 18 years of age or older.
12. The subject (women of childbearing potential [WOCBP] or fertile men with partners of childbearing potential) agrees to use adequate contraception during the study period and for 12 weeks after the last dose of study therapy.
13. The subject has provided signed informed consent.

14. The subject is accessible for treatment and follow-up; subjects enrolled in this trial must be treated at the study center.
15. The subject must undergo mandatory biopsies, including one pretreatment and one posttreatment tumor biopsy procedure (refer to tumor biopsy Section 7.2.1.1).

3.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. The subject has experienced acute pathologic fracture or spinal cord compression within 28 days prior to first dose of study therapy.
2. The subject has a known hypersensitivity to monoclonal antibodies or to agents of similar biologic composition as IMC-CS4.
3. The subject has received treatment with any monoclonal antibodies within 4 weeks prior to first dose of study therapy.
4. The subject has undergone a major surgical procedure, open biopsy, radiofrequency ablation, or has experienced a significant traumatic injury within 28 days prior to enrollment.
5. The subject has a history of another primary cancer, with the exception of a) curatively resected non-melanomatous skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid tumor treated with curative intent, no known active disease present, and no treatment administered during the last 3 years prior to study entry.
6. The subject is receiving concurrent treatment with other anticancer therapy, including other chemotherapy, immunotherapy, chemoembolization, targeted therapy, or any investigational agent within 4 weeks prior to study entry, or radiotherapy within 2 weeks prior to study entry. An exception is that subjects with metastatic breast or prostate cancer who have been on a stable dose (≥28 days) of an approved hormonal agent will not be excluded (ie, they will be eligible). Subjects with breast cancer may also continue with concurrent human epidermal growth factor receptor 2 (HER2)-directed therapy.
7. The subject has known muscle damage due to a primary, traumatic, or other muscle disease.
8. The subject is known to be human immunodeficiency virus (HIV) seropositive.
9. The subject has a known and uncontrolled infection.
10. The subject is known to have active tuberculosis, leishmaniasis, or listeriosis.
11. The subject has a history of and/or current: symptomatic coronary artery disease, confirmed left ventricular ejection fraction (LVEF) ≤50% or any cardiac insufficiency > New York Heart Association (NYHA) class II,* uncontrolled hypertension, or serious cardiac arrhythmia (well-controlled atrial fibrillation is permitted).
12. Subjects with known history, or clinical or laboratory evidence of, liver disease. Notably, subjects with any of the following liver function abnormalities will be excluded:
    a Cirrhosis with evidence of portal hypertension or bridging fibrosis
    b Alcoholic hepatitis
    c Esophageal varices
    d A history of bleeding esophageal varices
    e Hepatic encephalopathy
    f Ascites related to portal hypertension

g Chronic viral hepatitis with total serum bilirubin >3 mg/dL.

13. The subject has active bleeding.
14. The subject has leukemia or lymphoma.
15. The subject has a known psychiatric illness/social situation (including alcohol and/or drug dependency) that, in the Investigator's opinion, would limit compliance with study requirements.
16. The subject has known or suspected primary brain or leptomeningeal tumors or metastases (subjects with a history of brain metastases must have received definitive surgery or radiotherapy, be clinically stable, and may not be taking steroids; subjects receiving anticonvulsants are eligible).
17. The subject is pregnant (confirmed by serum beta human chorionic gonadotropin [β-hCG] test performed within 7 days prior to first dose of study therapy) or breastfeeding.
18. The subject has received a solid organ transplant.
19. The subject has any other serious uncontrolled medical disorders that, in the opinion of the Investigator, would compromise the subject's safety or the ability of the subject to participate in the study.

*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.

Throughout this protocol, "days" refers to calendar days, unless otherwise indicated.

3.4 Subject Enrollment

All subjects meeting the eligibility requirements will be considered for enrollment regardless of race, religion, or sex. Subjects will be recruited from a population of subjects with advanced solid tumors who have been previously evaluated at the participating institution or have been referred from other institutions. The Investigator will review the subject's medical record to determine his or her eligibility for the study. The criteria for enrollment must be followed explicitly. Exceptions to the eligibility criteria may not be granted by the Investigator or the Sponsor. If a subject who does not meet enrollment criteria is unintentionally enrolled, the Investigator informs the subject of the inadvertent enrollment, and the Sponsor or its designee must be contacted. In these rare cases, the Investigator must obtain documented approval from the Sponsor to allow the subject to continue in the study.

Subjects will be made aware of the protocol, its specific aims and objectives, and the potential risks and benefits the subject may incur. Each subject will be required to read, agree to, and sign a current Institutional Review Board (IRB)/approving Ethics Committee (aEC)-approved ICF prior to being enrolled and before any study-related procedure is performed. There will be no financial compensation for subjects enrolling on this protocol.

Individuals who do not meet the criteria for participation in this study (screen failure) within 14 days after study entry may be rescreened once. Sites are responsible for determining if the subject must sign a new ICF, based on regulatory and institutional or central IRB/aEC guidelines. All subjects who have signed an informed consent form will be assigned a study identification (ID) number.

Screening and other pretreatment evaluations will be performed as described in Section 7.1.

3.5 Method of Assigning Subjects to Treatment

Sites will enroll subjects into the study via facsimile and/or e-mail to the Sponsor. Each subject will be assigned a unique study ID number. The study ID number is to be recorded on all electronic case report forms (eCRFs) and correspondence regarding the subject, and will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other study-related data. Once the study ID number is obtained, the Investigator must administer the first dose of investigational agent to the subject within 7 days. Specific instructions regarding the enrollment and registration process will be provided in a separate procedure manual.

3.6 Blinding

This is an open-label Phase 1 dose-escalation study; no blinding will be utilized.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This open-label, dose-escalation, Phase 1 study will enroll a total of approximately 72 subjects to 2 parts - Parts A and B, in approximately 6 study sites in the United States. Part A consists of dose escalation of IMC-CS4 using weight-based dosing (Part A enrollment is planned to be discontinued as of 30 September 2015); Part B will consist of dose escalation of IMC-CS4 using non-weight-based dosing; the actual enrollment will depend on the number of DLTs observed and the resultant size of each cohort. Throughout this protocol, any information not indicated as "Part A only" or "Part B only" is relevant to both parts. In Part A, additional subjects were enrolled to the maximum tolerated dose (MTD) of 1.25 mg/kg q2w, in order to help establish the safety profile of IMC-CS4. In Part B, the cohort associated with the dose identified as the MTD may be expanded (up to a maximum of 12 evaluable subjects) in order to help establish the safety profile of IMC-CS4. Enrollment to the MTD expansion cohort may cease if the Sponsor (after conferring with the investigators) deems the toxicity profile precludes further enrollment. Refer also to Section 4.1.2.

Dose cohorts, including dose and dosing schedule, are summarized in Table 1. For each cohort, one cycle is 6 weeks. In each cohort, subjects will receive IMC-CS4 by I.V. infusion (with an observation period, in Part A only, for weekly [qw] and every-2-week [q2w] cohorts, in Cycle 1 only, as described in Table 1). Beginning with Protocol Amendment Version 7.0, enrollment to Part B of the study will start with Cohort 6a, then escalate to Cohorts 7a and 8a. In the event 2 or more subjects on Cohort 6a experience a DLT event, concurrent enrollment of 3 to 6 subjects to each of Cohorts 6b and 6c will start and further dose escalation (that is, to Cohort 7a) will cease. Likewise, the same algorithm will apply for Cohorts 7a and 8a if enrollment to those cohorts occurs. Subjects will be assigned to "b" and "c" cohorts by the Sponsor. Note that there will be no Cycle 1 observation period for Part B cohorts. No intra-subject dose-escalation is permitted for any subject. Dose escalation may be reduced or ceased at any time based on safety and PK behavior.

Table 1. Dose Cohort Assignment

Cohort	Dose Level	Dosing Schedule[a]	Cycle 1 Observation Period[b]	Number of Infusions
Part A (weight-based dosing)				
1	2.5 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
2	0.3 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
3	0.6 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
4	1.25 mg/kg	q2w	3 weeks (Weeks 4-6)	Cycle 1: 2 Subsequent cycles: 3
5	1.25 mg/kg	qw	2 weeks (Weeks 5-6)	Cycle 1: 4 Subsequent cycles: 6
Part B (non-weight-based dosing)				
6a	100 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
6b[c,d]	100 mg	qw on Weeks 1, 2, 4, and 5	None (Weeks 3 and 6 are rest)	Cycle 1: 4 Subsequent cycles: 4
6c[c]	75 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
7a	150 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
7b[c,d]	150 mg	qw on Weeks 1, 2, 4, and 5	None (Weeks 3 and 6 are rest)	Cycle 1: 4 Subsequent cycles: 4
7c[c]	125 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
8a	200 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6
8b[c,d]	200 mg	qw on Weeks 1, 2, 4, and 5	None (Weeks 3 and 6 are rest)	Cycle 1: 4 Subsequent cycles: 4
8c[c]	175 mg	qw	None	Cycle 1: 6 Subsequent cycles: 6

Abbreviations: aEC = approving Ethics Committee; DLT = dose-limiting toxicity;
IRB = Institutional Review Board; PK = pharmacokinetic(s); qw = weekly; q2w = every 2 weeks.

a – At the highest dose level where major toxicity is observed and that requires a longer recovery period between infusions, a change in the periodicity of dosing (that is, other dosing schedules based on safety and PK considerations) will be agreed upon with the Investigator and communicated to IRBs/aECs.

b – Observation following the fourth infusion in Cohorts 1, 2, 3, and 5 (qw dosing) and the second infusion in Cohort 4 (q2w dosing) in Cycle 1 only. No Cycle 1 observation period for Cohorts 6a, 6c, 7a, 7c, 8a, or 8c. Weeks 3 and 6 of all cycles are rest weeks in Cohorts 6b, 7b, and 8b (qw dosing on Weeks 1, 2, 4, and 5).

c – Concurrently enroll to Cohorts 6b/7b/8b and 6c/7c/8c, should ≥2 subjects in Cohort 6a/7a/8a experience DLT events.

d – For all cycles: Infusions on Weeks 1, 2, 4, and 5, and rest on Weeks 3 and 6.

It is recognized that in the course of clinical cancer care, it is not always possible to schedule therapeutic infusions at precise intervals (because of holidays, travel difficulties, or other circumstances). Accordingly, infusions administered within 2 days (all cohorts other than q2w

dosing) or 3 days (q2w dosing) before or after the planned infusion time point will be considered acceptable. Deviations beyond this window are not permitted in Cycle 1 and will be allowed thereafter only if medically indicated or if the subject cannot be treated on the scheduled day.

Following the first cycle of therapy (Cycle 1), subjects should continue to receive IMC-CS4 at the same dose and schedule until there is unequivocal evidence of disease progression (per immune-related response criteria [Wolchok et al. 2009]) or other withdrawal criteria are met. Radiographically confirmed disease progression (that is, numerical disease progression, per RECIST) only is not sufficient to discontinue treatment.* Radiographic assessment of tumor response will be performed at the end of the initial 6-week cycle and at the end of every subsequent cycle; radiographic assessment should be performed prior to the start of a cycle so that results are available before the subject receives a new cycle of treatment. However, if a DLT is observed in Cycle 1 in a subject who is benefitting from treatment, Cycle 2 dosing may be initiated within 4 weeks of Cycle 1, Day 1, with Sponsor approval; in this case, no radiographic disease assessment is required prior to dosing in Cycle 2.

*Note: Subjects with disease progression (per RECIST) but without clinical deterioration at Week 6 (the first response assessment) may continue to receive IMC-CS4, at the discretion of the Investigator; study treatment will be discontinued if, at the next disease assessment (performed at least 4 weeks later), disease progression is unequivocal (that is, radiographically confirmed disease progression alone is sufficient). On the other hand, subjects with disease progression (per RECIST) and with clinical deterioration (unequivocal) at Week 6 (the first response assessment) will be discontinued from study treatment.

The treatment schedule, radiographic tumor assessment schedule, and observation period for each dosing schedule are summarized in Table 2, Table 3, Table 4, and Table 5.

Table 2. Treatment Schedule (Part A - Weekly Dosing – Cohorts 1, 2, 3, and 5)

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
	Cycle 1						Cycle 2						Cycle 3						Cycle 4					
Tx[a]	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
O.P.[b]					X	X																		
Tumor eval[c]	X[d]					X						X						X						X

Abbreviations: eval = evaluation; O.P. = observation period; Tx = treatment.

a – Administer IMC-CS4; b – Observation period; c – Radiographic assessment of tumor status; d – Baseline assessment, within 28 days prior to the first dose of study therapy; subsequent assessment should be performed in the week prior to the onset of the new cycle.

Table 3. Treatment Schedule (Part A - Every-2-Week Dosing – Cohort 4)

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
	Cycle 1						Cycle 2						Cycle 3						Cycle 4					
Tx[a]	X		X				X		X		X		X		X		X		X		X		X	
O.P.[b]				X	X	X																		
Tumor eval[c]	X[d]					X						X						X						X

Abbreviations: eval = evaluation; O.P. = observation period; Tx = treatment.

a – Administer IMC-CS4; b – Observation period; c – Radiographic assessment of tumor status; d – Baseline assessment, within 28 days prior to the first dose of study therapy; subsequent assessment should be performed in the week prior to the onset of the new cycle.

Table 4. Treatment Schedule (Part B - Weekly Dosing – Cohorts 6a, 6c, 7a, 7c, 8a, and 8c)

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
	Cycle 1						Cycle 2						Cycle 3						Cycle 4					
Tx[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
O.P.[b]																								
Tumor eval[c]	X[d]					X						X						X						X

Abbreviations: eval = evaluation; O.P. = observation period; Tx = treatment.

a – Administer IMC-CS4; b – Observation period; c – Radiographic assessment of tumor status; d – Baseline assessment, within 28 days prior to the first dose of study therapy; subsequent assessment should be performed in the week prior to the onset of the new cycle.

Table 5. Treatment Schedule (Part B - Weekly Dosing on Weeks 1, 2, 4, and 5 – Cohorts 6b, 7b, and 8b)

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
	Cycle 1						Cycle 2						Cycle 3						Cycle 4					
Tx[a]	X	X		X	X		X	X		X	X		X	X		X	X		X	X		X	X	
O.P.[b]																								
Tumor eval[c]	X[d]					X						X						X						X

Abbreviations: eval = evaluation; O.P. = observation period; Tx = treatment.

a – Administer IMC-CS4; b – Observation period; c – Radiographic assessment of tumor status; d – Baseline assessment, within 28 days prior to the first dose of study therapy; subsequent assessment to be performed in the week prior to the onset of the new cycle.

4.1.1 Cohort Enrollment and Dose Escalation

Each cohort will initially enroll at least 3 subjects. In the first cohort (Cohort 1), subjects were to be enrolled sequentially. That is, there was to be a minimum of a 7-day waiting period between the time a subject receives the first dose of IMC-CS4 and when the next subject in Cohort 1 receives his or her first dose.

For all subsequent cohorts, no 7-day waiting period is required.

Beginning with Cohort 2 and provided safety is acceptable, concomitant enrollment of subjects at different sites will be permitted, in order to ensure that at least 3 subjects will be treated for at least 1 cycle. In a case where consent is obtained simultaneously for 2 subjects at 2 different sites, this may result in enrollment of 4 subjects rather than 3 in a cohort; however, no more than 4 subjects should be enrolled in a cohort before safety data from Cycle 1 are available for review.

