NCT #: NCT02694822

agenus

STATISTICAL ANALYSIS PLAN

FOR C-500-01 PHASE 2

A PHASE 1/2, OPEN-LABEL, MULTICENTER STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF AN ANTI–CTLA-4 HUMAN MONOCLONAL ANTIBODY (AGEN1884) IN SUBJECTS WITH ADVANCED OR REFRACTORY CANCER AND IN SUBJECTS WHO HAVE PROGRESSED DURING TREATMENT WITH A PD-1/PD-L1 INHIBITOR AS THEIR MOST RECENT THERAPY

VERSION: 2.0

DATE OF PLAN: 08 OCT 2021

VER 1.0 - 3 MAY 2021

BASED ON:

Amendment 9, 26 November 2019

Amendment 8, 20 February 2019

Amendment 7, 31 May 2018

Amendment 6, 06 November 2017

Amendment 5, 06 May 2017

Amendment 4, 03 February 2017

Amendment 3, 26 August 2016

Amendment 2, 29 July 2016

Amendment 1, 20 January 2016

Original Version, 30 November 2015

STUDY DRUG: ZALIFRELIMAB (AGEN1884)

PROTOCOL NUMBER: C-500-01

SPONSOR:

Agenus Inc.

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Lexington, MA 02421-7305
[redacted]

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

APPROVALS

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the study, and all applicable regulatory guidance and guidelines.

This document has been reviewed and accepted by:

[redacted] Agenus Inc.	Signature [redacted]	Date
[redacted] Agenus Inc.	Signature [redacted]	Date
[redacted] Agenus, Inc.	[redacted]	
[redacted] Agenus Inc.	Signature [redacted]	Date

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1 LIST OF ACRONYMS AND ABBREVIATIONS

Abbreviation	Term
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the drug concentration time curve
BMI	Body Mass Index
BOR	Best Overall Response
CI	Confidence Interval
CL	Systemic Clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
HCC	Hepatocellular Carcinoma
HR	Hart Rate
ICH	International Conference on Harmonization
irAE	Immune-related Adverse Event
IV	Intravenous
K-M	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities

NCI	National Cancer Institute
NE	Non-Evaluable
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Cell Death Protein 1 Ligand 1
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetic(s)
PR	Partial Response
PT	Preferred Term
QTcF	QT Interval Corrected Using Fridericia's Formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SD	Stable Disease
SDV	Source Data Verification
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time to Reach Maximum Drug Concentration
$t½$	Terminal Elimination Half-Life
ULN	Upper Limit of Normal
USA	United States of America
Vd	Volume of Distribution

AMENDMENT FROM PREVIOUS VERSION

This is the second version of the SAP for Phase 2 study.

2 INTRODUCTION

The objective of this Statistical Analysis Plan (SAP) is to provide a comprehensive and detailed description of the strategy, rationale, and statistical techniques that will be used for analysis of Phase 2 data in order to address the primary and secondary objectives of the dose expansion part of the protocol C-500-01, titled: "Phase 1/2, Open-Label, Multicenter Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of an Anti–CTLA-4 Human Monoclonal Antibody (AGEN1884) in Subjects with Advanced or Refractory Cancer and in Subjects who have Progressed During Treatment with a PD-1/PD- L1 (programmed cell death protein 1/programmed cell death protein 1 ligand 1) Inhibitor as their Most Recent Therapy."

This document has been prepared based on the protocol amendment 9, dated 26 November 2019 and the Case Report Form dated 14 January 2020. The statistical analyses adhere to principles specified in E9 guidance "Statistical Principles for Clinical Trials" of International Conference on Harmonisation (ICH). This SAP does not include pharmacokinetic (PK) analysis. The PK analysis will be described in a separate PK SAP.

