Statistical Analysis Plan I5F-IE-JSCA (v2.0)

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

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1 Title Page

Statistical Analysis Plan for Clinical Study

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

IMC-CS4 (LY3022855)

Indication: Solid tumor

This open-label, dose-escalation, Phase 1 study will investigate up to 5 dose levels and enroll approximately 24 subjects (if no dose-limiting toxicity [DLT] is observed). The study will evaluate weekly IMC-CS4 in subjects with advanced solid tumors that are refractory to standard therapy or for which no standard therapy is available and assess the MTD.

ImClone LLC, a wholly-owned subsidiary of Eli Lilly and company (ImClone)
Protocol CP24-1001 (I5F-IE-JSCA)
Phase 1
SAP Version 2.0

2 Table of Contents

Section **Page**

3 Revision history

3.1 Introduction

This statistical analysis plan for protocol CP24-1001 (I5F-IE-JSCA), Version 3.0, dated 28 March 2012, describes the detailed procedures for executing the planned statistical analyses for the clinical study report. Pharmacokinetic, pharmacodynamic and immunogenicity data will be analyzed by the ImClone LLC Clinical Pharmacology department.

The statistical analyses will be conducted by ImClone LLC or a contract research organization (CRO) using SAS® software Version 9.1.3 or higher.

3.2 Revision history

The SAP Version 1.0 was approved prior to First Patient Visit (FPV).

4 Study Objectives

4.1 Primary Objectives

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

4.2 Secondary Objectives

The secondary objectives of this study are:

- To define the recommended Phase 2 dose (RP2D);
- ~~To describe the pharmacokinetics (PK) of IMC-CS4;~~To characterize the pharmacodynamic profile of INC-CS4;
- ~~To assess the pharmacodynamic impact of IMC-CS4 on circulating CSF-1;~~
- To assess the development of antibodies against IMC-CS4 (immunogenicity); and
- ~~To assess the antitumor activity of IMC-CS4 as monotherapy in the treatment of advanced solid tumors.~~

4.3 Exploratory Objectives

The exploratory objectives of this study are:

- To assess the pharmacodynamic ~~impact of IMC-CS4 on selected RNA, protein, and circulating markers; and~~response markers including, but not limited to, CFS-1, soluble CSF-1R and interleukin-34 (IL-34)
- ~~To investigate potential correlation between selected biomarkers and the safety and efficacy of IMC-CS4.~~To assess the impact of IMC-CS4 monotherapy on LDH, CK, and alkaline phosphatase (AP) isoenymes;

- To assess the pharmacodynamic impact of IMC-CS-4 on selected cellular and molecular markers to establish a potential correlation with safety and anti-tumor activity
- To assess the pharmacodynamic impact of IMC-CS-4 on various components of the monocyte-macrophage system in hematologic or tissue specimens
- To assess the impacot 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.

5 A Priori Statistical Methods

5.1 Study populations

Subjects meeting the inclusion criteria and the exclusion criteria as specified in the study protocol are eligible for enrollment in this study.

5.1.1 All Enrolled Patients

Anyone who signed the informed consent will be included in this population.

5.1.2 Safety Population

All enrolled subjects who received at least one dose of IMC-CS4 will be included in the Safety Population, regardless of their eligibility for the study. The Safety population will be used for the analysis of baseline characteristics, efficacy data and safety data.

5.1.3 ~~Maximum Tolerated Dose~~Dose Limiting Toxicity (~~MTD~~DLT) Population

Subjects who complete the initial 6 weeks of therapy[1] or experience a DLT during the first cycle will be included in the ~~MTD~~ DLT Population. Patients who discontinued during the initial 6 weeks due to reasons other than DLT will be excluded from the ~~MTD~~ DLT population. The ~~MTD~~ DLTD population will be used for the evaluation of DLTs in order to determine the ~~MTD~~RP2D.