For all cohorts, all subjects who complete the first treatment cycle (that is, receive all scheduled treatments for Cycle 1 and complete the observation period, as needed) or discontinue therapy due to a DLT will be considered evaluable subjects and will be included in the DLT analyses. Subjects who do not complete Cycle 1 for reasons other than a DLT will be replaced for the analysis until the cohort includes 3 evaluable subjects (or 6 evaluable subjects in case of one DLT in the first 3 subjects); however, if benefitting from treatment (that is, no disease progression or other withdrawal criteria), any subject in Cohort 3 and beyond who experiences a DLT may continue to receive IMC-CS4 upon agreement of the Sponsor and according to the dose reduction guidelines for this study. Refer to Section 10.1 for details of general dose modifications for IMC-CS4.

If the first 3 subjects in a cohort complete Cycle 1 of therapy with no DLT (defined in Section 4.1.4), dose escalation to the next cohort may proceed. If one of the first 3 subjects in a cohort experiences a DLT, enrollment will proceed until there are at least 6 evaluable subjects in that cohort. If no additional subject experiences a DLT, dose escalation may proceed. If 2 or more subjects experience a DLT in a cohort (whether in the initial 3-subject cohort or following expansion to 6 subjects), dose escalation will not occur and the RP2D will be determined according to the instructions in Section 4.1.2.

In all cases, dose escalation will occur only if the criteria described in this section (Section 4.1.1) are met. Each subsequent cohort will be opened upon completion of the previous cohort. A safety review meeting will be held prior to each dose escalation.

4.1.2 Determination of the Recommended Dose for Phase 2

The provisional RP2D will be defined as the dose level at which pharmacodynamic effects are observed in the absence of clinically relevant toxic effects (that is, measurable pharmacodynamic effects with no DLT in the first 3 subjects or ≤1 DLT in the first 6 subjects enrolled at that dose level). After discussion with the Investigator, the Sponsor may choose to enroll additional subjects at or below the RP2D.

4.1.3 Continuation of Therapy

Planned duration of therapy is not fixed. After one cycle, subjects who are benefitting from treatment may continue to receive IMC-CS4 at the same dose and schedule until there is unequivocal evidence of disease progression or other withdrawal criteria are met. Radiographically confirmed disease progression (that is, numerical progression, per RECIST) only is not sufficient to discontinue treatment (refer to Note in Section 4.1). Permitted dose modifications are described in Section 10.1. Subjects who do not meet any withdrawal criteria are eligible to continue receiving study therapy in a subsequent cycle even if one or more doses have been missed during the prior cycle.

4.1.4 Dose-Limiting Toxicity Definition

A DLT is defined as any IMC-CS4-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. The following are considered DLTs :

- Grade 4 neutropenia lasting ≥7 days;
- Grade 3 or 4 neutropenia complicated by fever ≥38.0°C or infection;
- Grade 4 thrombocytopenia;
- Grade 3 thrombocytopenia complicated by hemorrhage;
- Grade 3 or 4 anemia;
- 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), aspartate aminotransferase (AST), and alanine aminotransferase (ALT), without evidence of hepatic injury
    - Transient Grade ≥2 bilirubin elevation in the presence of known liver metastases lasting ≤7 days
    - Laboratory abnormalities that are reversible to Grade ≤2 or baseline levels within 7 days after initial documentation or that are deemed not clinically significant
    - Grade 3 elevation of CK WITHOUT elevation in serum and urine myoglobin is NOT considered a DLT.

If benefitting from treatment (that is, no disease progression or other withdrawal criteria), any subject in Cohort 3 and beyond who experiences a DLT may continue to receive IMC-CS4 upon agreement of the Sponsor and according to the dose reduction guidelines for this study (Section 10.1).

4.2 Study Duration

All subjects should continue to receive treatment until there is unequivocal evidence of progressive disease (PD) (radiographically confirmed disease progression [that is, numerical disease progression, per RECIST, Section 11] only is not sufficient to discontinue treatment [refer to Note in Section 4.1]), toxicity requiring cessation, protocol noncompliance (in the opinion of the Investigator or Sponsor), withdrawal of consent by the subject, or until other withdrawal criteria are met (see Section 10.2).

4.3 Study Completion and End of Trial

The study will be considered complete (that is, the scientific evaluation will be complete [study completion]) after the last subject has completed the DLT assessment period (that is, has received all scheduled treatments for Cycle 1 and completed the observation period, as needed) OR has discontinued therapy due to a DLT.

IMC-CS4 may be made available after completion of the study to subjects who are still receiving and benefitting from study treatment.

"End of trial" refers to the date of the last visit or last scheduled procedure for the last subject.

4.4 Continued Access Period

All subjects remaining on study treatment without disease progression or unacceptable toxicity following the final analysis for RP2D 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, subjects 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 1 day after the subject and the Investigator agree that the subject will no longer continue treatment in the continued access period and lasts approximately 30 days. If it is deemed to be in the best interest of the subject 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.

Subjects must sign a new ICF before entering the continued access period. The Sponsor 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 eCRF.

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

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

4.5 Discontinuation of Study Sites and Discontinuation of the Study

Individual study site participation may be discontinued if the Sponsor, the Investigator, the IRB/aEC, or the regulatory authority deems it necessary for any scientific, medical, or ethical reason.

The study will be discontinued if the IRB/aEC or the Sponsor, while considering the rights, safety, and well-being of the subject(s), judges it necessary for any scientific, medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

5 STUDY TREATMENT

5.1 Treatment Administered

5.1.1 IMC-CS4 Drug Product

5.1.1.1 Part A Only

The dose of IMC-CS4 is based on the subject's body weight in kilograms. Subjects recruited in Cohort 1 have received IMC-CS4 infusions over a period of 90 minutes. Because of a change in the dosing scheme in Protocol Amendment 3.0, subjects in Cohorts 2 through 5 received IMC-CS4 I.V. via infusion over a period of 30 minutes. Subjects in the RP2D expansion cohort will receive IMC-CS4 I.V. via infusion over a period of 90 minutes for the first infusion, 60 minutes for the second infusion, and 30 minutes for the remaining infusions. The infusion rate should not exceed 25 mg/minute.

The first dose of IMC-CS4 is dependent upon the subject's baseline body weight in kilograms. Subsequent doses of IMC-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 subjects 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 Sponsor CRP or designee should be consulted regarding optimal assessment of dry weight).

5.1.1.2 Part B Only

The dose of IMC-CS4 is non-weight based. Subjects will receive IMC-CS4 I.V. via infusion over a period of 30 minutes. The infusion rate should not exceed 25 mg/minute.

5.1.1.3 Both Parts A and B

Aseptic technique is to be used when preparing and handling IMC-CS4. Different drug product lots must not be mixed in a single infusion.

IMC-CS4 is compatible with commonly used infusion containers. Refer to the IB for detailed information on acceptable infusion containers and infusion sets for administration of IMC-CS4.

Subjects recruited in Cohort 1 have been administered IMC-CS4 in a total volume of 250 mL. Because of the dose reduction, subjects in Cohort 2 and beyond will receive IMC-CS4 doses in a total volume of at least 100 mL. To this end, add (or remove from AVIVA I.V. bag which comes prefilled with 0.9% normal saline) a sufficient quantity of sterile normal saline (0.9% weight/volume) to the container to make the total volume 100 mL. For dose volumes greater than 100 mL, the addition of sterile normal saline is not required. The container should be gently inverted to ensure adequate mixing.

The infusion set must be flushed post infusion with sterile 0.9% normal saline equal to or exceeding the infusion line hold-up volume to ensure delivery of the calculated dose.

Subjects are to be observed closely from the start of the infusion until at least 1 hour after the end of the infusion of IMC-CS4 for any potential AEs 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 IMC-CS4 administration (see Section 9.1.2 for a definition of infusion-related reactions).

5.1.2 Premedication

Premedication is not recommended to be administered prior to the first infusion of IMC-CS4. If the subject experiences a Grade 1 or 2 infusion-related reaction (as detailed in Section 9.1.2), premedication must be provided prior to any subsequent doses of IMC-CS4. Any premedication administered should be documented in the eCRF, including dose and route of administration.

5.2 Treatment Compliance

Trained medical personnel will administer IMC-CS4. Treatment compliance will be monitored by drug accountability records (Section 5.5), and treatment administration data are recorded in the subject's medical record and subsequently transcribed in the eCRF.

The Investigator or his/her designee is responsible for the following:

- Explaining the correct use of the drug(s) and planned duration of each subject's treatment to the site personnel;
- Verifying that instructions are followed properly;
- Maintaining accurate records of study drug dispensing and collection (see Section 5.5); and
- Disposing of all unused medication as described in Sections 5.6 and 5.7.

Subjects will be instructed to contact the Investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be assessed.

5.3 Packaging and Labeling

5.3.1 IMC-CS4 Drug Product

IMC-CS4 drug product (DP) is a sterile, preservative-free injection for I.V. use formulated in histidine buffer at an IMC-CS4 drug substance (DS) concentration of 5 mg/mL (100 mg/20-mL vial). The buffer contains 10mM histidine, 100mM glycine, 100mM arginine, and 0.01% polysorbate 80. The pH is 6.0.

All excipients used for the manufacture of IMC-CS4 DP are of pharmacopeial grade. No animal-derived components are used in the manufacture of IMC-CS4 DP excipients.

IMC-CS4 DP is supplied in single-use, 20-mL nominal volume, United States Pharmacopeia Type I glass vials. Each vial contains 100 mg of IMC-CS4 at a concentration of 5 mg/mL (100 mg/20 mL) in a sterile, preservative-free solution. Each vial is stoppered with a chlorobutyl rubber stopper and sealed with an aluminum flip-off cap.

Each vial of IMC-CS4 is packaged in a single carton, and several cartons are contained in each shipment box. Each vial and each box contains a single-panel open label, including at a minimum, the following information: product description, strength, lot number, storage conditions, and cautionary statement.

5.4 Storage

5.4.1 IMC-CS4

Refer to the IB and Pharmacy Manual for detailed storage information for IMC-CS4 DP and prepared IMC-CS4 for infusion.

5.5 Accountability

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational products are inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- The amount received and placed in the storage area;
- The amount currently in the storage area;
- The label ID number or batch number;
- The dates and initials of the person responsible for each investigational product inventory entry/movement;
- The amount dispensed to each subject, including unique subject identifiers;
- The amount transferred to another area for dispensing or storage;
- Nonstudy disposition (for example, lost, wasted, broken);
- The amount returned to the Sponsor and its representative(s)/delegate(s);
- The amount destroyed at the study site, if applicable; and
- Retained samples sent to a third party for bioavailability/bioequivalence, if applicable.

The Sponsor and its representative(s)/delegate(s) will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements.

5.6 Return of Investigational Product

At the end of the study, all unused and/or partially used investigational products must be returned to the Sponsor or its representative/delegate, if not authorized by the Sponsor or its representative/delegate to be destroyed at the site.

All investigational products returned to the Sponsor or its representative/delegate must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. Returned supplies should be in the original containers. Empty containers should not be returned to the Sponsor or its representative/delegate. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that

appropriate records of disposal are kept. The return of unused investigational products should be arranged by the responsible study monitor.

5.7 Investigational Product Retention at Study Site

Opened vials may be disposed of at the investigation center as chemotherapy or biohazardous waste provided documented procedures for destruction have been provided to and approved by the Sponsor or its representative(s)/delegate(s). Otherwise, opened vials must be returned to the Sponsor or its representative(s)/delegate(s) for disposal. If IMC-CS4 is destroyed at the site, it is the Investigator's responsibility to ensure that procedures for proper disposal have been established according to applicable regulations and guidelines and institutional procedures, including that:

- Written authorization for disposal/destruction has been granted by the Sponsor or its representative/delegate;
- Arrangements have been made for the disposal; and
- Appropriate records of the disposal have been documented.

6 STUDY PROCEDURES

6.1 Informed Consent

Informed consent – Written permission will be given by each subject prior to undergoing any protocol-specific evaluations and prior to receiving treatment.

6.2 Medical History

Medical history – Past and current medical conditions (for example, LVEF assessment) and treatments, current medications, medications taken within 30 (calendar) days prior to first dose of study therapy, date of initial diagnosis, pathological confirmation of malignancy, prior cancer therapy and surgery, current TNM (tumor, nodes, and metastases) staging and TNM staging at the time of initial diagnosis (refer to American Joint Committee on Cancer Staging Manual, 7th edition [Edge et al. 2009] or higher). Any preexisting toxicity (for example, Grade 1 fatigue) should be documented, recorded, and graded (NCI-CTCAE, Version 4.0 grade) at this time.

Concomitant medication assessment – To be performed and documented as outlined in Section 7 (Study Activities).

6.3 Physical Examination

Complete physical examination – Evaluation by body system and height (at pretreatment only).

Weight measurement

ECOG performance status – According to the ECOG PS criteria.

6.4 Vital Signs

Vital signs measurements – Includes temperature, pulse rate, respiration rate, and blood pressure.

6.5 Clinical Laboratory Tests

Investigators must document their review of each laboratory report.

Samples collected for specified laboratory tests will be destroyed within 60 (calendar) days of receipt of confirmed test results. Tests are run and confirmed promptly whenever medically or scientifically appropriate. When medical and scientific circumstances warrant, however, it is

acceptable to retain samples to batch the tests run. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

Hematology profile – Includes a complete blood count with differential and platelet count, surface staining and flow cytometric analysis of peripheral leukocytes.

Coagulation profile – Includes INR, PT if available, and PTT.

Serum chemistry profile – Includes sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, glucose, total protein, albumin, AST, ALT, AP, total bilirubin, LDH, CK, lipase, amylase, calcium, magnesium, and phosphorus. Serum myoglobin levels will be analyzed in case of CK elevation (for CK increases ≥2.5 × ULN).

Isoenzymes of LDH, CK, and AP will be analyzed per Table 7, Table 8, and Table 9. In addition, isoenzymes (such as CK isoenzymes MB, MM, and BB) will be quantified on Week 1 of Cycle 2 and beyond only if that particular serum enzyme is ≥2.5 × ULN at Week 5 of Cycle 1.

Troponin (I or T or institutional standard) - Results are not needed prior to dosing, except for the Cycle 1, Day 1 dose.

C-reactive protein

Bone metabolism markers – Includes C-terminal cross-linking telopeptide of type I collagen (CTX-I) and procollagen type 1 N-terminal propeptide (P1NP).

Hepatic monitoring – The following selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with subjects in consultation with the Sponsor CRP:

- Hematology profile – See above;
- Hepatic chemistry – Includes total bilirubin, direct bilirubin, AST, ALT, AP, CK, and gamma-glutamyl transpeptidase;
- Haptoglobin;
- Coagulation profile – See above;

- Hepatic serology – Includes hepatitis A antibody, total; hepatitis A antibody, IgM; hepatitis B surface antigen; hepatitis B surface antibody; hepatitis B core antibody; hepatitis C antibody; hepatitis E antibody, IgG; hepatitis E antibody, IgM;
- Anti-nuclear antibody;
- Anti-smooth muscle antibody.

Urinalysis – Routine dipstick measurements and, if clinically indicated, microscopic analysis. Myoglobin levels in the urine will be analyzed in case of serum CK elevation ≥2.5 × ULN.

Beta human chorionic gonadotropin (β-hCG) pregnancy test – Within 7 (calendar) days prior to the first dose of study therapy for WOCBP and every 12 weeks following the first dose thereafter (or according to local regulations, whichever is more frequent). Serum pregnancy test required at pretreatment; serum or urine pregnancy test may be performed thereafter.