3 STUDY DESIGN OVERVIEW

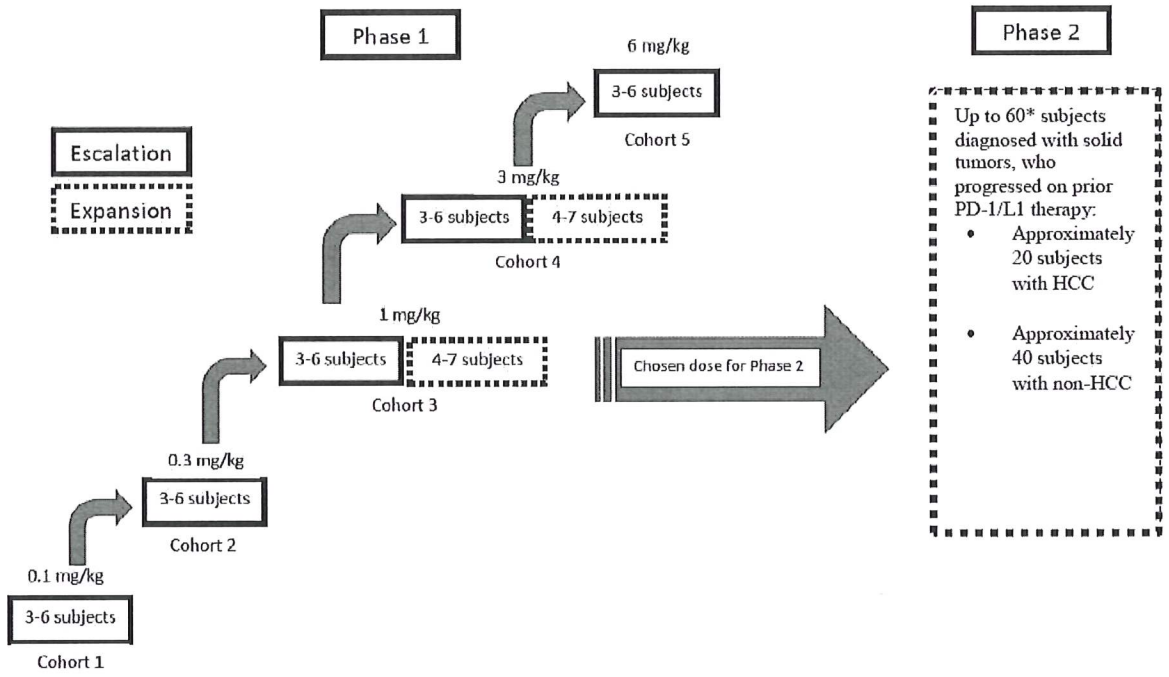
3.1 Overall Study Design

This is an open-label, Phase 1/2, multicenter study to evaluate the safety, PK, and pharmacodynamics, and activity of an anti–CTLA-4 human monoclonal antibody (AGEN1884) in subjects with advanced or refractory cancer. The Phase 1 portion of the study has been completed and contained a 3+3 dose escalation phase evaluating AGEN1884 at 0.1, 0.3, 1, 3, and 6 mg/kg dose levels, and an expansion phase at 1 mg/kg and 3 mg/kg. Dose levels >6mg/kg were not planned.

The Phase 2 portion of the study includes subjects who have progressed during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug). The dose for the Phase 2 portion of the study was based on clinical data from the Phase 1 portion evaluating AGEN1884 as monotherapy. At the time of the protocol amendment 9, based on data from the Phase 1 dose escalation, 1 mg/kg was chosen as the starting dose for Phase 2.

The study design is depicted in Figure 1.

Figure 1: Study Design



* Additional subjects may be enrolled in Phase 2 to either the hepatocellular carcinoma (HCC) or non-HCC populations as necessary to ensure that 20 subjects are evaluable for additional PK assessments.

AGEN1884 will be administered intravenously (IV) for each cycle (3 weeks) as a 60-min (-10/+20 min) infusion. Infusions will be followed immediately by a 15-min saline flush of the IV line. Treatment will be administered every 3 weeks for the first 4 cycles. At the 12-week evaluation timepoint, subjects may continue to receive AGEN1884 every 3, 6, or 12 weeks ($\pm$ 7 days) for a maximum duration of 1 year of treatment, provided they were not diagnosed with progressive disease and were tolerating the study drug.

3.2 Sample Size

Overall, there will be approximately 100 subjects enrolled in Phase 1 and Phase 2 of this study. After safety is established in the 1 mg/kg and 3 mg/kg cohorts, additional subjects will be enrolled into those dose levels to support the objectives and expand the number of correlates available for evaluation. The Phase 2 population will include up to 60 subjects who have progressed during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug) with a subpopulation to include approximately 20 subjects with advanced HCC and approximately 40 non-HCC subjects.

These sample sizes are not based on inferential statistics.

3.3 Randomization and Blinding

This is an open-label Phase 1/2 study. Subjects are not randomized to study treatment.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

- To evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) of AGEN1884 in subjects with advanced or metastatic cancer (solid tumors or lymphoma), including but not limited to carcinoma, sarcoma, or melanoma (Phase 1); and to evaluate the safety and tolerability of AGEN1884 in subjects who have progressed during treatment with a PD-1/PD-L1 inhibitor as their most recent therapy (Phase 2).
- To characterize AGEN1884 pharmacokinetics (PK).

4.2 Secondary Objectives

- To evaluate the preliminary efficacy of AGEN1884 by assessing objective response rate (ORR), disease control rate (DCR), and duration of response (DOR) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
- To evaluate the preliminary efficacy of AGEN1884 by assessing progression-free survival (PFS) and overall survival (OS).

4.3 Exploratory Objectives

- To explore biomarkers that may predict pharmacologic activity or response to AGEN1884.
- To characterize the effect of AGEN1884 on tumor tissue obtained post-treatment, if available.