5.2 Definitions and data handling conventions

5.2.1 Safety Data Handling and Definitions

5.2.1.1 Coding

- **Adverse events:** All adverse events (AE) will be coded by the Medical Dictionary for Regulatory Activities (MedDRA™) and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (version 4.0 includes all of the minor versions 4.0x).

[1] i.e. first four infusions completed, plus an observation period of 21 days after last dose in cycle 1 or entry into cycle 2 if start of cycle 2 occurs before completion of the 21 days observation.

- **Pre treatment Therapy and Concurrent Therapy**: Current medications, medications taken within 30 days prior to first dose of study therapy, prior cancer therapy will be coded using the WHOdrug.

5.2.1.2 Treatment-Emergent Adverse Events

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 if it occurs prior to first dose date and worsens while on study medication.

5.2.1.3 Partial Dates for Adverse Events, Concomitant Medications and Birthday

For the patient data listings no imputation of incomplete dates will be applied. The listings will show the incomplete dates without any change. Dates with missing day or both day and month, will adhere to the following conventions:

- The missing day of onset of an adverse event or start date of a concurrent therapy will be set to:
  - The date of the first study treatment, if the onset year and month is the same as year and month of the first study treatment
  - First day of the month that the event occurred, if the onset year and month is after the year and month of first study treatment
  - The date of informed consent, if the onset month/year is before the month/year of the first study treatment.
  -
- If the onset date of an adverse event or start date of a concurrent therapy is missing both, day and month, the onset date will be set to:
  - The date of the first study treatment, if the onset year is the same as the year of the first study treatment
  - January 1 of the year of onset, if the onset year is after the year of the first study treatment

- The missing day of resolution of an adverse event or end date of a concurrent therapy will be set to the last day of the month of the occurrence. If the patient died the same month, then set the imputed date as the date of death.
- If the resolution date of an adverse event or end date of a concurrent therapy is missing both the day and month, the date will be set to:
  - December 31 of the year of occurrence. If the patient died the same year, then set the imputed date as the date of death.

Only year of birth is collected in the study. Age will be derived from year of birth by setting the date to 1 July of the year of birth.

5.2.1.4 Study Drug 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 the cumulative dose unless the subject's weight changes ≥ 10%. For subjects with a weight change ≥ 10%, the revised weight will be used from the time point of the change and onwards.

For analysis of dose exposure **across all cycles** the following definitions will be used:

- ~~Duration of cycle:~~
  - ~~**Patients discontinuing during first cycle:** Duration of cycles (in weeks)[2] = (Date of last dose – date of first dose+21) / 7~~
  - ~~**Patients discontinuing treatment after start of Cycle 2**: Duration of cycles (in weeks)[3] = (Date of last dose – date of first dose+7) / 7~~
- Duration of treatment:
  - **Patients discontinuing during first cycle:** Duration of treatment (in weeks)[4] = (Date of last dose – date of first dose+7) / 7

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[2] ~~21 days added to duration of cycle because of a 2-week observation period after last dose in cycle 1 (ie, 21 days until the next dose).~~

[3] ~~7 days added to duration of cycle because administrations are planned every week (starting from Cycle 2).~~

[4] 7 days added to duration of treatment because administrations are planned every week. Duration of treatment does not include the 2-week observation period in Cycle 1.

- **Patients discontinuing treatment after start of Cycle 2**: Duration of treatment (in weeks)[5] = Duration of cycle -14

- Cumulative dose (mg/kg) = Sum of all [administered dosages (mg) / baseline weight[6] (kg)]
- Dose intensity (mg/kg/week) = Cumulative dose / Duration of treatment
- Planned weekly dose: Refer to Table 1: Planned Dose Regimens
- Relative dose intensity (%) = (Dose intensity / Planned weekly dose) * 100.
- Number of dose reductions: total number of reduction steps comparing the intended dose level before each infusion (as entered in the eCRF) to the protocol planned dose level as referenced in Table 2: General Dose Reduction Guidelines.
- Dose delay within a cycle: a dose is considered delayed if it is administered more than 3 days after the scheduled date relative to the previous administration.