6.6 Efficacy Assessments

Imaging studies

- Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the chest, abdomen, pelvis, and (if applicable) brain. CT or MRI of the neck should be performed, if clinically indicated. It is recommended that CT imaging of the abdomen/pelvis be performed with I.V. contrast, whenever possible. For subjects with known serious allergic reactions to CT contrast material, a CT of the chest without contrast and contrast-enhanced MRI of the abdomen/pelvis or a CT of the abdomen/pelvis with oral contrast should be performed, at the discretion of the Investigator.
- Chest x-rays are not permitted for tumor response assessment in this trial.
- Bone scans should be performed at baseline as clinically indicated. Routine bone scans during treatment must be performed only in the setting of bone-only disease (no lymph node, visceral, skin, or subcutaneous metastases), or as deemed appropriate by the Investigator. In the event that a positron emission tomography (PET) scan is performed within 28 (calendar) days prior to first dose of study therapy that is negative for bone disease, then no baseline bone scan is required.
- Imaging methods must be employed consistently during the course of each subject's evaluation during the study (that is, subjects who have MRI as baseline examination continue to have MRI assessments as a means of determining response/progression).

Tumor measurements/disease response assessment – The determination of unidimensional measurements and disease response as defined in Section 11.

6.7 Tissue Sampling

To assess the pharmacodynamic effect of IMC-CS4 administration on tumor-associated macrophages, all subjects enrolled in Cohort 2 and beyond will undergo tumor biopsies before study enrollment and as specified in Table 6. For these cohorts, investigators will carry out a tumor (core needle or excisional) biopsy (attempt to obtain at least 3 cores) before starting the treatment and at the end of Cycle 1 (to be done in the week prior to Cycle 2, at the same time as tumor evaluation), if the subject's condition allows it. If an enrolled subject undergoes a pretreatment tumor biopsy but is unable to tolerate a posttreatment tumor biopsy, then a skin punch biopsy will be acceptable.

At the time of disease progression, the Investigator will also perform a tumor biopsy if the subject consents to it and if the subject's condition allows it.

Previously archived tumor tissue from the primary tumor (paraffin block [whole or partial block] or 20 unstained slides), if available, will be collected (if possible) prior to receiving the first dose of study therapy.

Previously archived and/or biopsied tissue may be used for analysis that may include, but would not be limited to, factors related to the CSF-1R pathway, macrophages, and immune microenvironment. All tissue samples will be kept by the Sponsor for a maximum of 15 years after the main study is completed; then all samples will be destroyed.

6.8 Blood Sampling

Blood will be collected from all subjects for PK, pharmacodynamic, immunogenicity, and other analyses as described in Sections 6.8.1, 6.8.2, 6.8.3, and 6.8.4. Samples collected will be retained for a maximum of 15 years (pharmacodynamics, immunogenicity) or 1 year (PK) following the last subject visit for the study, or as previously described in Section 6.5.

6.8.1 Pharmacokinetics

The analytical methods used to determine serum drug concentration will be validated at a laboratory determined by the Sponsor. Serum concentrations of IMC-CS4 will be determined using an enzyme-linked immunosorbent assay.

Blood samples will be drawn in order to perform assessment of levels of IMC-CS4 in serum. Parameters to be reported may include, but not be limited to, C_{max}, trough serum concentration (C_{min}), AUC, $t_{1/2}$, clearance (Cl), and volume at steady state (V_{ss}) of IMC-CS4. Detailed instructions for collecting, processing, storing, and shipping of samples will be provided by the Sponsor or its representative(s)/delegate(s) in a separate procedural manual. Refer to Section 7.7 for a detailed schedule of collection time points. For each specified time point, one tube (approximately 7.5 mL/tube) of blood is required; if the timing of a PK sample should coincide with that of an immunogenicity sample, the same sample will suffice for both studies.

6.8.2 Immunogenicity Testing (Anti-IMC-CS4 Antibodies)

Blood samples for the assessment of antibodies against IMC-CS4 (immunogenicity) will be collected for all study subjects at specified time points throughout the study (Section 7.7). In addition, if a subject should have an infusion-related reaction to 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 (calendar) days following the event. For each specified time point, one tube (approximately 7.5 mL/tube) of blood is required; if the timing of a PK sample should coincide with that of an immunogenicity sample, the same sample will suffice for both studies.

In certain circumstances, including if antibodies against IMC-CS4 are detected, the subject's serum IMC-CS4 concentration will be analyzed using the same sample, in order to determine if there is any alteration of IMC-CS4 PK. Detailed instructions for collecting, processing, storing, and shipping of samples will be provided by the Sponsor and its representative(s)/delegate(s) in a separate procedure manual. Refer to Section 7.7 for a detailed schedule of collection time points.

6.8.3 Pharmacodynamics

Blood and tissue samples will be taken. Analyses may include, but are not limited to, the following parameters:

- Levels of potential circulating and tissue pharmacodynamic markers, including but not limited to CSF-1, IL-34, MCP-1, and macrophage-specific markers (for example, CD68 and CD163);
- Characterization of blood monocyte subsets by flow cytometry (CD14, CD16, and HLA/DR); and

- Serum markers of bone metabolism (CTX-I and P1NP).

Samples drawn for pharmacodynamic analyses will be separate from those collected for PK and immunogenicity analyses as described in Sections 6.8.1 and 6.8.2, respectively. Detailed instructions for collecting, processing, storing, and shipping of samples will be provided by the Sponsor or its representative(s)/delegate(s) in a separate procedural manual. Refer to Section 7.7 for a detailed schedule of collection time points.

6.8.4 Other Analyses

Refer to Section 6.5 for details of blood samples drawn for other analyses, including flow-cytometric analysis of peripheral leukocytes; isoenzymes of LDH, CK, and AP; troponin (I or T); and bone metabolism markers CTX-I and P1NP. These samples will be separate from those used for PK/immunogenicity and pharmacodynamic analyses, and drawn according to the schedule described in Sections 7.2.2.2, 7.2.2.3, 7.2.2.4, and 7.2.2.5.

6.9 Electrocardiogram

An electrocardiogram (ECG) including measurement of QT/corrected QT (QTc) interval will be obtained pretreatment (within 14 [calendar] days prior to first dose of study therapy), on study, and at the end of therapy according to the schedule in Section 7.2.

6.9.1 Triplicate ECG (Part A Only)

Triplicate ECG consisting of 3 individual ECGs performed consecutively within a period of approximately 4 minutes will be obtained at the time points specified in Section 7.2.3.1 from additional subjects enrolled at the RP2D.

6.10 Multigated Acquisition Scan or Echocardiogram

A multigated acquisition (MUGA) scan or an echocardiogram will be performed for all subjects during pretreatment evaluations (within 28 [calendar] days prior to first dose of study therapy), as an eligibility assessment of LVEF. Refer to exclusion criterion #11 (Section 3.3) for subject eligibility regarding LVEF.

6.11 Optional Study Procedures

6.11.1 Tumor Tissue Submission

In addition to the mandatory collections described in Section 6.7, specimens will be collected when available as described below from subjects who consent to these optional procedures.

If a core biopsy, surgical biopsy, or resection is performed in the course of the study as routine clinical care, the Sponsor requests a tissue block or unstained slides for analysis of potentially relevant surrogate biomarkers. Tissue will be kept with the intention to perform tests as new techniques, research tools, and biomarkers become available. All tissue samples will be kept by the Sponsor for a maximum of 15 years after the main study is completed, then all samples will be destroyed.

Detailed instructions for collecting, processing, storing, and shipping of samples will be provided by the Sponsor or its representative(s)/delegate(s) in a separate procedural manual.

6.12 Appropriateness of Measurements

The measures used to assess safety and efficacy in this study are consistent with those used in most conventional Phase 1 oncology trials.

7 STUDY ACTIVITIES

Throughout this protocol, "days" refers to calendar days, unless otherwise indicated.

7.1 Pretreatment Evaluations

Pretreatment evaluations are used to determine the subject's study eligibility and must be completed within 14 days prior to the first dose of study medication unless otherwise specified. Written informed consent must be obtained prior to any study-specific pretreatment evaluations. All subjects must undergo the following pretreatment evaluations:

- Medical history (any preexisting toxicity should be documented, recorded, and graded [NCI-CTCAE, Version 4.0 grade] as a part of the pretreatment history);
- Serum β-hCG pregnancy test in WOCBP (within 7 days prior to the first dose of study therapy);
- Baseline ECG;
- Baseline MUGA or echocardiogram for LVEF assessment (within 28 days prior to the first dose of study therapy);
- ECOG PS assessment;
- Complete physical examination (including height measurement);
- Vital signs (including temperature, pulse rate, respiration rate, and blood pressure);
- Weight measurement;
- Baseline toxicity/AE assessment;
- Concomitant medication assessment (including those medications taken 30 days prior to the first dose of study therapy);
- Hematology profile;
- Coagulation profile;
- Serum chemistry profile, including myoglobin;
- C-reactive protein assessment;
- Urinalysis;
- Blood samples for baseline PK analysis (on the day of and immediately prior to the first dose of study therapy), and immunogenicity and pharmacodynamic analyses (within 7 days prior to the first dose of study therapy);
- Blood samples for flow cytometry assessment and isoenzyme assessment of LDH, CK, and AP (within 7 days prior to the first dose of study therapy) for subjects in Cohort 2 and beyond;
- Blood sample for troponin (I or T) assessment (prior to the first infusion of Cycle 1 so that results are obtained before dosing);
- Blood sample for bone metabolism marker assessment (within 7 days prior to the first dose of study therapy);
- Imaging studies including a CT scan or MRI as described in Section 6.6 (performed and documented within 28 days prior to the first dose of study therapy);

- Bone scan, as clinically indicated (within 28 days prior to the first dose of study therapy; not required if PET is performed within 28 days prior to the first dose of study therapy that is negative for bone disease); and
- Tumor (core needle or excisional) biopsy (mandatory) (within 7 days prior to the first dose of study therapy) for subjects in Cohort 2 and beyond.

7.2 Treatment Period

In all cohorts, WOCBP or fertile men with partners of childbearing potential must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 12 weeks after the study.

A series of clinical tests and procedures will be performed at specified intervals throughout the study (see also Section 7.6). If, at any time during the study, tumor tissue is obtained as routine clinical care or through a biopsy, fine-needle aspiration (FNA), or resection, the Sponsor requests a portion of the sample for exploratory analyses.

IMC-CS4 is administered I.V. as shown in Section 4.1, Table 2, Table 3, Table 4, and Table 5. An observation period will occur, as needed, in Cycle 1 of Part A only, as described in Section 4.1. Radiographic assessment of tumor response will be performed at the end of every treatment cycle (prior to the first dose of study therapy in the subsequent cycle, approximately every 6 weeks assuming no treatment delays); radiographic assessment should be performed prior to the start of a cycle so that results are available before the subject receives a new cycle of treatment. However, if a DLT is observed in Cycle 1 in a subject who is benefitting from treatment, Cycle 2 dosing may be initiated within 4 weeks of Cycle 1, Day 1, with Sponsor approval; in this case, no radiographic disease assessment is required prior to dosing in Cycle 2. Routine bone scans during treatment must be performed only in the setting of bone-only disease (no lymph node, visceral, skin, or subcutaneous metastases), or as deemed appropriate by the Investigator.

Other assessments and evaluations will be performed as described in the following sections. Note that evaluations will be performed according to the same schedule in all cohorts, unless otherwise specified.

7.2.1 Regular Assessments

A serum or urine pregnancy test will be performed for WOCBP at Week 13 (that is, 12 weeks after the first dose), and every 12 weeks thereafter (or according to local regulations, whichever is more frequent).

Beginning with Week 1, Day 1, the following evaluations will be performed every week (±2 days for subjects in the qw cohorts and Cohorts 6b, 7b, and 8b and ±3 days for subjects in the q2w cohorts) for the first 12 weeks on therapy (this includes nontreatment weeks for subjects enrolled in the q2w cohorts and Cohorts 6b, 7b, and 8b), unless otherwise indicated:

- ECOG PS assessment;
- Vital sign measurements (vital signs to be checked and recorded prior to each infusion of IMC-CS4, midway through each infusion, at the end of each infusion, and every 15 minutes for the first hour following each infusion, including Week 1, Day 1 [also to be checked and recorded at nontreatment visits during Cycle 1]);
- Weight measurement;
- Toxicity/AE evaluations;
- Concomitant medication assessment;
- Hematology profile (evaluations performed within 7 days prior to the first dose do not need to be repeated at Week 1, Day 1);
- Serum chemistry profile (evaluations performed within 7 days prior to the first dose do not need to be repeated at Week 1, Day 1);
- C-reactive protein assessment;
- Tumor biopsy – At the end of Cycle 1, if the subject's condition allows it, a (mandatory) (core needle or excisional) biopsy of the tumor will be performed, regardless of whether the tumor progressed, stabilized, or regressed (refer to Section 7.2.1.1 for the timing of non-mandatory tumor biopsies);
- Blood samples for PK, immunogenicity, and pharmacodynamic analyses, per Section 7.7 (Table 7, Table 8, and Table 9); and
- Blood samples for the following assessments, per Section 7.7 (Table 7, Table 8, and Table 9): flow cytometry of peripheral leukocytes; isoenzymes of LDH, CK, and AP; troponin (I or T); and bone metabolism markers CTX-I and P1NP.

After study Week 12 (that is, after Cycle 2), ECOG PS assessment, vital sign measurements, weight measurement, toxicity/AE evaluations, and concomitant medication assessment will continue to be performed every week, while C-reactive protein assessment will be performed q2w. After Week 12, hematology and serum chemistry will be performed: q2w for Cohorts 1, 2, 3, 4, 5, 6a, 6c, 7a, 7c, 8a, and 8c, and every 3 weeks (q3w) for Cohorts 6b, 7b, and 8b (such that these hematology and serum chemistry assessments are done on rest Weeks 3 and 6).

A physical examination will be performed q2w for the first 12 weeks of the study, and every 6 weeks thereafter.

Coagulation profile and urinalysis will be performed at the beginning of each cycle (that is, approximately every 6 weeks following the first dose of study therapy).

7.2.1.1 Tumor Biopsy

Tumor (core needle or excisional) biopsy will be performed at the following time points:

Weekly Cohorts and Cohorts 6b, 7b, and 8b

Mandatory (unless medically contraindicated)

- Prior to the first IMC-CS4 infusion of Cycle 1 (≤7 days)
- At the end of Cycle 1, if the subject's condition allows it, a (core needle or excisional) biopsy of the tumor will be performed, regardless of whether the tumor progressed, stabilized, or regressed.

Non-mandatory

- In cases of tumor progression, if the subject's condition allows it, a (core needle or excisional) biopsy will be performed.

Every-2-Week Cohorts

Mandatory (unless medically contraindicated)

- Prior to the first IMC-CS4 infusion of Cycle 1 (≤7 days)
- At the end of Cycle 1, if the subject's condition allows it, a (core needle or excisional) biopsy of the tumor will be performed, regardless of whether the tumor progressed, stabilized, or regressed.

Non-mandatory

- In cases of tumor progression, if the subject's condition allows it, a (core needle or excisional) biopsy will be performed.

7.2.2 Blood Sampling

7.2.2.1 Pharmacokinetic, Pharmacodynamic, Immunogenicity Sampling

Blood samples will be collected from all enrolled subjects according to the detailed schedule in Section 7.7, and used for PK, pharmacodynamic, and immunogenicity analyses.

7.2.2.2 Flow Cytometry Analysis

Blood samples for flow cytometric analysis of peripheral leukocytes will be collected at the following time points:

Weekly Cohorts and Cohorts 6b, 7b, and 8b

- Prior to the first IMC-CS4 infusion of Cycle 1 (≤7 days)
- 1 day (approximately 24 hours) after the first IMC-CS4 infusion in Cycle 1
- 2 days (approximately 48 hours) after the first IMC-CS4 infusion in Cycle 1
- 3 days (approximately 72 hours) after the first IMC-CS4 infusion in Cycle 1
- Immediately prior to the second IMC-CS4 infusion of Cycle 1
- Immediately prior to the third IMC-CS4 infusion of Cycle 1
- Immediately prior to the fourth IMC-CS4 infusion of Cycle 1
- Cohorts 6b, 7b, and 8b only: 1 day after the first IMC-CS4 infusion in Cycle 3 (approximately 24 hours)
- Immediately prior to the second IMC-CS4 infusion of Cycle 3.