4.4 Primary Endpoints

- Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of drug-related adverse events; by completing physical examinations; by evaluating changes in vital signs and electrocardiogram (ECG); through clinical evaluations; and laboratory blood and urine sample evaluations.
- PK parameters to be estimated and reported may include, but may not be limited to, maximum drug concentration at steady-state ($C_{max\text{-}ss}$), minimum drug concentration at steady state ($C_{min\text{-}ss}$), area under the drug concentration-time curve within time span t1 to t2 at steady-state ($AUC_{(t1\text{-}t2)\text{-}ss}$), area under the drug concentration-time curve from time of dosing to time of last observation ($AUC_{(0\text{-}t)}$), area under the drug concentration-time curve

from time of dosing extrapolated to infinity ($AUC_{(0-\infty)}$), time to reach maximum drug concentration (t_{max}), terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{½}$), systemic clearance (CL), and volume of distribution (Vd).

4.5 Secondary Endpoints

- Objective response rate, (ORR), defined as the percentage of subjects having complete response (CR) or partial response (PR), as determined by radiographic disease assessments per RECIST 1.1.
- Disease control rate (DCR) will include subjects that have best overall response (BOR) of CR, PR and stable disease (SD) for at least 12 weeks.
- Progression-free survival (PFS), defined as the interval from the date of first dose of investigational agent until the earliest date of disease progression (PD), as determined by investigator assessment of objective radiographic disease assessments per RECIST 1.1, or death due to any cause if occurring sooner than progression.
- Duration of response, (DOR), defined as the interval from the date measurement criteria are met for CR or PR (whichever is first recorded) until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease assessments per RECIST 1.1, or death due to any cause if occurring sooner than progression. Only subjects who achieve an initial response will be evaluated for DOR.
- Overall survival (OS), defined as the interval from the date of first dose of investigational agent until the date of death.
- The pharmacologically active dose of AGEN1884, determined through clinical signs of drug activity, surrogate markers, or pharmacodynamic studies, including but not limited to the presence of immune-related adverse events.

4.6 Exploratory Endpoints

- Other biomarker effects and outcome predictors for AGEN1884 in peripheral blood and/or tumor tissue will be evaluated as exploratory analyses.

5 PLANNED ANALYSIS

5.1 Summary of Changes to the Planned Statistical Analysis Described in the Protocol

None.

5.2 Interim Analyses and Data Monitoring

No formal interim analyses are planned. Draft and interim data will be reviewed on a rolling basis to inform study progress.

5.3 Final Analysis and Reporting

A separate final analysis will be performed on Phase 1 and Phase 2 data. All final planned analyses per protocol and this analysis plan must be performed after either locking records for relevant subjects or visits included in the analysis or the full database lock. See Section 8 for discussion of requirements for data freeze, locking, and source data verification in the context of COVID-19 pandemic.

6 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

6.1 Definition of Baseline

For all evaluations, unless otherwise noted, baseline is defined as the most recent non-missing measurement prior to the first administration of study drug.

6.2 Definition of Study Days

Unless otherwise noted, study days of an evaluation are defined as the number of days relative to the first dose date which is designated as Day 1, and the preceding day is Day -1, the day before that is Day -2, etc.

Study days are calculated as

- (Date of assessment – first dose date + 1) for assessments on/after first dose date
- (Date of assessment – first dose date) for assessments before first dose date

6.3 Definition of On-Treatment Period

An on-treatment period is defined as the time from the first dose of study treatment until the end of treatment safety follow-up (4 weeks ± 7 days from the last dose of study drug, i.e., until 35 days from the last dose) or end of the study, whichever occurs first.

6.4 Definition of an Extended On-Treatment Period

An extended on-treatment period (follow-up) is defined as the time from the first dose of study treatment through 90 days after the last dose of study treatment or end of the study, whichever

occurs first. This is used for reporting immune-related AEs and cluster terms and also as a sensitivity analysis for reporting all treatment-emergent adverse events.

6.5 Analysis Visit Window

Data will be analyzed by scheduled visits, where appropriate. Data collected out of the prescribed timing window will be analyzed as scheduled (i.e., at intended visits). Data that are collected from an unscheduled visit will not be included in the by-visit summary tables but will be presented in the listings. However, data collected at an unscheduled visit will also be considered for toxicity grading, in particular, for laboratory assessments. Additionally, both unscheduled and out of window imaging assessments will be included in the efficacy analysis.

6.6 Handling of Partial Dates for Adverse Events

When determining treatment-emergent adverse events (TEAEs), partial dates will be handled as follows.

- If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, the onset date will be assumed to be the first dose date of treatment.
- If the onset day and month are both missing, the day and month will be assumed to be 1 January, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the first dose date of treatment to conservatively report the event as treatment-emergent.
- A missing onset date will be coded as the first dose date of treatment. If the resulting onset date is after a reported date of resolution, the onset date will be set equal to the date of resolution.
- A partially missing resolution date will be conservatively imputed as the latest date in the range of missing date element(s) (for example 2020-10-31 if the date is 2020-10-UNK), date of last dose + 90 days, day of study discontinuation, or death, whichever comes first.

Data listings will present the partial date as recorded in the electronic case report form (eCRF).

6.7 Handling of Partial Dates for Medications

When determining prior or concomitant medications, partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date.