Table 1: Planned Dose Regimens

Cohort	All cycles	Dosing Frequency
1	2.5 mg/kg	Weekly
2	0.3 mg/kg	Weekly
3	0.6 mg/kg	Weekly
4	1.25 mg/kg	Every 2 weeks
5	1.25 mg/kg	Weekly
6	2.5 mg/kg	Every 2 weeks

For analysis of dose exposure **in Cycle 1 only** the same definitions as across all cycles will be used except the following:

- Duration of cycles (in weeks)[7] = (Date of last dose – date of first dose+21) / 7
  Or if start of cycles 2[8] occurs before last dose of cycle 1 + 21 days:
  Duration of cycles (in weeks)= (Date of start Cycle 2-date of first dose)/7

[5] 14 days is subtracted from the duration of cycle because the 2-week observation period is excluded from the duration of treatment.
[6] Except in case of weight change from baseline ≥10% as described above.
[7] 21 days added to duration of cycle, because of a 2-week observation period after last dose in Cycle 1 (i.e. 21 days until the next dose).
[8] Start of Cycle 2 is defined as day of first infusion of Cycle 2.

- Cumulative dose (mg/kg) = Sum of [all administered dosages during cycle 1 (mg) / baseline weight (kg)]

Table 2: General Dose Reduction Guidelines

Cohort	Planned Starting dose	First Reduction	Second Reduction
1	2.5 mg/kg weekly	Discontinue IMC-CS4	-
2	0.3 mg/kg weekly	Discontinue IMC-CS4	-
3	0.6 mg/kg weekly	0.3 mg/kg weekly	Discontinue IMC-CS4
4	1.25 mg/kg every 2 weeks	0.6 mg/kg every 2 weeks	0.3 mg/kg every 2 weeks
5	1.25 mg/kg weekly	0.6 mg/kg weekly	0.3 mg/kg weekly
6	2.5 mg/kg every 2 weels	1.25 mg/kg every 2 weeks	0.6 mg/kg every 2 weeks

Note: Actual dose levels entered in the CRF will be rounded to the nearest dose level listed in this table (e.g. any IMC-CS4 dose level >5 and < 7.5 mg/kg will be rounded to 5 mg/kg for the purpose of the dose reduction calculation). No dose reductions are allowed after a DLT. In the setting of non-life-threatening reversible Grade ≤ 3 IMC-CS4-related toxicities that do not meet the definition of a DLT, IMC-CS4 may be held (if appropriate in the opinion of the Investigator) for a maximum of 3 weeks, until resolution to Grade < 2.

5.2.2 Efficacy Data Handling and Definitions

Study evaluations will take place in accordance with the flow chart in Section 7.6 of the CP24-1001 Study Protocol.

Subjects will be evaluated for response according to RECIST 1.1 guidelines.[i] Subjects will be evaluated for response every 6 weeks (± 3 days) following the first dose of study therapy until radiographic documentation of PD, even if therapy is delayed due to toxicity or for other reasons.

5.2.2.1 Determination of Best Overall Response (BOR)

The Best Overall Response (BOR) will be determined using the RECIST (Version 1.1) guidelines. It is defined as the best response across all time points from the start of the treatment until disease progression based on investigators assessment. When SD is believed to be best overall response, it needs to be assessed a minimum of 39 days (ie, 6 weeks – 3 days as allowed per protocol) after start of treatment. Otherwise, the best overall response will be NE, unless any PD was further documented, in which case BOR will be PD. Tumor response (ie, for complete response [CR] or partial response [PR]) will not be confirmed following initial documentation of objective response.