Every-2-Week Cohorts

- Prior to the first IMC-CS4 infusion of Cycle 1 (≤7 days)
- 3 days (approximately 72 hours) after the first IMC-CS4 infusion in Cycle 1
- Immediately prior to the second IMC-CS4 infusion of Cycle 1
- Immediately prior to the second IMC-CS4 infusion of Cycle 3.

In all cohorts, blood samples for flow cytometric analysis will be collected at the 30-Day Follow-up visit.

7.2.2.3 LDH, CK, and AP Isoenzymes

A sample for analysis of LDH, CK, and AP isoenzymes will be collected at the following time points:

Weekly Cohorts and Cohorts 6b, 7b, and 8b

- Prior to the first IMC-CS4 infusion of Cycle 1 (≤7 days)
- Prior to the second IMC-CS4 infusion of Cycle 1 (≤3 days)
- Prior to the third IMC-CS4 infusion of Cycle 1 (≤3 days)
- On Week 1 of Cycle 2; collected only if serum enzymes are ≥2.5 × ULN at Week 5 of Cycle 1
- Cohorts 6b, 7b, and 8b only: Prior to the second IMC-CS4 infusion of Cycle 3 (≤3 days); collected only if serum enzymes are ≥2.5 × ULN at Week 5 of Cycle 1.

Every-2-Week Cohorts

- Prior to the first IMC-CS4 infusion of Cycle 1 (≤7 days)
- Prior to the second IMC-CS4 infusion of Cycle 1 (≤3 days)
- On Week 1 of Cycle 2; collected only if serum enzymes are ≥2.5 × ULN at Week 5 of Cycle 1.

In all cohorts, blood samples for isoenzyme analysis will be collected at the end of therapy and at the 30-Day Follow-up visit only if that particular serum enzyme is ≥2.5 × ULN at Week 5 of Cycle 1.

7.2.2.4 Troponin

Serum levels of troponin (I or T) will be assessed at the following time points:

Weekly Cohorts and Cohorts 6b, 7b, and 8b

- Prior to the first IMC-CS4 infusion of Cycle 1 (sample to be collected prior to the first infusion of Cycle 1 so that results are obtained before dosing)
- Prior to the second IMC-CS4 infusion of Cycle 1 (≤3 days)
- Prior to the third IMC-CS4 infusion of Cycle 1 (≤3 days)
- On Week 1 of Cycle 2; collected only if serum CK levels are ≥2.5 × ULN at Week 5 of Cycle 1
- Cohorts 6b, 7b, and 8b only: Prior to the second IMC-CS4 infusion of Cycle 3 (≤3 days); collected only if serum CK levels are ≥2.5 × ULN at Week 5 of Cycle 1
- When deemed appropriate by the Investigator.

Every-2-Week Cohorts

- Prior to the first IMC-CS4 infusion of Cycle 1 (sample to be collected prior to the first infusion of Cycle 1 so that results are obtained before dosing)
- Prior to the second IMC-CS4 infusion of Cycle 1 (≤3 days)
- On Week 1 of Cycle 2; collected only if serum CK levels are ≥2.5 × ULN at Week 5 of Cycle 1
- When deemed appropriate by the Investigator.

In all cohorts, blood samples for troponin analysis will be collected at the end of therapy and at the 30-Day Follow-up visit only if CK ≥2.5 × ULN at Week 5 of Cycle 1.

With the exception of the first IMC-CS4 infusion of Cycle 1, IMC-CS4 may be administered as planned while troponin results are pending, provided no cardiac symptoms have been revealed upon ECG or physical examination. For the first IMC-CS4 infusion of Cycle 1 (all cohorts), troponin results should be obtained before dosing.

7.2.2.5 Bone Metabolism Markers CTX-I and P1NP

Serum levels of CTX-I and P1NP (bone metabolism markers) will be assessed at the following time points:

Weekly Cohorts and Cohorts 6b, 7b, and 8b

- Prior to the first IMC-CS4 infusion of Cycle 1 (≤7 days)
- Prior to the second IMC-CS4 infusion of Cycle 1 (≤3 days)
- Prior to the fourth IMC-CS4 infusion of Cycle 1 (≤3 days)
- Prior to the second IMC-CS4 infusion of Cycle 3 (≤3 days).

Every-2-Week Cohorts

- Prior to the first IMC-CS4 infusion of Cycle 1 (≤7 days)
- Prior to the second IMC-CS4 infusion of Cycle 1 (≤3 days).

7.2.3 ECG Assessment

ECG assessment will be performed at the following time points (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):

- Prior to the first infusion of Cycle 1 and 1 hour (±30 minutes) following the completion of the first infusion of Cycle 1
- Prior to the last infusion of Cycle 1 and 1 hour (±30 minutes) following the completion of the last infusion of Cycle 1
- Prior to the last infusion of all subsequent cycles and 1 hour (±30 minutes) following the completion of the last infusion of all subsequent cycles
- When deemed appropriate by the Investigator.

7.2.3.1 Triplicate ECG Schedule (Part A Only)

As described in Section 4.1.2, additional subjects may be enrolled at the RP2D. These subjects only will undergo triplicate ECG testing (see Section 6.9.1) at each of the following time points:

- Prior to the first infusion of Cycle 1 and 1 hour (±30 minutes) following the completion of the first infusion of Cycle 1
- Prior to the last infusion of Cycle 1 and 1 hour (±30 minutes) following the completion of the last infusion of Cycle 1 (qw cohorts)
- Prior to the last infusion of Cycle 3 and 1 hour (±30 minutes) following the completion of the last infusion of Cycle 3 (q2w cohorts only)
- Prior to the last infusion of all subsequent cycles and 1 hour (±30 minutes) following the completion of the last infusion of all subsequent cycles.

Note that subjects undergoing triplicate ECG testing according to this schedule are not required to undergo additional single ECG per the schedule outlined in Section 7.2 (that is, these subjects will undergo triplicate ECG only).

7.3 End-of-Therapy Evaluations

End-of-therapy evaluations will be assessed on subjects who are no longer receiving study therapy. The end-of-therapy evaluations will include:

- ECG (triplicate ECG for Part A only, as described in Sections 6.9.1 and 7.2.3.1);
- ECOG PS assessment;
- Physical examination;
- Vital signs (including temperature, pulse rate, respiration rate, and blood pressure);
- Weight measurement;
- Toxicity/AE evaluations;
- Concomitant medication assessment;
- Hematology profile;
- Serum chemistry profile;
- C-reactive protein assessment;

- Troponin (I or T) analysis and isoenzyme assessment of LDH, CK, and AP only if serum enzymes are ≥2.5 × ULN at Week 5 of Cycle 1; and
- Urinalysis.

In cases of tumor progression, if the subject's condition allows it, a (core needle or excisional) biopsy of the tumor will be performed. For subjects who discontinue study therapy for any reason other than PD, every effort will be made to obtain radiographic tumor assessments at 6 and 12 weeks following the first dose of study therapy and/or until radiographic documentation of PD.

7.4 30-Day Follow-up Evaluations

All subjects will be followed for a minimum of 30 days after the last dose of study therapy; AEs occurring during this period will be documented and reported according to the guidelines in Section 8. A follow-up evaluation will be conducted approximately 30 days (+0-7 days) after the last dose of study therapy, and will include:

- Serum β-hCG pregnancy test in WOCBP;
- ECOG PS assessment;
- Physical examination;
- Vital signs (including temperature, pulse rate, respiration rate, and blood pressure);
- Weight measurement;
- Toxicity/AE evaluations;
- Concomitant medication assessment;
- Hematology profile;
- Serum chemistry profile, including myoglobin;
- C-reactive protein assessment;
- Troponin (I or T) analysis and isoenzyme assessment of LDH, CK, and AP only if serum enzymes are ≥2.5 × ULN at Week 5 of Cycle 1;
- Urinalysis;
- Blood samples for PK, immunogenicity, and pharmacodynamic evaluations; and
- Blood sample for flow cytometry analysis of peripheral leukocytes.

7.5 Extended Follow-up Evaluations

All SAEs and 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).

7.6 Study Events Table

Table 6 summarizes assessments, tests, and treatments scheduled to occur as part of Study IMCL CP24-1001. "Days" refers to calendar days, unless otherwise indicated.

Table 6. Flow Chart for Protocol

Procedures	Pretreatment (Prior to first dose)			Treatment Cycles[a]					End of Therapy	30-Day Follow-up	Extended Follow-up
	Within 28 Days	Within 14 Days	Within 7 Days	Every Week[b]	Every 2 Weeks	Every 3 Weeks	Every 6 Weeks	Every 12 Weeks			
Eligibility Assessments											
Informed consent		X[c]		N/A							
Medical history		X		N/A							
β-hCG Pregnancy test			X[d]					X[d]		X[d]	
ECG		X		X[e]					X		
MUGA/echocardiogram	X										
Triplicate ECG (Part A only)				X[ef]					X[f]		
ECOG PS assessment		X		X					X	X	
Safety Assessments											
Physical examination		X[g]			X[h]		X[h]		X	X	
Vital signs		X[i]		X[i]					X[i]	X	
Weight measurement		X		X					X	X	
Toxicity/AE assessment		X[j]		X					X	X	X[k]
Concomitant medication assessment		X[l]		X					X	X	
Laboratory Tests											
Hematology profile		X		X[m,n]	X[m]	X[m]			X	X	
Coagulation profile		X					X[o]				
Serum chemistry profile		X		X[m,n]	X[m]	X[m]			X	X	
C-reactive protein assessment		X		X[m,n]	X[m]				X	X	

Table 6. Flow Chart for Protocol

Procedures	Pretreatment (Prior to first dose)			Treatment Cycles[a]					End of Therapy	30-Day Follow-up	Extended Follow-up
	Within 28 Days	Within 14 Days	Within 7 Days	Every Week[b]	Every 2 Weeks	Every 3 Weeks	Every 6 Weeks	Every 12 Weeks			
Urinalysis		X					X[o]		X		
Blood Sampling											
All blood sampling	Refer to Table 7 (qw cohorts), Table 8 (q2w cohorts), and Table 9 (Cohorts 6b, 7b, and 8b).										
Efficacy Assessments											
Imaging studies (CT/MRI)	X						X[p]				
Bone scan	X[q]			X[r]							
Tumor assessments	X						X[p]				
Tumor (core needle or excisional) biopsy			X				X[s]		X[t]		
Tumor tissue submission				X[u]							
Study Therapy Administration											
Administer IMC-CS4	N/A			Refer to Table 2 (Part A - qw cohorts), Table 3 (q2w cohorts), Table 4 (Part B – qw cohorts), and Table 5 (Cohorts 6b, 7b, and 8b).					N/A		

Abbreviations: β-hCG = beta human chorionic gonadotropin; AE = adverse event; CK = creatine kinase; CT/MRI = computed tomography (scan)/magnetic resonance imaging; DLT = dose-limiting toxicity; ECOG PS = Eastern Cooperative Oncology Group performance status; ECG = electrocardiogram;MUGA = multigated acquisition; N/A = not applicable; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PET = positron emission tomography; PK = pharmacokinetic(s); qw = weekly; q2w = every 2 weeks; q3w = every 3 weeks; RP2D = recommended Phase 2 dose; ULN = upper limit of normal; WOCBP = women of childbearing potential.

a Visit windows will coincide with the study therapy administration windows; that is, ±2 days for subjects in the qw cohorts and Cohorts 6b, 7b, and 8b, and ±3 days for subjects in the q2w cohorts.

b Evaluations performed as part of the pretreatment assessment do not need to be repeated on Day 1 of Week 1 unless required in the opinion of the Investigator.

c Written permission will be given by each subject prior to undergoing any protocol-specific pretreatment evaluations and prior to receiving treatment.

d At baseline, serum pregnancy test is required for WOCBP. Thereafter, including at Week 13 (that is, 12 weeks after the first dose), every 12 weeks (or according to local regulations, whichever is more frequent), and at the 30-Day Follow-up visit, a serum or urine pregnancy test may be performed.

e ECG assessment will be performed at the following time points: Prior to the first infusion of Cycle 1 and 1 hour (±30 minutes) following the completion of the first infusion of Cycle 1; prior to the last infusion of Cycle 1 and 1 hour (±30 minutes) following the completion of the last infusion of Cycle 1; prior to the last infusion of all subsequent cycles and 1 hour (±30 minutes) following the completion of the last infusion of all subsequent cycles; and when deemed appropriate by the Investigator. 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.

Table 6. Flow Chart for Protocol

f For additional subjects enrolled at the RP2D of Part A only; they will undergo triplicate (instead of single) ECG testing, according to the following schedule: Prior to the first infusion of Cycle 1 and 1 hour (±30 minutes) following the completion of the first infusion of Cycle 1; prior to the last infusion of Cycle 1 and 1 hour (±30 minutes) following the completion of the last infusion of Cycle 1 (qw cohorts); prior to the last infusion of Cycle 3 and 1 hour (±30 minutes) following the completion of the last infusion of Cycle 3 (q2w cohorts only); and prior to the last infusion of all subsequent cycles and 1 hour (±30 minutes) following the completion of the last infusion of all subsequent cycles.

g The complete physical examination includes height (at baseline only).

h Every 2 weeks for the first 12 weeks of the study, and every 6 weeks thereafter.

i Vital signs include temperature, pulse rate, respiration rate, and blood pressure. Vital signs will be checked and recorded prior to each infusion of IMC-CS4, midway through each infusion, at the end of each infusion, and every 15 minutes for the first hour following each infusion, including Week 1, Day 1 (also to be checked and recorded at nontreatment visits during Cycle 1).

j Any preexisting toxicity should be documented, recorded, and graded (NCI-CTCAE, Version 4.0 grade) as a part of the pretreatment medical history.

k All SAEs and 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.

l Including those medications taken within 30 days prior to the first dose of study therapy.

m Every week for the first 12 weeks on therapy. After Week 12, C-reactive protein assessment will be performed q2w; hematology and serum chemistry will be performed q2w for Cohorts 1, 2, 3, 4, 5, 6a, 6c, 7a, 7c, 8a, and 8c and q3w for Cohorts 6b, 7b, and 8b (that is, on rest Weeks 3 and 6).

n Hematology and serum chemistry evaluations performed within 7 days prior to the first dose do not need to be repeated at Week 1, Day 1.

o Coagulation profile and urinalysis will be performed at the beginning of each cycle (that is, approximately every 6 weeks following the first dose of study therapy).

p Radiographic assessment of tumor response should be performed prior to the start of a cycle so that results are available before the subject receives a new cycle of treatment. However, if a DLT is observed in Cycle 1 in a subject who is benefitting from treatment, Cycle 2 dosing may be initiated within 4 weeks of Cycle 1, Day 1, with Sponsor approval; in this case, no radiographic disease assessment is required prior to dosing in Cycle 2.

q Not required if PET is performed within 28 days prior to the first dose of study therapy that is negative for bone disease.

r Bone scan at baseline, as clinically indicated. Routine bone scans during treatment must be performed only in the setting of bone-only disease (no lymph node, visceral, skin, or subcutaneous metastases), or as deemed appropriate by the Investigator.

s At the end of Cycle 1, if the subject's condition allows it, a biopsy of the tumor will be performed, regardless of whether the tumor progressed, stabilized, or regressed. If the subjects's condition does not safely permit a tumor biopsy, then a skin biopsy may be submitted.

t In cases of disease progression, if the subject's condition allows it, a tumor biopsy will be performed.

u 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. Subjects must consent to these optional procedures.