- Medication start dates with a missing day and non-missing month will be assumed to have occurred on the first day of the non-missing month, except for medications occurring in the first month of dosing, in which case the date will be one day before the first day of dosing.

- Medication start dates with missing day and month will be assumed to have occurred on the first day of the non-missing year (i.e., 1 January), except for medications occurring in the first year of dosing, in which case the date will be the informed consent date.
- For post anti-cancer medications only, if both Month and Day are missing, then the start date will be set to December 31 or the end date of this medication, whichever occurs first.
- For post anti-cancer medications only, if only Day is missing, then the start date will be set to the last day of the month or the end date of this medication, whichever occurs first.
- Medications that are not ongoing and have a medication stop date with a missing day and non-missing month will be assumed to have stopped on the last day of the non-missing month.
- Medications that are not ongoing and have a medication stop date with a missing month will be assumed to have stopped on the last day of the non-missing year (i.e., 31 December).

When imputing start date of a medication ensure that the new imputed date is sensible, i.e., is prior to the end date. If start date and/or end date of a prior/concomitant medication is completely missing, do not impute.

6.8 Handling of Partial Dates for Procedures

For records with a missing procedure date, the following procedure will be employed to determine whether the procedure is prior or concomitant:

- For a procedure with a missing or partially missing date performed on a scheduled visit, the date of the scheduled visit will be used.
- If a procedure was not scheduled, the missing part of the date will be imputed as discussed in Section 6.9.

6.9 Handling of Partial Dates for Other Data

Other data (such as disease history) with partial dates will be listed as collected. For calculation of time intervals, the dates will be imputed with the first day of the month (if the day is missing) or with 1 January (if both day and month are missing).

6.10 Handling of Missing Data

Missing data will not be imputed, except for:

- Missing date parts, i.e., partial dates, discussed above
- Missing AEs grade severity and relationship to study drug of AEs, discussed in Section 8.6.2.
- Missing efficacy assessments discussed in Section 8.7.

7 ANALYSIS SETS

The following analysis sets will be used for analysis of Phase 2 data:

7.1 All Subjects Analysis Set

All Subjects Analysis Set includes all subjects who signed informed consent form, irrespective if they passed or failed screening for Inclusion and Exclusion criteria. This set will be used for listing of all subjects who received study treatment and all subjects excluded from the study during the screening period due to failure to meet eligibility criteria.

7.2 Safety Analysis Set

Safety analysis set includes all subjects who received at least one dose of study drug. This set is considered as a Full Analysis Set that will be used for both safety and efficacy analysis.

7.3 Efficacy Analysis Set

Efficacy analysis set includes subjects who have received ≥2 doses of study drug. Efficacy analysis on efficacy analysis set will be performed as a sensitivity analysis.

8 STATISTICAL CONSIDERATIONS

All analyses described in this plan are considered a priori analyses as they have been defined prior to database availability for analysis. The COVID-19 pandemic may impact Agenus ability to complete data monitoring, collection, and cleaning to achieve the data lock as originally planned for our clinical programs. As a result, a priori analysis of Agenus clinical trial data may be completed prior to all data locked; however, all analysis will occur using locked and frozen clinical database records and ensuring trial data integrity is maintained as locked or frozen on the subject and visit levels. Clinical data management will notify the team when data are available (all locked or frozen) for download and the planned analysis. The impact of lack of source data verification or principal investigator (PI) signature will be performed at the time of data download. Only significant impact/risks to analysis of data, with the planned mitigation, will be discussed in the clinical study report (CSR). Clinical data management will post queries requesting data changes after the data download for the analysis, result of completion of Source Data Verification (SDV) or new information provided. Requested changes will be reviewed by the team before changes are made to the database by the sites. An additional analysis may be performed if data changes would affect study conclusions; additional analysis will be described in the applicable SAP. All other analyses, if any, designed after completing analysis specified in

this SAP and additional analysis plans referred by the SAP, will be considered post-hoc analyses and will be described in a separate exploratory analysis plan (if applicable).

All summaries and statistical analysis will be performed using SAS Software (SAS Institute Inc., Cary, NC, USA), version 9.4 or later, or R (R Foundation for Statistical Computing, Vienna, Austria), version 3.6.3 or later.

8.1 General Statistical Procedures

Frequency distributions for categorical variables will be provided as number of subjects in the category and the percentages of the total number of subjects in the given population as noted. Counts of missing observations will be included in the denominator and presented as a separate category. Percentages will be reported to one decimal place.

A 2-sided 95% Wilson score confidence interval (CI) for categorical variables without multiplicity adjustment will be provided where appropriate for efficacy analysis.

The descriptive statistics for continuous variables will be number of subjects, mean, standard deviation, median, minimum, and maximum. Mean and median will be reported to 1 more decimal place than the raw data, while the standard deviation will be reported to 2 more decimal places than the raw data. Minimum and maximum will be reported the same as the original data.

All listings (with the exception of All Subject listings) will be performed using the Safety Analysis Set and sorted by subject ID and, if applicable, by visit date unless otherwise specified.