5.2.3 General Data Handling

- **Continuous variables** will be summarized using descriptive statistics, ie, number of non-missing records (n), mean, median, standard deviation, minimum, and maximum.
- **Categorical variables** will be summarized by frequency and its corresponding percentage.
- **Missing Data**: All analyses and descriptive summaries will be based on the observed data. Unless otherwise specified, missing data will not be imputed or "carried forward."
- **Baseline Measurement**: Unless otherwise specified, the last valid (ie, non-missing) measurement prior to the first dose of study medication will serve as the baseline measurement.
- **Date of Birth**: CRF records only the year of birth. For analysis purposes, July 1 will be used as the month and day of birth
- **Age (years) =** (Date of informed consent – Date of birth + 1) / 365.25
- **Duration**: Duration is calculated as:
  - Duration (days) = (End Date – Start Date + 1)
  - Duration (weeks) = (End Date – Start Date + 1) / 7

- Duration (months) = (End Date – Start Date + 1) / 30.4375[9]
- Duration (years) = (End Date – Start Date + 1) / 365.25[10]

5.3 Data analysis

5.3.1 Disposition of Patients

The number of patients enrolled and the number of screening failures will be presented. Number (percent) of patients who were in the Safety population and in the ~~MTD~~ DLT population, discontinued treatment and discontinued study as of data cut-off date will be summarized. A patient will be considered as off treatment if the End of Treatment form has been completed. A patient will be considered as off study if the End of Study visit has been completed or withdrew consent (ie, discontinued treatment due "withdrawal of consent" according to the End of Treatment form). Number (percent) of patients who discontinued will also be summarized by reason for discontinuation. A listing of patients with protocol deviations will be provided.

5.3.2 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized using the Safety population:

Demographic:

- Age (years) and age categories (<65 years vs. ≥65 years)
- Gender
- Race and Ethnicity
- Height (cm)
- Weight (kg)
- Eastern Cooperative Oncology Group (ECOG) performance status

[4]Days in months = average number of days in a year / 12.
[5]Average number of days in a year = 365.25, reflecting the Julian Year of three years with 365 days each and one leap year of 366 days.

Medical history

Pre-treatment disease characteristics:

- Cancer type
- Initial and current TNM staging
- Pathological confirmation of malignancy
- Sites of Metastatic Disease
- Duration of disease (months from pathological confirmation of malignancy to first dose; if the day of confirmation of malignancy is unknown it will be replaced by 15MMMYYYY)

Prior anticancer treatments or surgery:

- Type of therapy
- Prior Surgery

Baseline vital signs, physical examination, laboratory assessments, tumor assessments will be included in the tables summarizing these variables across scheduled study visits.

5.3.3 Analysis of Efficacy Data

Efficacy data will be analyzed overall using the Safety population.

5.3.3.1 Response

Best 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 and overall. In addition all tumor assessments will be included in patient listings.

5.3.4 Analyses of Safety Data

5.3.4.1 Study Drug Exposure

The following variables will summarized according to the definitions provided in section 5.2.1.4. Exposure analyses will include the following:

Cycle 1 only using the MTD population:

- Number of infusions
- Cumulative dose (mg/kg)
- Dose intensity (mg/kg/week)
- ~~Adjusted dose intensity (mg/kg/week)~~
- Relative dose intensity (%)
- Number (%) of subjects with dose modifications (reduced or change of infusion rate).

Across all cycles using the Safety population

- Duration of treatment (weeks)
- Duration of cycles (weeks)
- Number (%) of subjects treated by cycle.
- Number of infusions
- Cumulative dose (mg/kg)
- Dose intensity (mg/kg/week)
- Adjusted dose intensity (mg/kg/week)
- Relative dose intensity (%)
- Number (%) of subjects with dose modifications (reduced or change of infusion rate).

5.3.4.2 Dose Delays and Dose Modifications

The number and percentage of patients with dose delays > 3 days (within Cycle 1 and overall) will be presented. The number and percentage of patients with any dose reduction (reduction to first or second dose level) will also be presented.