7.7 Pharmacokinetic and Other Sampling

Table 7, Table 8, and Table 9 summarize PK and other sampling scheduled to occur as part of Study IMCL CP24-1001.

Table 7. Blood Collection Schedule (Parts A and B - Weekly Cohorts 1, 2, 3, 5, 6a, 6c, 7a, 7c, 8a, and 8c)

Blood Collection Time Point[a]	Analyses						
	PK[b]	IGx[b]	PD	FC	Iso	Trop	Bone
Pretreatment							
Prior to the first infusion	X[c]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Cycle 1 (Week 1)							
Immediately after the end of the first infusion of Cycle 1	X						
1 hr after the end of the first infusion	X		X				
2 hr after the end of the first infusion	X		X				
4 hr after the end of the first infusion	X		X				
24 hr (Day 2) after the end of the first infusion	X		X	X			
48 hr (Day 3) after the end of the first infusion	X		X	X			
72 hr (Day 4) after the end of the first infusion	X		X	X			
168 hr (Day 8) after the end of the first infusion immediately (unless otherwise footnoted) prior the second infusion of Cycle 1	X	X	X	X	X[e]	X[e]	X[e]
Cycle 1 (Week 3)							
Immediately (unless otherwise footnoted) prior to the third infusion of Cycle 1				X	X[e]	X[e]	
Cycle 1 (Week 4)							
Immediately (unless otherwise footnoted) prior to the fourth infusion of Cycle 1	X	X	X	X			X[e]
Cycle 2 (Week 1)							
Prior to the first infusion of Cycle 2					X[f]	X[g]	
Cycle 2 (Week 6)							
Immediately prior to the sixth infusion of Cycle 2	X		X				
Cycle 3 (Week 1)							
Immediately prior to the first infusion of Cycle 3	X	X	X				
Immediately after the end of the first infusion	X						
1 hr after the end of the first infusion	X		X				
2 hr after the end of the first infusion	X						
4 hr after the end of the first infusion	X		X				
24 hr (Day 2) after the end of the first infusion	X						
48 hr (Day 3) after the end of the first infusion	X						
96 hr (Day 5) after the end of the first infusion	X						
168 hr (Day 8) after the end of the first infusion, immediately (unless otherwise footnoted) prior to the second infusion of Cycle 3	X		X	X			X[e]
Cycle 3 (Week 4)							
Immediately prior to the fourth infusion of Cycle 3	X	X	X				
Cycles 4-6[h]							
Prior to the last infusion of each cycle	X		X				

Table is continued on the next page.

Table 7. Blood Collection Schedule (Parts A and B - Weekly Cohorts 1, 2, 3, 5, 6a, 6c, 7a, 7c, 8a, and 8c)

Blood Collection Time Point[a]	Analyses						
	PK[b]	IGx[b]	PD	FC	Iso	Trop	Bone
Cycle 5							
Immediately prior to the first infusion of Cycle 5 (6 months after the first infusion of Cycle 1)		X					
End of Therapy							
At the End-of-Therapy visit					X[f]	X[g]	
Follow-up							
30-Day Follow-up visit[i]	X	X	X	X	X[f]	X[g]	

Abbreviations: Bone = assessment of bone metabolism markers (CTX-I and P1NP); CK = creatine kinase; CTX-I = C-terminal cross-linking telopeptide of type I collagen; ECG = electrocardiogram; FC = flow cytometry analysis; IGx = immunogenicity; Iso = isoenzyme analysis; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamic markers; PK = pharmacokinetic(s); Trop = troponin (I or T) assessment; ULN = upper limit of normal.

a It is understood that it may not be feasible to collect samples at precise intervals following the end of the infusions. Every attempt should be made to collect each of these samples as close to the time point as possible. The date and time of all PK samplings must be clearly and accurately recorded.

b PK samples will be collected from all subjects. The date and time of all samplings must be clearly and accurately recorded. The blood samples collected for PK will also be used for immunogenicity analyses. For each specified time point, 1 tube of blood is required to be drawn for any combination of PK or immunogenicity analyses. As an example, if the timing of a PK sample should coincide with that of an immunogenicity sample, the same sample will suffice for these studies and the same total amount of blood (1 tube, approximately 7.5 mL/tube) will be collected.

c Pretreatment sampling should be collected on the day of and immediately prior to the first infusion.

d IGx, PD, FC, isoenzyme analysis, and bone metabolism markers: Sample to be collected ≤7 days prior to the first infusion of Cycle 1. Troponin (I or T) analysis: Sample to be collected prior to the first infusion of Cycle 1 so that results are obtained before dosing.

e Sample to be collected at any time ≤3 days prior to the infusion. IMC-CS4 may be administered as planned while troponin (I or T) results are pending, provided no cardiac symptoms have been revealed upon ECG or physical examination.

f Analysis to be performed only if serum enzymes are ≥2.5 × ULN at Week 5 of Cycle 1.

g Analysis to be performed only if serum CK levels are ≥2.5 × ULN at Week 5 of Cycle 1. IMC-CS4 may be administered as planned while troponin (I or T) results are pending, provided no cardiac symptoms have been revealed upon ECG or physical examination.

h For subjects who proceed to Cycles 4 to 6, blood samples will be collected prior to the last infusion of each cycle. In the event that a subject does not proceed to these cycles, these samples will not be collected.

i A sample will be collected 30 days after last dose of investigational agent, regardless of duration of therapy.

Note: If at any time a subject experiences an infusion-related reaction to 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.

Table 8. Blood Collection Schedule (Part A - Every-2-Week Cohort 4)

Blood Collection Time Point[a]	Analyses						
	PK[b]	IGx[b]	PD	FC	Iso	Trop	Bone
Pretreatment							
Prior to the first infusion	X[c]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Cycle 1 (Week 1)							
Immediately after the end of the first infusion of Cycle 1	X						
1 hr after the end of the first infusion	X		X				
2 hr after the end of the first infusion	X		X				
4 hr after the end of the first infusion	X		X				
24 hr (Day 2) after the end of the first infusion	X		X				
72 hr (Day 4) after the end of the first infusion	X		X	X			
168 hr (Day 8) after the end of the first infusion	X		X				
336 hr (Day 15) after the end of the first infusion, immediately (unless otherwise footnoted) prior to the second infusion of Cycle 1	X	X		X	X[e]	X[e]	X[e]
Cycle 1 (Week 3)							
Immediately after the end of the second infusion of Cycle 1	X						
1 hr after the end of the second infusion	X		X				
2 hr after the end of the second infusion	X		X				
4 hr after the end of the second infusion	X		X				
24 hr (Day 2) after the end of the second infusion	X		X				
72 hr (Day 4) after the end of the second infusion	X		X				
168 hr (Day 8) after the end of the second infusion	X		X				
336 hr (Day 15) after the end of the second infusion (Week 5)	X		X				
504 hr (Day 22) after the end of the second infusion (Week 6) of Cycle 1	X		X				
Cycle 2 (Week 1)[h]							
Prior to the first infusion of Cycle 2					X[f]	X[g]	
Cycle 2 (Week 5)[h]							
Immediately prior to the third infusion of Cycle 2	X		X				
Cycle 3 (Week 1)[h]							
Immediately prior to the first infusion of Cycle 3	X	X	X				
Immediately after the end of the first infusion	X						
1 hr after the end of the first infusion	X		X				
2 hr after the end of the first infusion	X						
4 hr after the end of the first infusion	X		X				
24 hr (Day 2) after the end of the first infusion	X						
72 hr (Day 4) after the end of the first infusion	X						
168 hr (Day 8) after the end of the first infusion	X						
336 hr (Day 15) after the end of the first infusion, immediately prior to the second infusion of Cycle 3	X		X	X			
Cycle 3 (Week 5)[h]							
Immediately prior to the third infusion of Cycle 3	X	X	X				
Cycles 4-6[h]							
Prior to the last infusion of each cycle	X		X				

Table is continued on the next page.

Table 8. Blood Collection Schedule (Part A - Every-2-Week Cohort 4)

Blood Collection Time Point[a]	Analyses						
	PK[b]	IGx[b]	PD	FC	Iso	Trop	Bone
Cycle 5							
Immediately prior to the first infusion of Cycle 5 (6 months after the first infusion of Cycle 1)		X					
End of Therapy							
At the End-of-Therapy visit					X[f]	X[g]	
Follow-up							
30-Day Follow-up visit[i]	X	X	X	X	X[f]	X[g]	

Abbreviations: Bone = assessment of bone metabolism markers (CTX-I and P1NP); CK = creatine kinase; CTX-I = C-terminal cross-linking telopeptide of type I collagen; ECG = electrocardiogram; FC = flow cytometry analysis; IGx = immunogenicity; Iso = isoenzyme analysis; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamic markers; PK = pharmacokinetic(s); Trop = troponin (I or T) assessment; ULN = upper limit of normal.

a It is understood that it may not be feasible to collect samples at precise intervals following the end of the infusions. Every attempt should be made to collect each of these samples as close to the time point as possible. The date and time of all PK samplings must be clearly and accurately recorded.

b PK samples will be collected from all subjects. The date and time of all samplings must be clearly and accurately recorded. The blood samples collected for PK will also be used for immunogenicity analyses. For each specified time point, 1 tube of blood is required to be drawn for any combination of PK or immunogenicity analyses. As an example, if the timing of a PK sample should coincide with that of an immunogenicity sample, the same sample will suffice for these studies and the same total amount of blood (1 tube, approximately 7.5 mL/tube) will be collected.

c Pretreatment sampling should be collected on the day of and immediately prior to the first infusion.

d IGx, PD, FC, isoenzyme analysis, and bone metabolism markers: Sample to be collected ≤7 days prior to the first infusion of Cycle 1. Troponin (I or T) analysis: Sample to be collected prior to the first infusion of Cycle 1 so that results are obtained before dosing.

e Sample to be collected at any time ≤3 days prior to the second infusion of Cycle 1. IMC-CS4 may be administered as planned while troponin (I or T) results are pending, provided no cardiac symptoms have been revealed upon ECG or physical examination.

f Analysis to be performed only if serum enzymes are ≥2.5 × ULN at Week 5 of Cycle 1.

g Analysis to be performed only if serum CK levels are ≥2.5 × ULN at Week 5 of Cycle 1. IMC-CS4 may be administered as planned while troponin (I or T) results are pending, provided no cardiac symptoms have been revealed upon ECG or physical examination.

h For subjects who proceed to Cycles 2 to 6, blood samples will be collected as shown in this table. In the event that a subject does not proceed to these cycles, these samples will not be collected.

i A sample will be collected 30 days after last dose of investigational agent, regardless of duration of therapy.

Note: If at any time a subject experiences an infusion-related reaction to 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.

Table 9. Blood Collection Schedule (Part B - Cohorts 6b, 7b, and 8b)

Blood Collection Time Point[a]	Analyses						
	PK[b]	IGx[b]	PD	FC	Iso	Trop	Bone
Pretreatment							
Prior to the first infusion	X[c]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Cycle 1 (Week 1)							
Immediately after the end of the first infusion of Cycle 1	X						
1 hr after the end of the first infusion	X		X				
2 hr after the end of the first infusion	X		X				
4 hr after the end of the first infusion	X		X				
24 hr (Day 2) after the end of the first infusion	X		X	X			
48 hr (Day 3) after the end of the first infusion	X		X	X			
72 hr (Day 4) after the end of the first infusion	X		X	X			
168 hr (Day 8) after the end of the first infusion immediately (unless otherwise footnoted) prior the second infusion of Cycle 1	X	X	X	X	X[e]	X[e]	X[e]
Cycle 1 (Week 2)							
1 hr after the end of the second infusion of Cycle 1	X						
2 hr after the end of the second infusion	X						
4 hr after the end of the second infusion	X						
24 hr (Day 2) after the end of the second infusion	X						
48 hr (Day 3) after the end of the second infusion	X						
72 hr (Day 4) after the end of the second infusion	X						
168 hr (Day 8) after the end of the second infusion of Cycle 1	X						
Cycle 1 (Week 4)							
Immediately (unless otherwise footnoted) prior to the third infusion of Cycle 1			X	X	X[e]	X[e]	
Cycle 1 (Week 5)							
Immediately (unless otherwise footnoted) prior to the fourth infusion of Cycle 1	X	X	X	X			X[e]
Cycle 2 (Week 1)							
Prior to the first infusion of Cycle 2					X[g]	X[h]	
Cycle 2 (Week 4)							
Immediately prior to the third infusion of Cycle 2	X						
Cycle 3 (Week 1)							
Immediately prior to the first infusion of Cycle 3	X	X	X				
Immediately after the end of the first infusion	X						
1 hr after the end of the first infusion	X		X				
2 hr after the end of the first infusion	X		X				
4 hr after the end of the first infusion	X		X				
24 hr (Day 2) after the end of the first infusion	X		X	X			
48 hr (Day 3) after the end of the first infusion	X		X				
72 hr (Day 4) after the end of the first infusion	X		X				
168 hr (Day 8) after the end of the first infusion immediately (unless otherwise footnoted) prior to the second infusion of Cycle 3	X		X	X	X[f]	X[g]	X[e]

Table is continued on the next page.

Table 9. Blood Collection Schedule (Part B - Cohorts 6b, 7b, and 8b)

Blood Collection Time Point[a]	Analyses						
	PK[b]	IGx[b]	PD	FC	Iso	Trop	Bone
Cycle 3 (Week 2)							
1 hr after the end of the second infusion of Cycle 3	X						
2 hr after the end of the second infusion	X						
4 hr after the end of the second infusion	X						
24 hr (Day 2) after the end of the second infusion	X						
48 hr (Day 3) after the end of the second infusion	X						
72 hr (Day 4) after the end of the second infusion	X						
168 hr (Day 8) after the end of the second infusion	X						
Cycle 3 (Week 4)							
Immediately prior to the third infusion of Cycle 3	X	X					
Cycles 4-6[h]							
Prior to the last infusion of each cycle	X	X	X				
Cycle 5							
Immediately prior to the first infusion of Cycle 5 (6 months after the first infusion of Cycle 1)		X					
End of Therapy							
At the End-of-Therapy visit					X[f]	X[g]	
Follow-up							
30-Day Follow-up visit[i]	X	X	X	X	X[f]	X[g]	

Abbreviations: Bone = assessment of bone metabolism markers (CTX-I and P1NP); CK = creatine kinase; CTX-I = C-terminal cross-linking telopeptide of type I collagen; ECG = electrocardiogram; FC = flow cytometry analysis; IGx = immunogenicity; Iso = isoenzyme analysis; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamic markers; PK = pharmacokinetic(s); Trop = troponin (I or T) assessment; ULN = upper limit of normal.

a It is understood that it may not be feasible to collect samples at precise intervals following the end of the infusions. Every attempt should be made to collect each of these samples as close to the time point as possible. The date and time of all PK samplings must be clearly and accurately recorded.

b PK samples will be collected from all subjects. The date and time of all samplings must be clearly and accurately recorded. The blood samples collected for PK will also be used for immunogenicity analyses. For each specified time point, 1 tube (approximately 7.5 mL/tube) of blood is required to be drawn for any combination of PK or immunogenicity analyses. As an example, if the timing of a PK sample should coincide with that of an immunogenicity sample, the same sample will suffice for these studies and the same total amount of blood (1 tube, approximately 7.5 mL/tube) will be collected.

c Pretreatment sampling should be collected on the day of and immediately prior to the first infusion.

d IGx, PD, FC, isoenzyme analysis, and bone metabolism markers: Sample to be collected ≤7 days prior to the first infusion of Cycle 1. Troponin (I or T) analysis: Sample to be collected prior to the first infusion of Cycle 1 so that results are obtained before dosing.

e Sample to be collected at any time ≤3 days prior to the infusion. IMC-CS4 may be administered as planned while troponin (I or T) results are pending, provided no cardiac symptoms have been revealed upon ECG or physical examination.

f Analysis to be performed only if serum enzymes are ≥2.5 × ULN at Week 5 of previous cycle.

g Analysis to be performed only if serum CK levels are ≥2.5 × ULN at Week 5 of previous cycle. IMC-CS4 may be administered as planned while troponin (I or T) results are pending, provided no cardiac symptoms have been revealed upon ECG or physical examination.

h For subjects who proceed to Cycles 4 to 6, blood samples will be collected prior to the last infusion of each cycle. In the event that a subject does not proceed to these cycles, these samples will not be collected.

i A sample will be collected 30 days after last dose of investigational agent, regardless of duration of therapy.