The study drug name may be abbreviated in TLFs as "Zal" for zalifrelimab (AGEN1884).

Time intervals (in days), unless specified otherwise, will be calculated as difference between ending and start day + 1 day. For conversion to months, interval days will be divided by 30.4375.

8.2 Subject Enrollment

The number of subjects in each analysis set will be summarized. In addition, a listing will be provided for All Subjects Analysis Set, including informed consent date, screening status (screen failure/enrolled), date of first dose, and analysis sets membership (Yes/No).

8.3 Subjects Disposition

Subject disposition will be summarized including

- Number of subjects treated
- Number of subjects who completed study treatment as per protocol
- Number of subjects who discontinued treatment and primary reasons of discontinuation
- Number of subjects who completed the study as per protocol
- Number of subjects who discontinued study and primary reasons of discontinuation

The Safety Analysis Set and the Efficacy analysis Set will be applied to summary tables. Subject disposition will be listed.

8.4 Protocol Deviations

Protocol deviations will be reviewed by study team to designate important protocol deviations. These important protocol deviations will be summarized by category, and all protocol deviations will be listed for the Safety Analysis Set.

8.5 Demographics and Baseline Characteristics

8.5.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be tabulated using descriptive statistics in both the Safety Analysis Set and the Efficacy Analysis Set. The following variables will be included:

- Age at screening (years)
- Age category (age < 55 vs age ≥ 55, age < 65 vs age ≥ 65, age < 75 vs age ≥ 75)
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (body mass index, kg/m^2), defined as weight (kg) / height $(m)^2$
- Eastern Cooperative Oncology Group (ECOG) performance status
- Tumor type

Demographics and baseline characteristics will be listed.

8.5.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1.

Conditions and symptoms that were ongoing at baseline will be summarized. Previous medical history data will be summarized separately as "medical history".

The frequency count and percentage of subjects experiencing any medical conditions will be tabulated by system organ classifications (SOC) and preferred term (PT). If a PT or SOC was reported more than once for a subject, the subject would only be counted once in the incidence for that PT or SOC.

The Safety Analysis Set will be applied for this analysis.

8.5.3 Cancer History

Subjects' cancer history prior to study entry will be summarized, including:

- Status at diagnosis
- The number of subjects with HCC, non-HCC and PD-1/PD-L1 refractory, or non-HCC and PD-1/PD-L1 naïve
- Time from original diagnosis to first dose date (years), calculated as (first dose date – initial diagnosis date)/365.25
- Current cancer diagnosis
- Localization of metastases (lymph nodes vs other [i.e., all non-lymph nodes])
- Tumor burden (sum of baseline target lesions) using descriptive statistics and frequency $\leq$ 50 mm vs $>$ 50 mm.

A listing of prior anti-cancer treatment will be provided to the sponsor for review for the purpose of determining if patients are PD-1/PD-L1 refractory or naïve. Individual cancer history will be listed.

The Safety Analysis Set will be applied for this analysis.

8.5.4 Prior Cancer Therapies and Procedures

Prior cancer systemic therapies will be summarized and listed including:

- Any prior cancer medication
- BOR on the last treatment/therapy before enrollment
- Time from last day of last treatment to first dose date (months), defined as (first dose date – date of last day of last treatment + 1)/30.4375

Anti-cancer therapies will be coded using WHODrug-B3 September 2019. Prior anti-cancer treatment, radiotherapies, and surgeries will be listed.

The Safety Analysis Set will be applied for this analysis.

8.5.5 Prior and Concomitant Medications

Prior and concomitant medications will be summarized and listed in the Safety Analysis Set. Medications will be coded using WHODrug-B3 September 2019. The count and percentage of subjects who took concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) level 2 and PT. Prior medication is defined as any non-study medication started before the first dose of study drug. Concomitant medication is defined as any non-study medication that was dosed on or after first study drug administration.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of study drug. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant medication.

The Safety Analysis Set will be applied for this analysis.

8.6 Safety Analysis

The Safety Analysis Set will be applied for all safety analyses.

8.6.1 Drug Exposure

Overall drug exposure will be summarized in Safety Analysis Set by the following parameters:

- Duration of treatment (week), calculated as: (last dose date – first dose date + 1)/7
- Number of treatment infusions received
- Total cumulative dose (mg), defined as the sum of the actual doses (mg) taken
- Dose compliance, defined as percentage of actual dose taken relative to planned dose
- Planned/actual dose intensity for the first 4 cycles, defined as total planned or actual dose from the first 4 cycles (mg) divided by actual duration of the first 4 cycles (weeks)

  Note: if patients permanently withdraw from the treatment before Cycle 4 due to reasons other than disease progression or death, the remaining cycles will be calculated with planned length, i.e., 3 weeks, and zero dose. If patients withdraw from the treatment due to disease progression or death, the number of cycles actually completed will be used.