5.3.4.3 Treatment Emergent Adverse events

Treatment-emergent AEs will be summarized by MedDRA® System Organ Class (SOC) and preferred term (PT), 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 grade. Causality (relationship to study drug) will be summarized separately. If more than one AE is recorded for a patient within any SOC or PT term, the patient will only be counted once on the most severe grade and the closest relationship to treatment.

AEs reported with a causal relationship of 'possibly related'and 'probably related' to study medication or 'does not know' will be considered related to study medication. Missing classifications concerning study medication relationship will be considered as related to study medication.

The following will be summarized using the Safety population for all AEs, and the MTD population for AEs with onset date in Cycle 1 (ie, within 21 days after last dose in Cycle 1 and prior to start of Cycle 2):

- All AEs,
- SAEs,
- NCI-CTCAE Grade 3 or higher AEs,
- Related AEs, SAEs, and NCI-CTCAE Grade 3 or higher AEs,
- AEs leading to dose modification, study medication discontinuation, and death will be summarized according to MedDRA® Preferred Terms.
- Duration of AE will be determined and included in listings along with action taken and outcome.

5.3.4.4 Dose-Limiting toxicity

The number of subjects who experience any DLT during Cycle 1 (ie, within 21 days after last dose in Cycle 1 and prior to start of Cycle 2) will be presented based on all DLT-evaluable subjects (MTD population).

5.3.4.5 Death

All deaths that occur within 30 days of last dose of study medication as well as cause of death will be listed using the Safety population.

5.3.4.6 Performance Status, Physical Exams, Vital Signs, ECG and Laboratory Evaluations

5.3.4.6.1 Laboratory Evaluation

Laboratory results will be classified according to NCI-CTCAE grade. Laboratory results not corresponding to an NCI-CTCAE 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 will be presented in the listings as below, within, or above the normal limits of the local laboratory.

5.3.4.6.2 ECOG Performance status, Physical Exams and ECG

The results from physical examination, ECOG performance status and ECG will be tabulated.

The frequency of physical examination abnormalities will be summarized by scheduled time point.

ECOG performance status will be presented in a shift table.

Additionally, the frequency of abnormal ECG parameters will be tabulated by scheduled time point.

5.3.4.6.3 Vital signs

Vital sign measurements will be summarized using the following categories:

- Body Temperature (C): <36, 36-38.5, ≥38.5
- Systolic Blood Pressure (mmHg): <140, 140-160, ≥160
- Diastolic Blood Pressure (mmHg): <90, 90-100, ≥100
- Arterial Pulse (beats/min): <60, 60-120, ≥120
- Respiratory Rate (breaths/min): <20, 20-30, ≥30

Vital signs will be obtained weekly during the Treatment period. At every visit that includes administration of study medication, 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

Pre-infusion and post-infusion measurements at each visit will be presented as shift tables from:

- Preinfusion to Highest-on-Infusion
- Preinfusion to Lowest-on-Infusion
- Preinfusion to End-of-Infusion

5.3.5 Other Assessments or Analyses

5.3.5.1 Pharmacokinetic Assessments

Blood samples for PK will be analyzed by the ImClone Department of Clinical Pharmacology. 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.

5.3.5.2 Pharmacodynamic Assessments

Tissue (DNA, RNA and protein analyses) and whole blood analyses, including analyses of circulating levels of CSF-1, will be descriptive, and correlations to safety and/or

efficacy will be performed as appropriate. There will be a separate SAP describing the analysis of pharmacodynamic assessments.

5.4 Interim analyses and data monitoring committees

For more details about safety reviews and monitoring committees please refer to Section 12.~~6.2~~8 of the protocol.

5.5 Changes in planned analyses from the protocol

None

6 Planned summary tables and Listings

Planned table numbering and title may be modified for the clinical study report (CSR), with the final list to be reflected in a separate table shell document.