Note: If at any time a subject experiences an infusion-related reaction to 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.

8 ADVERSE EVENTS ASSESSMENTS

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

The Investigator is responsible for the appropriate medical care of subjects during the study.

The Investigator remains responsible for following, through an appropriate health care option, AEs that are serious or are reportedly related to study treatment or that caused the subject to discontinue treatment before completing the study. The subject should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stabilized or returns to baseline, the event is deemed irreversible or otherwise explained, a new treatment is initiated for the subject, or the subject dies or is lost to follow-up. Frequency of follow-up evaluation is left to the discretion of the Investigator.

The timing of all safety evaluations is shown in the study schedule (see Section 7.6).

8.1 Adverse Events

The Sponsor 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. Any clinically significant findings from ECGs, laboratory assessments, vital sign measurements, or other procedures that result in a diagnosis should be reported to the Sponsor or its designee.

Lack of drug effect is not an AE in clinical trials, because part of the purpose of a clinical trial is to establish drug effect.

Cases of pregnancy that occur during maternal or paternal exposures to study treatment and up to 12 weeks following last study treatment dose should be reported immediately. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

For all entered subjects, study site personnel will record the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. While the subject 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 the Sponsor or designee.

In addition, all AEs occurring after the subject receives the first dose of study treatment until 30 days following the discontinuation of study treatment must be reported to the Sponsor or its designee via eCRF.

Investigators will be instructed to report to the Sponsor or its designee their assessment of the potential relatedness of each AE to protocol procedure or investigational product via eCRF.

The Investigator will decide whether he or she interprets the observed AEs as 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 or procedure, the following terminologies are defined:

- **Probably 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.
- **Does not know:** The Investigator cannot determine.
- **Not related:** Without question, the AE is definitely not associated with the study treatment.

All "probably related," "possibly related," or "does not know" AEs will be defined as related to study drug/study procedure.

Subjects will be evaluated for AEs at each visit and will be instructed to call their study physician to report any AEs between visits.

NCI-CTCAE, Version 4.0 will serve as the reference document for grading the severity of all AEs and other symptoms. For AEs without matching terminology within the NCI-CTCAE, Version 4.0, the Investigator will be responsible for selecting the appropriate System Organ Class and assessing severity grade based on the intensity of the event.

In addition to collecting the AE verbatim and NCI-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 (MedDRA®).

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

8.2 Serious Adverse Events

Serious adverse event collection begins after the subject has signed the ICF and has received study treatment. If a subject experiences an SAE after signing the ICF, but prior to receiving study treatment, the event will NOT be collected unless the Investigator feels the event may have been caused by a protocol procedure.

Study site personnel must alert the Sponsor or its designee of any SAE within 24 hours of Investigator awareness of the event via a Sponsor-approved method. Alerts issued via telephone 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. An SAE is any adverse event from this study that results in one of the following outcomes:

- Death;
- Initial or prolonged inpatient hospitalization;
- A life-threatening experience (that is, immediate risk of dying);
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect; and/or
- 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 upon appropriate medical judgment, they may jeopardize the subject 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.

Previously planned (that is, planned prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the subject'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. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

Serious adverse events occurring after a subject has taken the last dose of study treatment will be collected for 30 days after the discontinuation of study treatment, regardless of the Investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the Investigator feels the events were related to either study treatment or a protocol procedure.

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System. If an Investigator becomes aware of an SAE occurring after the subject'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 SAE to the Sponsor, and the SAE will be entered into the Lilly Safety System.

8.3 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are not listed in the Development Core Safety Information (DCSI) or 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.

8.4 Safety Monitoring

The Sponsor CRP or designee will monitor safety data throughout the course of the study.

The Sponsor CRP or designee will review SAEs within time frames mandated by company procedures. The Sponsor CRP or designee, will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist (CRS), and periodically review trends and laboratory analytes.

If a subject experiences elevated ALT ≥5 × ULN and elevated total bilirubin ≥2 × ULN, clinical and laboratory monitoring should be initiated by the Investigator. For subjects 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 subject safety and comply with regulatory guidance, the Investigator is to consult with the Sponsor CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. Refer to Section 6.5 for a list of the hepatic monitoring tests to be performed.

All reportable SAEs will be submitted to the FDA in accordance with Title 21 Code of Federal Regulations (CFR) Part 312.32.

8.5 Complaint Handling

The Sponsor collects product complaints on study treatment and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to concomitant drugs/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

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

- Recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose; and
- Faxing the completed product complaint form within 24 hours to the Sponsor 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.

9 TREATMENT-RELATED ADVERSE EVENTS

Subjects will be closely monitored for treatment-related AEs, especially infusion-related reactions, immune-related adverse events (irAE), periorbital edema, and signs indicative of hepatic impairment, leukocyte alterations, and inflammation. Subjects will be evaluated for AEs at each visit and will be instructed to call their study physician to report any AEs between visits.

Adverse event collection will include verbatim term, onset and resolution dates, action taken, outcome, severity (NCI-CTCAE, Version 4.0 grade), relationship to the study therapy, and, if the event is serious, a clear indication of the seriousness.

9.1 IMC-CS4

9.1.1 Immune-Related Adverse Events

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 irAE occurring following infusion of investigational therapy, investigators are encouraged to refer to Table 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. Table 10 is a guideline for the management of irAEs; local standards may supersede recommendations when deemed appropriate by the Investigator.

Table 10. 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.
			Symptomatic	Continue drug. Administer thyroid replacement.
	Hypotension, altered mental status, headache, fatigue		Endocrine issues aside from thyroid (for example, hypophysitis)	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.
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		Permanently discontinue drug. Administer steroids (1-2 mg/kg/d prednisone), except if the possibility of perforation exists. If >3 days' duration despite steroids, also administer nonsteroidal immunosuppressive.
	Pancreatitis	1-2		Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Can resume drug during taper.
		≥3		Permanently discontinue drug.

Table 10. 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	
Hepatobiliary	Transaminitis, elevated bilirubin		**Subjects with baseline AST or ALT ≤2.5 × ULN:** AST or ALT >5 × ULN but ≤7.5 × ULN and total bilirubin ≤ULN	Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Resume drug when AST or ALT ≤5 × ULN.
			Subjects with baseline AST or ALT >2.5 × ULN and ≤5 × ULN: AST or ALT >7.5 × but ≤10 × ULN and total bilirubin ≤ ULN	Withhold drug. Administer steroids (1-2 mg/kg/d prednisone). Resume drug when AST or ALT ≤7.5 × ULN.
			Subjects with baseline AST or ALT ≤2.5 × ULN: AST or ALT >7.5 × ULN or total bilirubin > 3× ULN	Permanently discontinue drug. Administer steroids (1-2 mg/kg/d prednisone).
			Subjects with baseline AST or ALT >2.5 × ULN and ≤5 × ULN: AST or ALT >10 × ULN or total bilirubin >3× ULN	Permanently discontinue drug. Administer steroids (1-2 mg/kg/d prednisone).
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.
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).

Table 10. 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	
Renal and urinary	Elevated creatinine, decreased urine output, blood in urine, edema	1	<1.5 × baseline	Continue drug.
		2-3	>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.
		4	>6 × ULN	Permanently discontinue drug. Administer steroids (1-2 mg/kg/d prednisone).
Skin	Rash, pruritus		≤50% skin affected	Withhold drug. 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 regarding steroids: Steroids should be tapered over 1 month after symptoms have resolved; if withheld drug may be resumed (that is, not permanently discontinued), it can be resumed only after taper has begun. Other steroid options (besides those shown in this table) may be administered at equivalent doses. For severe adverse events, administration of I.V. steroids is recommended. In the case of adrenal crisis, mineralocorticoid should be administered in addition to steroids.

9.1.2 IMC-CS4 Infusion-Related Reactions

Symptoms occurring during or following infusion of investigational therapy will be defined according to the NCI-CTCAE, Version 4.0 definition of infusion-related reaction (General Disorders and Administration Site Conditions) or as allergic reaction, anaphylaxis, or cytokine release syndrome (under "Immune System Disorders" in NCI-CTCAE, Version 4.0) as detailed in Table 11.

In the setting of symptoms occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE term "infusion-related reaction" and any additional terms (including those not listed here) that best describe the event. Those described above should be graded as follows:

Table 11. NCI-CTCAE, Version 4.0, Infusion-Related Reactions

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, I.V. fluids); prophylactic medications indicated for ≤24 hr	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse reaction to the infusion of pharmacological or biological substances.					
Allergic reaction	Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤24 hr	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.					
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, I.V. fluids); prophylactic medications indicated for ≤24 hr	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilator support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					

Consistent with usual medical practice, selected parenteral medications may be utilized for Grade 2 allergic/hypersensitivity reaction as detailed below. The Sponsor CRP should be contacted immediately if questions arise concerning the grade of the reaction. The following are treatment guidelines for IMC-CS4 infusion-related reactions:

Grade 1

- Slow the infusion rate by 50%.
- Monitor the subject for worsening of condition.
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent); additional premedication may be administered at the Investigator's discretion.

Grade 2

- Stop the infusion.
- Administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally for fever, and oxygen.
- Resume the infusion at 50% of the prior rate once the infusion-related reaction has resolved to Grade ≤1; the infusion duration should not exceed 3 hours.
- Monitor for worsening of condition.
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent); additional premedication may be administered at the Investigator's discretion.

For a second Grade 1 or 2 infusion-related reaction, administer dexamethasone 10 mg I.V. (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally, and dexamethasone 10 mg I.V. (or equivalent). Once the infusion rate has been reduced for a Grade 1 or 2 infusion-related reaction, it is recommended to maintain the lower infusion rate for all subsequent infusions.

Grade 3

- Stop the infusion and disconnect the infusion tubing from the subject.
- Administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), dexamethasone 10 mg I.V. (or equivalent), bronchodilators for bronchospasm, and other medications/treatment as medically indicated.
- Subjects who have a Grade 3 infusion-related reaction will not receive further IMC-CS4 treatment, but will continue to be followed on the protocol.

Grade 4

- Stop the infusion and disconnect the infusion tubing from the subject.
- Administer diphenhydramine hydrochloride 50 mg I.V. (or equivalent), dexamethasone 10 mg I.V. (or equivalent), and other medications/treatment as medically indicated.
- Give epinephrine or bronchodilators as indicated.
- Hospital admission for observation may be indicated.
- Subjects who have a Grade 4 infusion-related reaction will not receive further IMC-CS4 treatment, but will continue to be followed on the protocol.

If a subject should have an infusion-related reaction to IMC-CS4, all attempts will be made to obtain an anti-IMC-CS4 antibody blood sample as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. In addition, these same samples may be assessed for levels of IMC-CS4 and for pharmacodynamic markers to provide information on the nature of the infusion-related reaction. The procedure for sample collection and handling is described in a separate procedural manual.

9.1.3 Other Adverse Events

Based on observations in nonclinical toxicological studies with IMC-CS4 and/or observations in one clinical trial with another monoclonal antibody targeting CSF-1 (Sadis et al. 2009), subjects receiving 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 Section 1.3.3 of this protocol and the IMC-CS4 IB.

10 DOSE MODIFICATIONS

10.1 General Dose Modifications – IMC-CS4

10.1.1 During Cycle 1

No IMC-CS4 dose reductions were permitted for any subject (in Cohort 1 or 2) following a DLT. If a subject (in Cohort 1 or 2) experienced a DLT during Cycle 1, IMC-CS4 was permanently discontinued.

If benefitting from treatment (that is, no disease progression or other withdrawal criteria), any subject in Cohort 3 and beyond who experiences a DLT may continue to receive IMC-CS4 upon agreement of the Sponsor and according to the dose reduction guidelines for this study (Table 12).

In the setting of non-life-threatening reversible Grade ≤3 IMC-CS4-related toxicities in Cycle 1 that do not meet the definition of a DLT, IMC-CS4 may be held (if appropriate, in the opinion of the Investigator and upon agreement with the Sponsor) for a maximum of 3 weeks, until resolution to baseline or improvement to Grade ≤2. Upon resolution to baseline or improvement to Grade ≤2, IMC-CS4 may be administered at a reduced dose (according to Table 12) beginning with Cycle 2, if appropriate, in the opinion of the Investigator and upon agreement with the Sponsor (no dose reductions are permitted during Cycle 1 [for subjects in Cohort 1 or 2]; subjects [in Cohort 1 or 2] who would require dose reductions during Cycle 1 must be discontinued). If toxicity does not resolve to baseline or improve to Grade ≤2 within 3 weeks following the last administered dose, IMC-CS4 should be permanently discontinued.

10.1.2 After Cycle 1

Dose reductions, if required during Cycle 2 or after, in the context of IMC-CS4-related toxicity, may be implemented according to the guidelines in Table 12. Any individual subject (including those experiencing an event that occurred after the DLT assessment period that otherwise would have been considered a DLT) may be dose reduced a maximum of 2 times during the course of the study (except as noted in Table 12; for example, subjects in Cohort 3 are only permitted to have one dose reduction). Once a subject 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 subject experiencing toxicity that would necessitate more than 2 dose reductions must discontinue treatment. Dose reductions must be confirmed by the Sponsor.

Any subject who experiences a Grade 4 toxicity after Cycle 1 may continue to receive study treatment only if agreed upon by the Investigator and the Sponsor CRP and according to the dose reduction guidelines for this study (Table 12).

Table 12. General Dose Reduction Guidelines

Cohort	Starting Dose Level and Schedule	First Reduction	Second Reduction
Part A Only			
1	2.5 mg/kg (qw)	Discontinue	Discontinue
2	0.3 mg/kg (qw)	Discontinue	Discontinue
3	0.6 mg/kg (qw)	0.3 mg/kg (qw)	Discontinue
4	1.25 mg/kg (q2w)	0.6 mg/kg (qw)	0.3 mg/kg (qw)
5	1.25 mg/kg (qw)	1.25 mg/kg (q2w)	0.6 mg/kg (qw)
Part B Only			
6a	100 mg (qw)	75 mg (qw)	50 mg (qw)
6b	100 mg (Weeks 1, 2, 4, and 5)	75 mg (Weeks 1, 2, 4, and 5)	50 mg (Weeks 1, 2, 4, and 5)
6c	75 mg (qw)	50 mg (qw)	40 mg (qw)
7a	150 mg (qw)	125 mg (qw)	100 mg (qw)
7b	150 mg (Weeks 1, 2, 4, and 5)	125 mg (Weeks 1, 2, 4, and 5)	100 mg (Weeks 1, 2, 4, and 5)
7c	125 mg (qw)	100 mg (qw)	75 mg (qw)
8a	200 mg (qw)	175 mg (qw)	150 mg (qw)
8b	200 mg (Weeks 1, 2, 4, and 5)	175 mg (Weeks 1, 2, 4, and 5)	150 mg (Weeks 1, 2, 4, and 5)
8c	175 mg (qw)	150 mg (qw)	125 mg (qw)

Abbreviations: qw = weekly; q2w = every 2 weeks.