- Number of doses with infusion related reactions (as reported on drug administration eCRFs)
- Number of subjects with at least one infusion related reaction
- Number of subjects with any dose interrupted/not completed
- Number of doses interrupted/not completed
- Occurrences and number of actual doses exceeding adjusted planned dose by more than 5% (adjusting for up to 10 % weight loss.)

  Per pharmacy manual, no adjustment in dose was required for body weight changes within 10%, therefore dose exceeding planned dose by > 5% will be interpreted as any dose 5% greater than the highest daily dose prescribed by the clinical trial protocol, after accounting for up to 10% changes due to decrease in body weight. Adjusted planned dose is calculated by multiplying prescribed dose level by adjusted weight W_{adj}. Denoting by W_0 and W the baseline and the most recent weights, adjusted weight is: $W_{adj} = W$ for $W \geq W_0$ and $W_{adj} = \min(W_0, 1.1 \times W)$ for $W < W_0$.

Missing weight measurements in drug exposure analysis will be imputed by last observation carried forward, multiple measurements for the same timepoint will be averaged.

Details of study treatment exposure will be listed for Safety Analysis Set.

8.6.2 Adverse Events

Adverse events (AEs) will be coded using MedDRA version 22.1 and will be classified by SOC and PT.

Severity of AEs will be assessed by investigators according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5, and AEs will be classified by investigators as either related or not related to the study drug. If the AE is reported as "Possible Related", "Probable Related", or "Highly Probable/Definite Related" in the eCRF, it will be considered as related; if it is reported as "Unrelated" or "Unlikely Related", it will be considered as unrelated.

Pre-existing conditions are those that started before and continued after signing of informed consent. Prior AEs (not treatment-emergent) are those occurring after the subject signed the informed consent and before the administration of the first dose of study treatment. Immune-related AEs will be evaluated in the extended on-treatment period to account for late toxicities. A separate listing will be provided for AEs incurred after on-treatment period.

Unless otherwise specified, TEAEs are AEs with onset during or after administration of first dose, or the worsening of a pre-existing condition during the on-treatment period. Immune-related AEs will be considered TEAEs during the extended on-treatment period. In a sensitivity analysis, TEAEs will be defined as AEs with onset during or after administration of first dose, or the worsening of a pre-existing condition during the extended on-treatment period. A separate listing will be provided of all AEs with onset date, or worsening date between end of "On-treatment period" (35 days) and end of "Extended on-treatment period" (90 days).

Any missing onset date, causality, or severity must be queried for resolution. Unresolved/missing causality and severity will be handled according to the following rules:

- An unresolved causality will be considered treatment-related
- An unresolved severity will be identified as an unknown severity

AEs with partial dates will be considered TEAEs unless the AE can unequivocally be determined as not treatment-emergent.

The following AEs are considered as AEs of special interest (AESIs):

- Infusion-related reactions per definition in NCI-CTCAE version 5 specification *(per investigator assessment)*
- Any elevated liver function test by investigators
- Any AE suspected to be immune-mediated (i.e. an irAE) by investigators
- Other AEs of special interest determined by investigators

Unless otherwise stated, the number of subjects with an event (subject-wise) and the number of events (event-wise) will be provided for each summary.

Immune-related AEs will be tabulated using investigator-reported irAEs.

Infusion related AEs will be tabulated using infusion-related reactions as reported by the investigators.

The following summaries by either SOC and PT or by PT and by severity grade will be provided. Summaries will be sorted by decreasing incidence of PT (within SOC, if applicable).

- TEAEs by SOC and PT, and by PT
- TEAEs by relationship to study drug, severity grade, SOC, and PT
- Drug-related TEAEs by SOC and PT, and by PT
- TEAEs leading to permanent treatment discontinuation by PT
- TEAEs leading to death by PT
- Drug-related TEAEs leading to permanent treatment discontinuation by PT
- Drug-related TEAEs leading to death by PT
- Serious TEAEs by SOC and PT, and by PT
- Serious TEAEs by relationship to study drug and severity grade, by SOC and PT
- Drug related serious TEAEs by SOC and PT, and by PT
- irAEs by SOC and PT, and by PT
- irAEs by severity grade, SOC, and PT
- Infusion-related TEAEs by SOC and PT, and by PT
- Infusion-related TEAEs by severity grade, SOC, and PT
- Laboratory abnormalities worsening (in at least one on-study measurement, relative to baseline) by NCI-CTCAE version 5 criteria.
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin normal at baseline but with elevations $\geq 2 \times$ upper limit of normal (ULN)

The overall summary of TEAEs will be reported by age (age < 55 vs age ≥ 55, age < 65 vs age ≥ 65, and age < 75 vs age ≥ 75), by race group including at least 5 subjects (groups with < 5 subjects will be reported summarily as "Other"), by normal vs abnormal creatinine and bilirubin levels at baseline, and by drug manufacturing process. Subgroup analyses will be provided for HCC patients, non-HCC and PD-1/PD-L1 refractory patients, and non-HCC and PD-1/PD-L1 naïve patients.