6.1 Planned Demographic Tables

Table Number	Table Title	Population
14.1.1	Patient Disposition	All enrolled patients
14.1.2	Demographic and Baseline Characteristics	Safety
14.1.3	Pre-Treatment Disease Characteristics	Safety
14.1.4	Sites of Metastatic Disease at Screening	Safety
14.1.5	Prior Anti-Cancer Therapy or Surgery	Safety
14.1.6	Medical History	Safety

6.2 Planned Efficacy Tables

Table Number	Table Title	Population
14.2.1	Best Overall Response, Disease Control Rate and Response Rate	Safety

6.3 Planned Safety Tables

Table Number	Table Title	Population
	Dose Exposure	
14.3.1.1	IMC-CS4 Dose Exposure in Cycle 1	DLT
14.3.1.2	IMC-CS4 Dose Exposure	Safety
14.3.2	IMC-CS4 Dose Delays and Modifications in Cycle 1	DLT
14.3.2	IMC-CS4 Dose Delays and Modifications	Safety
	Adverse events	
14.3.5	Summary of Adverse Events	Safety
14.3.6	DLTs by SOC and PT (Cycle 1)	DLT
14.3.7.1	Adverse Events by SOC and PT	Safety
14.3.7.2	Adverse Events by SOC and PT (Cycle 1)	DLT
14.3.8.1	Severe Adverse Events by SOC and PT	Safety
14.3.8.2	Severe Adverse Events by SOC and PT (Cycle 1)	DLT
14.3.9.1	Serious Adverse Events by SOC and PT	Safety
14.3.9.2	Serious Adverse Events by SOC and PT (Cycle 1)	DLT
14.3.10.1	Related Adverse Events by SOC and PT	Safety
14.3.10.2	Related Adverse Events by SOC and PT (Cycle 1)	DLT
14.3.11.1	Related Severe Adverse Events by SOC and PT	Safety
14.3.11.2	Related Severe Adverse Events by SOC and PT (Cycle 1)	DLT
14.3.12.1	Related Serious Adverse Events by SOC and PT	Safety
14.3.12.2	Related Serious Adverse Events by SOC and PT (Cycle 1)	DLT
14.3.13.1	Adverse Events Resulting in Treatment Delay or Modifications by SOC and PT	Safety
14.3.13.2	Adverse Events Resulting in Treatment Delay or Modifications by SOC and PT (Cycle 1)	DLT

14.3.14.1	Adverse Events Resulting in Treatment Discontinuation by SOC and PT	Safety
14.3.14.2	Adverse Events Resulting in Treatment Discontinuation by SOC and PT (Cycle 1)	DLT
14.3.15.1	Adverse Events Resulting in Death by SOC and PT	Safety
14.3.15.2	Adverse Events Resulting in Death by SOC and PT (Cycle 1)	DLT
14.3.16.1	Adverse Events by SOC and PT and Worst Grade	Safety
14.3.16.2	Adverse Events by SOC and PT and Worst Grade (Cycle 1)	DLT
14.3.17	Deaths	Safety
	Physical Examination, Vital Signs, Laboratory Assessments, ECG	
14.3.18	Physical Examination Abnormalities by Scheduled Time	Safety
14.3.19	ECOG Performance Status Shift Table	Safety
14.3.20.3	Vital Signs Shift from Pretreatment to End-of-Study	Safety
14.3.21.1	Vital Signs Shift from Preinfusion to Highest-on-Infusion	Safety
14.3.21.2	Vital Signs Shift from Preinfusion to Lowest-on-Infusion	Safety
14.3.21.3	Vital Signs Shift from Preinfusion to End-of-Infusion	Safety
14.3.22.1	Laboratory CTC Grade Shift from Baseline to Worst Post Baseline Grade- Tests Graded in Single Direction(Either Above or Below Normal Range)	Safety
14.3.22.2	Laboratory CTC Grade Shift from Baseline to Worst Post Baseline Grade- Tests Graded in Single Direction(Either Above or Below Normal Range)	Safety
14.3.22.3	Laboratory CTC Grade Shift from Baseline to Worst Low Post Baseline Grade -Tests Graded in Both Directions (Above and Below Normal Range)	Safety
14.3.23	Laboratory CTC Grade Shift Shift from Pretreatment to End-of-Study	Safety
14.3.24	Electrocardiogram	Safety
14.3.25	Pharmacodynamic Biomarkers	Safety
14.3.26	IMC-CS4 Antibodies	Safety