10.1.3 Infusion-Related Reactions

Apart from measures for preemptive and/or therapeutic medical treatment as detailed in Section 9.1.2, the following recommendations regarding the administration of IMC-CS4 should be followed:

If a subject experiences Grade 1 infusion-related reaction/allergic reaction, infusion rate should be decreased by 50% for the duration of the infusion. In case of a Grade 2 infusion-related reaction/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 infusion-related reaction, it is recommended to maintain the lower infusion rate for all subsequent infusions. (Premedication must be provided prior to any subsequent doses of IMC-CS4 if the subject has experienced a Grade 1 or 2 infusion-related reaction.) Occurrence of a Grade 3 or 4 infusion-related reaction requires immediate and permanent discontinuation of IMC-CS4.

10.2 Removal of Subjects from Therapy

The Investigator must withdraw a subject from IMC-CS4 for any of the following reasons:

- The Sponsor or Investigator terminates the study;
- The Investigator/physician or Sponsor decides that the subject should be withdrawn from the study or study drug;
- The subject, 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 to occur prior to introduction of the other agent);
- An unacceptable AE/toxicity (for example, a persistent moderate toxicity that is intolerable to the subject or requires >2 dose reductions);
- A DLT occurring in a subject in Cohort 1 or 2 only (a DLT occurring in a subject in Cohort 3 or beyond would not necessarily be a withdrawal criterion);
- A Grade 3-4 infusion-related reaction;
- Any therapy-related event that is deemed life-threatening, regardless of NCI-CTCAE, Version 4.0 grade;
- Any event that would warrant IMC-CS4 therapy to be held for more than 3 weeks following the last administered dose, or to be dose reduced more than 2 times;
- Radiographic documentation of PD (refer to Note in Section 4.1);
- A decline in ECOG PS that, in the opinion of the Investigator, necessitates discontinuation of study therapy;
- Subject noncompliance (in the opinion of the Investigator or Sponsor) with this study protocol;
- Subject pregnancy or breastfeeding;
- Enrollment by the subject 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;
- An intercurrent illness or change in the subject's condition that renders the subject unsuitable for further treatment in the opinion of the Investigator and/or Sponsor; and/or
- Withdrawal of consent.

After termination of study therapy, the subject will be treated as clinically indicated by the Investigator or referring physician. If the reason for withdrawal from the trial is the death of the subject, the 2 options for categorizing withdrawal are either: (1) PD or (2) an AE (more than one

AE may be documented as a reason for withdrawal). Only one event will be recognized as the cause of death.

If a subject is discontinued from all study therapy:

- The reason(s) for discontinuation should be documented in the subject's medical record and eCRF. The date of discontinuation from study treatment is to be reported on the eCRF.
- An end-of-therapy evaluation should be performed.
- A follow-up evaluation should be performed approximately 30 days after the last dose of study medication. Subjects who discontinue will have follow-up procedures performed as shown in Table 6.
- In addition, all subjects with unresolved SAEs or IMC-CS4-related AEs will be followed at regularly scheduled intervals beyond the 30-Day Follow-up visit until the event is resolved, the event is no longer considered to be drug-related, the event becomes stabilized or returns to baseline, the event is deemed irreversible or otherwise explained, a new treatment is initiated for the subject, or the subject dies or is lost to follow-up.

10.3 Concomitant Therapy

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be offered to all subjects on this trial. Details of interventions (for example, medications such as sedatives, antibiotics, analgesics, antihistamines, steroids, erythropoietin), procedures (for example, paracentesis, thoracentesis), or blood products (for example, blood cells, platelets, or fresh frozen plasma transfusions) should be recorded in eCRFs.

10.4 Prohibited and Restricted Therapies during the Study

10.4.1 Prohibited Therapies

Additional concurrent chemotherapy, radiation therapy, biologic response modifiers, or other investigational anticancer agents may not be administered to subjects on this study. Palliative radiation to symptomatic sites of disease will not be permitted while on study. An exception to these prohibited therapies is that subjects with metastatic breast or prostate cancer who have been on a stable dose (≥28 days) of an approved (anticancer) hormonal agent will not be excluded (ie, they will be eligible).

10.4.2 Restricted Therapies

None, other than detailed above and in the inclusion/exclusion criteria (Sections 3.2 and 3.3).

10.4.3 Precautions

See Section 9.1.2 regarding infusion-related reactions.

10.5 Nontherapy Precautions and Restrictions

None, other than detailed above and in the inclusion/exclusion criteria (Sections 3.2 and 3.3).

10.6 Supportive Care Guidelines

10.6.1 Granulocyte Colony-Stimulating Factors

Although neutropenia is not an expected side effect of IMC-CS4, the use of granulocyte colony-stimulating factors (G-CSFs) is permitted during investigational therapy, based on American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2015). G-CSF or similar agents are strongly recommended following Grade 3 or 4 neutropenia lasting more than 5 days duration or following any incidence of febrile neutropenia.

10.6.2 Erythroid Growth Factors

The use of erythroid stimulating factors (for example, erythropoietin) is permitted at the Investigator's discretion based on current American Society of Hematology/ASCO guidelines (Rizzo et al. 2010).

10.6.3 Transfusion of Blood Products

Transfusions of red blood cells, platelets, or other blood products are permitted at the Investigator's discretion.

10.6.4 Antiemetic Therapy

Both prophylactic and symptom-directed antiemetic therapies are permitted and should be used in accordance with institutional guidelines (when existent) and/or at Investigator's discretion.

10.6.5 Premedication for IMC-CS4

Premedication such as antihistamines or steroids for the prophylaxis of hypersensitivity is not recommended to be administered prior to the first infusion of IMC-CS4 administration. Premedication must be implemented in the setting of a prior Grade 1-2 IMC-CS4-related infusion-related reaction and is detailed in Section 9.1.2.

11 CRITERIA FOR TUMOR RESPONSE EVALUATION

Study evaluations will take place in accordance with the flow chart in Section 7.6.

Subjects will be evaluated for response according to RECIST 1.1 guidelines (Eisenhauer et al. 2009). Radiographic assessment of tumor response will be performed at the end of the initial 6-week cycle, and the end of every subsequent cycle. However, if a DLT is observed in Cycle 1 in a subject who is benefitting from treatment, Cycle 2 dosing may be initiated within 4 weeks of Cycle 1, Day 1, with Sponsor approval; in this case, no radiographic disease assessment is required prior to dosing in Cycle 2.

Refer to Note in Section 4.1 regarding the possibility of study treatment continuation in subjects until there is unequivocal evidence of PD. (Radiographically confirmed disease progression [that is, numerical disease progression, per RECIST] only is not sufficient to discontinue treatment.)

11.1 Baseline Tumor Assessments

The baseline tumor burden (unidimensionally measurable and nonmeasurable disease) will be assessed as closely as possible to the beginning of treatment and never more than 28 days prior to first dose of study therapy. The Investigator will prospectively identify the lesions to be followed to evaluate the subject's response to therapy (see Section 11.4).

11.2 Method of Tumor Response Assessment

All measurements should be taken and recorded in metric notation.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and at reassessment during treatment. Only imaging-based evaluations will be used to evaluate the antitumor effect of a treatment. CT will be considered the best currently available and reproducible imaging method to measure target lesions (as defined in Section 11.4.1). CT should be performed with cuts of 5 mm or less in slice thickness (as a general rule, lesion diameter should be no less than double the slice thickness). This applies to tumors of the chest, abdomen, and pelvis (RECIST guidelines specify that lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and

surrounded by aerated lung; however, chest CT is strongly preferred by RECIST guidelines and mandatory in this study). MRI is also acceptable in certain conditions (for example, for body scans). Ultrasound is not an acceptable method by which to measure disease. Bone scans, PET scans, or plain films are not sufficient to measure bone lesions, but may be used to confirm the presence or disappearance of such lesions. Tumor markers alone are not sufficient to assess objective response.

11.3 Definitions

11.3.1 Measurable

Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm (this requirement based on a CT slice thickness of ≤5 mm; for slice thicknesses >5 mm, measurable lesions must have a longest diameter ≥2 times the slice thickness).

A lymph node will be considered pathologically enlarged and measurable if its short axis is ≥15 mm; the short axis should be measured and followed throughout. Nodes with a short axis ≥10 mm and <15 mm will be considered pathologically enlarged but nonmeasurable (see below).

Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft-tissue components will be considered measurable if the soft-tissue component can be evaluated by cross-sectional imaging (that is, CT scan) and meets the general definition of measurability.

Simple cysts will not be considered malignant lesions, and will be neither measurable nor nonmeasurable. Cystic lesions believed to be metastases may be considered measurable if they meet the general definition of measurability, but noncystic lesions are preferred as target lesions.

A lesion located in a previously irradiated area, or in an area previously subjected to any locoregional therapy, will be considered measurable only if there has been a documented increase in lesion size subsequent to prior treatment but prior to study entry.

11.3.2 Nonmeasurable

All other lesions including small lesions (longest diameter <10 mm or pathological lymph nodes with a short axis of ≥10 mm and <15 mm) and truly nonmeasurable lesions.

Lesions considered to be truly nonmeasurable include the following: bone lesions; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques. Blastic bone lesions are nonmeasurable.

11.4 Definitions of Response

Overall tumor response, as defined in Table 13, will be based on an integration of the evaluation of target, nontarget, and new lesions, as described below:

11.4.1 Target Lesions

Target lesions are all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs. Target lesions should be selected on the basis of their size (those with the longest diameters) and their suitability for accurate repeated measurements.

The short axis of any lymph nodes selected as target lesions at baseline (≥15 mm) will be measured and recorded at each evaluation time point, even if the nodes become nonpathological (short axis <10 mm).

The sum of the diameters of all target lesions (longest for non-nodal lesions, short axis for nodal lesions) will be calculated at baseline and reported as the baseline sum diameter. This baseline sum diameter will be used as the reference by which to characterize the objective tumor response. For lesions measurable in 2 or 3 dimensions, always report the longest diameter at the time of each assessment.

Complete Response (CR):
The disappearance of all non-nodal target lesions, with the short axes of any target lymph nodes reduced to <10 mm.

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

Stable Disease (SD):

Neither sufficient shrinkage to qualify for partial response (PR) nor sufficient increase to qualify PD, taking as reference the smallest sum diameter since the treatment started.

Progressive Disease (PD):

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

Inevaluable or Non-evaluable (NE):

A target lesion present at baseline which is subsequently not measured or which is unable to be evaluated or there is a change in the method of measurement from baseline that impacted the ability to make a reliable evaluation of response, leading to an inability to determine the status of that particular tumor for the time point in question. This category also includes scans that are not performed at this time point to evaluate the target lesion(s). The reason(s) explaining the absence of the evaluation or non-evaluable (NE) nature of the lesion(s) should be specified at the time of the assessment (for example, early death due to malignant disease; early death due to toxicity; tumor assessments not repeated or incomplete; other [specify]).

11.4.1.1 Lesions Too Small to Measure

Lesions that become too small to measure during treatment must be assigned a default measurement of either 0 mm (if the Investigator believes the lesion has disappeared) or 5 mm (if the lesion is still present).

11.4.1.2 Lesions That Split or Coalesce

If a target lesion splits into multiple fragments during treatment, the longest diameters of each fragment should be added together to generate the total sum for that lesion. When lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements for each individual lesion. If the lesions are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

11.4.2 Nontarget Lesions

All lesions (or sites of disease) not characterized as target lesions (see Section 11.4.1), both measurable and nonmeasurable, will be identified as nontarget lesions and will be recorded at baseline. Measurements will not be required, and these lesions will be followed as "present," "absent," or "unequivocal progression" (see below).

Complete Response (CR):

The disappearance of all nontarget lesions, the normalization of the tumor marker level (if tumor markers are measured and are initially above the ULN, those must normalize for a subject to be considered in complete clinical response). All lymph nodes must be <10 mm (short axis).

Non-CR/Non-PD:

The persistence of one or more nontarget lesions and/or the maintenance of the tumor marker level above normal limits.

Progressive Disease (PD):

The appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions. Progressive disease may be declared on the basis of "unequivocal progression" in cases where the overall tumor burden increases significantly enough to require a change in therapy; in most cases, a modest increase in the size of one or more nontarget lesions is not sufficient to qualify (especially in the presence of stable disease [SD] or PR in target disease).

Inevaluable or Non-evaluable (NE):

A nontarget lesion present at baseline that is subsequently not measured or which is unable to be evaluated or there is a change in the method of measurement from baseline that impacted the ability to make a reliable evaluation of response, leading to an inability to determine the status of that particular tumor for the time point in question. This category also includes scans that are not performed at this time point to evaluate the nontarget lesion(s). The reason(s) explaining the absence of the evaluation or NE nature of the lesion(s) should be specified at the time of the assessment (for example, early death, malignant disease; early death, toxicity; tumor assessments not repeated or incomplete; other [specify]).

11.4.3 New Lesions

The finding of a new lesion should be unequivocal (that is, not attributable to a change in scanning technique or imaging modality, and not thought to represent something other than a tumor). If a possible new lesion is equivocal, treatment and radiological evaluation should continue per this protocol until confirmation of disease progression or until additional scans confirm the presence of a new lesion. In such a case, the date of progression will be the date of the initial scan at which the equivocal new lesion was observed.

A lesion identified on a follow-up study of an anatomical location *not* studied at baseline will qualify as a new lesion.

Fluorodeoxyglucose (FDG)-PET scanning may be employed as a complement to CT scanning in the assessment of possible new lesions. A negative FDG-PET scan at baseline with a positive scan on study will be evidence of PD. If there is no FDG-PET scan at baseline and a positive FDG-PET scan during the study, it will be considered evidence of PD if the positive FDG-PET corresponds to a new site of disease confirmed by CT scan. A positive on-study FDG-PET result corresponding to a preexisting site of disease with no radiological evidence of progression will not be considered evidence of PD.

11.5 Determination of Overall Response

Each response parameter (target, nontarget, and new lesions) will be reported independently at each radiologic read. The Investigator will make a determination of overall response based on the evaluation of target, nontarget, and new lesions, as shown in Table 13.

Table 13. Overall Response

Target Lesions	Nontarget 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[a]	No	PR
SD	Non-PD or not all evaluated[a]	No	SD
Not all evaluated[a]	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 = non-evaluable or inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

a In general, if only a subset of lesion measurements are taken at a given assessment time point, the subject as a whole is considered NE for that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.

For subjects who discontinue therapy for reasons other than disease progression (for example, toxicity), every effort will be made to document tumor measurements and the extent of disease, even after discontinuation of therapy, in order to classify subjects for overall response as described above.

Symptomatic deterioration sufficient to warrant discontinuation of therapy will *not* be considered a descriptor of response, but rather only a reason for stopping therapy. Whenever possible, subjects removed from therapy solely for symptomatic progression should be followed for subsequent radiographic progression. Response evaluation in a subject who discontinues treatment due to symptomatic deterioration in the absence of radiological confirmation of PD should be based on evaluation of target and nontarget lesions as described above.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated and ruled out (for example, by FNA/biopsy) before confirming the CR status. FDG-PET scanning may also be used to confirm a response of CR under appropriate circumstances (for example, similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring).

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

Statistical analysis of this study will be the responsibility of the Sponsor.

The interpretation of the study results will be the responsibility of the investigators with the Lilly CRP or CRS, pharmacokineticist, and statistician. The CRP or CRS and statistician will also be responsible for the appropriate conduct of an internal review for both the final study report and any study-related material to be authorized by Lilly for publication.