In addition, the overall summary of AE incidence per month of drug exposure will be presented. Such a summary will report #patients/(total time of exposure in months) and #AEs/(total time of exposure in months.)

The analysis of irAEs in the above summaries will be performed using data as reported by investigators (the primary analysis). In addition, as an exploratory analysis, TEAEs using sponsor's definition of irAEs, will be summarized. If an AE falls within any of the cluster terms listed below, it will be considered as an irAE by sponsor's definition. For each irAE, the summary will include median time (and range) to onset, median duration (and range) in days of

the first instance of such AE per patient. Finally, descriptive statistics will be provided for time of onset, cycle of onset, and cumulative dose at onset of first irAE by SOC.

If an SOC or PT was reported more than once for a subject, the subject would only be counted once in the incidence for that SOC or PT.

In tabulation by severity grade:

- For a given SOC, only the most severe SOC for each subject will be included
- For a given PT, only the most severe PT for each subject will be included

In addition, TEAEs (evaluated within the extended treatment period) will be reported for the following clusters of immune-mediated AEs: pneumonitis, colitis, diarrhea, hepatitis, hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis, adrenal insufficiency, diabetes, nephritis, rash, pruritus, and other immune-related AEs. These clusters will be defined by the following MedDRA version 22.1 Preferred Terms:

- **Pneumonitis**: interstitial lung disease; pneumonitis; acute interstitial pneumonitis; immune-mediated pneumonitis
- **Colitis:** allergic colitis, autoimmune colitis, colitis, colitis erosive, colitis microscopic, enterocolitis hemorrhagic, eosinophilic colitis, necrotizing colitis, neutropenic colitis, enterocolitis, immune-mediated enterocolitis,
- **Diarrhea:** diarrhoea, diarrhoea hemorrhagic
- **Hepatitis:** acute hepatic failure, autoimmune hepatitis, hepatic failure, hepatitis, hepatitis acute, hepatoxicity, liver injury, hepatocellular injury, immune-mediated hepatitis, immune-mediated hepatic disorder, drug-induced liver injury
- **Hypothyroidism:** autoimmune hypothyroidism, hypothyroid goiter, hypothyroidism, immune-mediated hypothyroidism, myxoedema, thyroid atrophy
- **Hyperthyroidism**: Basedow's disease, hyperthyroidism, Marine Lenhart syndrome, primary hyperthyroidism, immune-mediated hyperthyroidism, secondary hyperthyroidism, tertiary hyperthyroidism, thyroid dermatopathy, thyroid crisis, thyrotoxic periodic paralysis, toxic goiter, toxic nodular goiter,
- **Thyroiditis**: autoimmune thyroiditis, thyroiditis, thyroid acute, thyroiditis chronic, thyroiditis fibrous chronic, thyroiditis subacute, immune-mediated thyroiditis
- **Hypophysitis:** hypophysitis, lymphocytic hypophysitis, hypopituitarism
- **Adrenal insufficiency:** Addison's disease, adrenal androgen deficiency, adrenal insufficiency, adrenal suppression, adrenocortical insufficiency acute, glucocorticoid deficiency, hypoaldosteronism, mineralocorticoid deficiency,
- **Diabetes** without prior history: type 1 diabetes mellitus, diabetes mellitus, latent autoimmune diabetes in adults, diabetic ketoacidosis, and hyperosmolar coma
- **Nephritis**: autoimmune nephritis, lupus nephritis, nephritis, nephritis hemorrhagic, immune-mediated nephritis

- **Rash**: pemphigoid, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash papular, immune-mediated dermatitis
- **Pruritus**: pruritus, pruritus allergic, pruritus generalized
- **Other Immune-related AEs**: myocarditis, immune-mediated myocarditis, uveitis, immune-mediated uveitis, iritis, vitiligo, psoriasis, myositis, immune-mediated myositis, rheumatoid arthritis, systemic inflammatory response syndrome, sarcoidosis, autoimmune disorder, meningitis, encephalitis, encephalitis autoimmune, immune-mediated encephalitis, encephalopathy, autoimmune encephalopathy, immune-mediated encephalopathy, Guillain-Barre syndrome, myasthenia gravis, demyelination, stomatitis, pancreatitis, autoimmune pancreatitis, pancreatitis acute, immune-mediated pancreatitis, immune-mediated gastritis, lichen planus, colitis ulcerative, Crohn's disease, inflammatory bowel disease, hemolytic anemia, immune-thrombocytopenia, immune thrombocytopenic purpura, aplastic anemia, bicytopenia, pancytopenia, immune-mediated pancytopenia

For each cluster, the analysis will summarize: the total incidence and number of all TEAEs included in the cluster and by severity grade, % of pts who received treatment with pituitary and hypothalamic hormones and analogues, with corticosteroids for systemic use, or with thyroid therapy (concomitant medications in, respectively, H01, H02, or H03 ATC2 groups indicated for AE and started following AE onset but no later than the date of AE resolution or 21 days from AE onset, whichever comes earlier), % leading to dose hold, % leading to drug discontinuation, % resolved, time to onset of first TEAE and duration of all TEAEs and TEAEs of grade ≥ 3.