6.4 Planned Patient Data Listings

Listing Number	Listing Title	Population
	Baseline Characteristics	
1	Patient Disposition	All enrolled patients
2.1	Definition of In- and Exclusion Criteria	NA
2.2	Inclusion Criteria	All enrolled patients
2.3	Exclusion Criteria	All enrolled patients
2.4	Exemption of In- and Exclusion Criteria	All enrolled patients
3	Protocol Deviations	Safety
4	Demographic and Baseline Characteristics	Safety
5	Pre-Treatment Disease Characteristics	Safety
6	TNM Staging	Safety
7	Site of Metastatic Disease at Screening	Safety
8	Previous Anti-Cancer Therapy	Safety
9	Prior Disease Related Radiotherapy	Safety
10	Prior Disease-Related Surgery	Safety
11	Medical History	Safety
12	Pregnancy Test	Safety
	Efficacy	
13.1	Tumor Measurements – Target Lesions	Safety
13.2	Tumor Measurements – Non-Target Lesions	Safety
13.3	Tumor Measurements – New Lesions	Safety
13.4	Tumor Measurements – Comments	Safety
13.5	Best Overall Response	Safety
13.6	Radiographic Scans	Safety
	Dose Exposure	
14.1	IMC-CS4 Administration	Safety
14.2	IMC-CS4 Modifications	Safety
14.3	IMC-CS4 Infusion Interruptions	Safety

14.4	IMC-CS4 Dose intensity	Safety
	Adverse Events	
15.1	Dose-Limiting Toxicities	DLT
15.2	Adverse Events	Safety
15.3	Serious Adverse Events	Safety
15.4	Adverse Events Resulting in IMC-CS4 Modifications	Safety
15.5	Adverse Events Resulting in IMC-CS4 Treatment Discontinuation	Safety
15.6	Adverse Events Resulting in Death	Safety
15.7	Adverse Event Comments	Safety
16.1	Concurrent Therapy and Procedures for the Treatment of AEs	Safety
16.2	Concurrent Therapies and Procedures not for the Treatment of AEs	Safety
17	Death Reports	Safety
	Physical Examination, Vital Signs, Laboratory Assessments	
18	Weight, Height and ECOG Performance Status	Safety
19	Physical Examination	Safety
20	Vital Signs	Safety
21.1	Laboratory Reference Ranges	NA
21.2	Listing of Patients With ≥Grade 3 Abnormal Laboratory Results	Safety
22	Laboratory - Hematology	Safety
23	Laboratory - Coagulation	Safety
24	Laboratory - Serum Chemistry	Safety
25	Laboratory - Urinanalysis	Safety
26	Electrocardiogram	Safety
27	Hospitalization	Safety
28	Pharmacodynamic Biomarkers	Safety
29	IMC-CS4 Antibodies	Safety

Appendix 1: List of Abbreviations

AE	adverse event
BOR	best overall response
CR	complete response
CRO	contract research organization
CSF-1	colony-stimulating factor-1
CSF-1R	colony-stimulating factor-1 receptor
CSR	Clinical study report
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FPV	first patient visit
MedDRA®	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	non-evaluable
PD	progressive disease
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
TNM	tumor, nodes, and metastases
WHOdrug	world health organization drug information

Appendix 2: References

i Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer. 2009;45:228-247.

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