The analyses for this study will be descriptive, except for possible exploratory analyses as deemed appropriate. Data analyses will be provided by dose levels and for all subjects combined, wherever appropriate. For continuous variables, summary statistics will include number of subjects (N), mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using N, frequency, and percentages. Missing data will not be imputed. Exploratory analyses of the data that are not described in the protocol will be conducted as deemed appropriate. A detailed description of data analyses will be provided in a separate statistical analysis plan document for this study.

This is a Phase 1 study with an open-label, dose-escalation design. Subjects will be enrolled into cohorts sequentially without randomization to dose level. During dose escalation, the total sample size per cohort will be guided by the standard oncology 3+3 method and determined by the occurrences of DLTs for the treated subjects. The total sample size for Parts A and B is estimated to be approximately 72 treated subjects. In Part A, the sample size is estimated to be approximately 30 subjects. In Part B, the sample size is estimated to be approximately 9 to 42 subjects.

Pretreatment and posttreatment anti-IMC-CS4 samples will be assayed using an immunoassay. A sample will be considered positive for IMC-CS4 antibodies if it exhibits a postbaseline antibody level that exceeds the upper 95% confidence interval of the mean determined from the normal anti-IMC-CS4 level seen in healthy untreated individuals.

12.2 Analysis Populations

All enrolled subjects who received at least one dose of IMC-CS4 will be included in the safety population.

Subjects who complete the initial 6 weeks of therapy (that is, receive all scheduled treatments for Cycle 1 and complete the observation period, as needed) or experience a DLT will be included in the DLT population. The DLT population will be used for the determination of the RP2D, including evaluation of DLTs. All other variables (including demographic and baseline subject characteristics, efficacy and safety variables) will be analyzed using the safety population.

12.3 Subject Disposition

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

Additional summary of subject participation flow will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements. A participant flow will describe how many enrolled subjects completed the study, and for those who did not, the frequency of each reason for not completing.

12.4 Demographics and Baseline Characteristics

Baseline demographics, disease characteristics, prior anticancer therapy, and medical history will be listed and/or tabulated by cohort.

12.5 Analyses of Safety Data

12.5.1 Extent of Exposure

Exposure analyses will be based on the actual dose administered (in mg) and body weight (in kg) per the eCRF. The baseline body weight will be used for calculating each dose unless the subject's weight changes ≥10% from baseline and a dose change is required. Dose intensity and relative dose intensity will be calculated based on the dose administered and the most recent body weight recorded prior to treatment administration. Exposure analyses will include duration of treatment (weeks), number of subjects treated by cycle, number of infusions per subject,

cumulative dose, dose intensity and relative dose intensity, and number (%) of subjects with dose modifications (reduced or delayed).

12.5.2 Safety Analysis

The number of subjects who experience any DLT will be presented based on all DLT-evaluable subjects (DLT population). All other safety analyses will be performed using the safety population (that is, all subjects who received any dose of study therapy).

All subjects will be assessed regularly for potential occurrence of AEs from the time that the subject provides informed consent, until 30 days after the last dose of study therapy. An AE will be regarded as treatment-emergent if its onset date occurs: any time after the administration of the first dose of study medication, up to 30 days after the last dose of study medication (or up to any time if related to study medication), or prior to first dose date and worsens while on study medication.

AEs will be summarized by MedDRA System Organ Class and Preferred Term, classified from verbatim terms. The incidence and percentage of subjects with at least one occurrence of a Preferred Term will be included, according to the most severe NCI-CTCAE, Version 4.0 grade. Causality (relationship to study drug) will be summarized separately.

All treatment-emergent AEs, SAEs, and NCI-CTCAE, Version 4.0 Grade 3 or higher AEs; related AEs, SAEs, and NCI-CTCAE, Version 4.0 Grade 3 or higher AEs; AEs leading to dose modification and study medication discontinuation; and deaths will be summarized according to MedDRA Preferred Terms. Duration of AE will be determined and included in listings along with action taken and outcome.

Laboratory results will be classified according to NCI-CTCAE, Version 4.0. Laboratory results not corresponding to an NCI-CTCAE, Version 4.0 term will not be graded. Laboratory toxicity shifts from baseline to worst grade will be provided. The last measurement before study medication will serve as the baseline measurement. Results for variables that are not part of the NCI-CTCAE, Version 4.0 will be presented in the listings as below, within, or above the normal limits of the local laboratory.

The results from physical examination, vital sign measurement, and other assessments will be tabulated, if appropriate.

12.6 Analyses of Antitumor Response

Radiographic assessment of tumor response will be performed at the end of the initial 6-week cycle and the end of every subsequent cycle. However, if a DLT is observed in Cycle 1 in a subject who is benefitting from treatment, Cycle 2 dosing may be initiated within 4 weeks of Cycle 1, Day 1, with Sponsor approval; in this case, no radiographic disease assessment is required prior to dosing in Cycle 2. Tumor response data will be summarized, if appropriate.

12.7 Other Assessments or Analyses

12.7.1 Pharmacokinetic Assessments

Blood samples for PK will be analyzed at a laboratory designated by the Sponsor. Parameters to be reported may include, but not be limited to, C_{max}, C_{min}, AUC, $t_{1/2}$, Cl, and V_{ss} of IMC-CS4, and will be generated using a noncompartmental model. PK parameters will be summarized using descriptive statistics.

12.7.2 Pharmacodynamic Assessments

Pharmacodynamic analyses will be descriptive, and correlations to safety and/or efficacy will be performed as appropriate. Those biomarkers collected from different types of tissues or assays will be analyzed separately. Whether a subject is available or willing to provide tissue samples may be considered as a potential confounding variable for exploratory pharmacodynamic analysis.

12.8 Data Safety Monitoring Plan

In order to track and clearly document/record the occurrence of DLTs and identify the decisions made regarding dose escalation, the study investigators, the Sponsor CRP, and other members of the study team, as appropriate, will meet at specific times throughout this clinical study to review subject safety data. They will make the determination regarding dose escalation based upon their review of the safety/tolerability data and upon availability the PK data from the previous cohorts. At a minimum, they will meet:

- If there are 2 subjects with DLTs within a single cohort during the DLT assessment period;
- At the completion of each dose cohort, in order to determine if dose escalation will proceed (as described in Section 4.1). This review will include safety data collected to date, across all dose cohorts;
- After the RP2D is determined, to determine whether dose escalation should proceed; and
- At least quarterly.

The aforementioned team will determine if the number of subjects experiencing DLTs, as well as any events that occurred after the DLT assessment period that otherwise would have been considered DLTs, exceeds that expected with IMC-CS4 and recommend action, if necessary. The recommended actions may include protocol modification, termination, or additional safety review at specified time points. The Sponsor CRP may perform additional periodic reviews of relevant safety data (such as a review of Council for International Organizations of Medical Sciences [CIOMS] reports); these evaluations will be documented according to the trial-level safety review plan (a separate, study-specific document that will further detail the process).

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Organizational Structure of the Study

The study sponsor, Eli Lilly and Company, may delegate certain tasks to designees, including a contract research organization or other third-party vendor.

13.2 Institutional Review Board/Approving Ethics Committee Approval

The IRB/aEC must operate in accordance with 21 CFR Part 56, or applicable local regulatory requirements, which at a minimum complies with Part 312.120. Before study initiation, the Investigator must have specified written and dated approval from the IRB/aEC for the protocol, ICF, subject recruitment materials/process (for example, advertisements), and any other written information to be provided to the subjects. Any member of the IRB/aEC who is directly affiliated with this study as an Investigator or as site personnel must abstain from the vote on the approval of the protocol. The Investigator also should provide the IRB/aEC with a copy of the IB or product labeling, information to be provided to the subjects, any relevant curricula vitae, and any updates.

The Investigator should provide the IRB/aEC with reports, updates, and other information (for example, safety updates, amendments, and administrative letters) according to all regulatory requirements and institution procedures.

13.3 Ethical Conduct of the Study

The findings of this study are expected to significantly contribute to subsequent global regulatory submissions. The Investigator is responsible for ensuring that the clinical study is conducted in accordance with the protocol, FDA GCP guidelines, FDA Financial Disclosure regulations, as well as International Conference on Harmonisation (ICH) guidelines, consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines, and any other regional/national requirements for clinical trials, as applicable.

13.4 Compliance with the Protocol and Protocol Revisions

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 Sponsor representative.

The Investigator must comply with all requirements of the protocol. If a situation occurs that requires a temporary departure from the protocol, the Investigator or other physician in attendance must contact the Sponsor CRP as soon as possible to discuss the situation and agree on an appropriate course of action. The Investigator will describe the departure from the protocol and the circumstances requiring it on the applicable subjects' eCRFs and will notify the IRB/aEC as appropriate.

The Investigator may not modify this protocol. Modifications to the protocol initiated by the Sponsor or its designee will be confirmed in writing in the form of a protocol amendment. All such amendments must be approved by the IRB/aEC; however, amendments initiated by the Sponsor that reduce risks to the subjects may be implemented prior to obtaining IRB/aEC approval. Subjects may not be enrolled in an amended protocol until that amendment has been approved by the IRB/aEC. Documentation of approval signed by the chairperson or designee of the IRB/aEC must be sent to the Sponsor or its designee. If the revision is an administrative letter, investigators must inform and obtain approval from their IRB/aEC.

13.5 Subject Information and Consent

Written informed consent will be given by each subject before entering the study, in accordance with FDA regulations (21 CFR Parts 50.20 through 50.27), ICH guidelines as implemented in the European Union and Japanese guidelines, GCP guidelines, and/or applicable local regulatory requirements.

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical trials in which they volunteer to participate, including answering any questions the subject may have throughout the study and sharing in a

timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the study in a timely manner.

13.5.1 Informed Consent Procedures

The ICF will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered into the study and to document that the subject 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 Sponsor must agree with all ICFs before they are submitted to the IRB/aEC or used at investigative sites(s). The ICF must include all elements required by the FDA, ICH guidelines as implemented in the European Union and Japanese guidelines, GCP, and/or applicable local regulatory requirements. The ICF also must include a statement that the Sponsor, its agents, and the regulatory authorities have direct access to subject records. Prior to the beginning of the study, the Investigator must have the IRB/aECs written approval/favorable opinion of the written ICF and any other information to be provided to the subjects.

The Investigator is ultimately responsible for ensuring that informed consent is given by each subject 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 procedures and prior to the administration of study drug.

The Investigator must provide the subject with a copy of the ICF and written information about the study in the language in which the subject is most proficient. The language must be nontechnical and easily understood. The Investigator should allow time necessary for the subject to inquire about the details of the study; the ICF must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The subject should receive a copy of the signed ICF and any other written information provided to study subjects prior to the subject's participation in the trial.

13.5.2 Update of the Informed Consent

The ICF and any other information provided to subjects should be revised whenever important new information becomes available that is relevant to the subject's consent and should receive

IRB/aEC approval/favorable opinion prior to use. The Investigator, or a person designated by the Investigator, should fully inform the subject of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented. During a subject's participation in the trial, any updates to the ICF and any updates to the written information will be provided to the subject.

If a protocol amendment substantially alters the study design or increases the potential risk to the subject: (1) the ICF must be revised and submitted to the IRB/aEC for review and approval, (2) the revised ICF must be used to obtain consent from subjects currently enrolled in the study, and (3) the new ICF must be used to obtain consent from new subjects prior to first dose of investigational agent.

13.6 Study Monitoring

The Sponsor and its representatives must be allowed to visit all study site locations periodically to assess the data, quality, and study integrity. On site, they will review study records and directly compare them with source documents, review regulatory documents, verify investigational agent accountability, discuss the conduct of the study with the Investigator, verify compliance with the study protocol, and verify that the facilities remain acceptable.

13.7 Case Report Forms and Study Records

For this study, the Sponsor will be using an electronic data capture (EDC) system for the collection of all study-related data. Any data for which the eCRF will serve as the source document will be identified and documented by each site in that site's study file.

An Investigator is required to prepare and maintain adequate case histories designed to record all observations and other data pertinent to the investigation on each subject enrolled in this trial. All data reported on the eCRF must be derived from source documents and be consistent with those source documents, or the discrepancies must be explained.

The confidentiality of records and information that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

The Investigator will maintain, in confidence, all information furnished by the Sponsor or designees and all data generated in the study, except as provided or required by law, and will divulge such information to the IRB/aEC with the understanding that confidentiality will be maintained by the committee.

The eCRFs should be completed as soon as possible when the data are available. If an item is not available or is not applicable, it must be documented as such by either entering "NA" in the comment field or checking the corresponding "NA" box; do not leave a space blank.

The Investigator will maintain a Delegation of Authority Page to document all persons authorized to make entries and corrections on eCRFs. A correction is made by changing the corresponding entry on the eCRF. The system will automatically ask for a reason for the change and store the original value, the new value, the date and time of the change, and the person who made the change in the audit trail.

The completed eCRF must be reviewed, electronically signed, and dated by a qualified physician who is an Investigator or subinvestigator using the built-in electronic signature feature of the EDC system. If any changes are made or additional data are added to an eCRF after the Investigator has signed and dated the form, the electronic signature will be automatically invalidated and the form will have to be re-signed. All changes and signatures are automatically stored in the audit trail of the eCRF.

13.8 Access to Source Documentation

The study may be evaluated by auditors designated by the Sponsor and by government inspectors who must be allowed access to eCRFs, source documents, and all other study files. Sponsor audit reports will be kept confidential.

THE INVESTIGATOR MUST NOTIFY THE SPONSOR PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO THE SPONSOR.

13.9 Retention of Data

The Investigator must retain disposition records, copies of electronic files, and source documents (including scans) for the maximum period required by applicable regulations and guidelines, institution procedures, or the period specified by the Sponsor or its designee, whichever is longer. The Investigator must contact the Sponsor and its designee before destroying any records associated with the study. The Sponsor and its designee will notify the Investigator when the trial records are no longer needed. If the Investigator withdraws from the study (for example, relocation, retirement), all records will be transferred to a mutually agreed-upon designee (for example, another Investigator, IRB/aEC) who will assume responsibility for the study and its conduct. Notice of such transfer will be given in writing to the Sponsor or its designee.

13.10 Financial Disclosure

Financial disclosure information must be provided by all investigators and sub-investigators and will be collected by the Sponsor before the start of the study.

13.11 Publication and Disclosure Policy

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study. In addition, the Sponsor's responsible medical officer and responsible 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.

All information concerning the investigational agent supplied by the Sponsor in connection with this study and by any other party collaborating with the Sponsor within this study, and not previously published, is considered confidential and proprietary information. This information includes, but is not limited to, the IB, clinical protocol, workbooks (if applicable), eCRFs, assay methods, Sponsor technical methodology, and basic scientific data. This confidential and proprietary information shall remain the sole property of the Sponsor and shall not be disclosed

to others without prior written consent from the Sponsor with respect to their confidential and proprietary nature and shall not be used except in the performance of this study.

To allow for the use of the information derived from this clinical study and to ensure compliance with current regulations, the Investigator is obligated to provide the Sponsor with complete test results and all data obtained in this study.

No publication, abstract, or presentation of the study will be made without the approval of the Sponsor. The Sponsor will review the manuscript to prevent forfeiture of patent rights to data not in the public domain. Prior to publication, the authorship list will be agreed upon by the Sponsor. The results of the study may be published as an original article in an appropriate medical journal. The choice of the journal will be made by the Sponsor in agreement with the coauthors.

Lilly's authorship criteria are based on the International Committee of Medical Journal Editors (ICMJE) *Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals* (www.ICMJE.org, updated August 2013):

1. Substantial contributions to conception and design of the work, or the acquisition, analysis, or interpretation of data for the work
2. Drafting the article or revising it critically for important intellectual content
3. Final approval of the version to be published
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

NOTE: Authors must meet conditions 1, 2, 3, and 4.

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