The median duration of TEAE (in days) will be calculated using Kaplan Meier analysis for all patients and AE included in a cluster. Unresolved AEs or AEs with missing resolution information and date will be treated as censored data with the end of the extended on-treatment period as censoring date.

Death summary table will present reasons for deaths on treatment period, in survival follow-up, and overall.

Death details will also be listed (if applicable) including:

- Number of doses of study drug
- Number of cycles
- Age at death
- Study days relative to first dose date, calculated as (death date – first dose date + 1)
- Number of days to death from last dose, calculated as (death date – last dose date + 1)
- Precipitating AE (if death is an outcome of AE)
- Immune-related AE (if death is an outcome of irAE per investigator)
- Cause of deaths

The following listings will be provided in Safety Analysis Set:

- All AEs (with TEAEs flagged)
- Related TEAEs
- Serious TEAEs
- TEAEs leading to treatment discontinuation
- TEAEs leading to death

Adverse events observed between signing the informed consent and first dose of study drug will be listed with negative study days.

8.6.3 Anti-Drug Antibodies

Results of the anti-drug antibodies (ADA) tests will be listed and the number of subjects with a confirmed positive sample will be summarized.

8.6.4 Clinical Laboratory Tests

For clinical laboratory parameters, descriptive summary tables for observed values and changes from baseline will be provided by visit.

Laboratory values will also be categorized according to their NCI-CTCAE version 5 toxicity grade, for the following parameters: ALT, AST, Bilirubin, Creatinine, Hemoglobin, Platelets, Neutrophils, and Lymphocytes. For applicable parameters, shift tables will be presented from the baseline toxicity grade to the worst post-baseline visit value (scheduled or unscheduled). All test results and associated normal ranges from local laboratories will be reported in SI units. All tests with numeric values will have a unique unit per test. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units. For the limited number of cases where the associated normal ranges from a local laboratory cannot be obtained despite due diligence, if query is unsuccessful at resolving issue and analysis is mandatory then the clinical scientist and medical monitor can provide a suitable normal range to be used in determining CTC grading and flags for above and below normal and the inferred normal range will be flagged in listings.

If a test value is reported with "<" or ">" sign (as below or above some detection limit), the test value will be imputed in summaries at the limit of detection (that is ignoring "<" or ">" signs), however the measurement will be listed as originally reported.

A standard 'eDISH' (evaluation of Drug-Induced Serious Hepatotoxicity) plot will be presented to display on the log-log scale the correlation between peak total bilirubin and alanine aminotransferase (ALT), both in multiples of ULN, with horizontal and vertical lines for Hy's law thresholds, i.e., 3×ULN for ALT and 2×ULN for total bilirubin.

Listing will be provided for Safety Analysis Set.

8.6.5 Body Weight and Vital Signs

The observed value and percentage of changes from baseline will be summarized and listed by visit for Safety Analysis Set. If there are multiple measurements per visit, these measurements will be averaged.

Mean values of body weight, with 95% confidence interval will be plotted by each scheduled visit.

Listing will be provided for Safety Analysis Set.

8.6.6 12-lead Electrocardiogram

Number of subjects with abnormal clinically not significant and abnormal clinically significant electrocardiogram (ECG) results, as well as number of subjects with QTc_F (QT interval corrected using Fridericia's formula) greater than 450 or 480milliseconds will be summarized by visit and timing with respect to drug dose. In addition, QTc_F changes from pre-dose will be summarized for number of patients with a change exceeding a threshold of 30 msec or 60 msec. In these summaries, QTc intervals will be averaged for ECG taken in triplicate.

Other ECG parameters will be reported and summarized. Hart rate (HR) will be summarized as for number of patients $\leq$ 50 bpm and $\geq$ 120 bpm, PR interval for number of patients with PR $\geq$ 220 msec, and duration of QRS complex for number of patients with QRS $\geq$ 120 msec.

In all these summaries, QT, PR, QRS durations, and HR will be averaged for ECG taken in triplicate.

8.6.7 Pregnancy Tests

Dates and results of pregnancy tests will be listed within Safety Analysis Set.

8.6.8 ECOG Performance Status

Shift from baseline ECOG to worst on-study ECOG will be summarized. Listing will be provided for Safety Analysis Set.

8.7 Efficacy Analysis

All efficacy analyses will be performed based on the Safety Analysis Set and the Efficacy Analysis Set.

8.7.1 Best Overall Response and Objective Response per RECIST 1.1

Best overall response (BOR) will be derived from time-point RECIST 1.1 assessments by investigators. In the primary analysis, BOR will be evaluated over all on-study time-point assessments recorded before start of a new anti-cancer therapy, in consideration of RECIST 1.1 definition: "The best overall response is the best response recorded from the start of the study

treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response" (Eisenhauer et al 2009). Since all assessments are considered for BOR, the confirmed objective response or stable disease (SD) may occur after a transient time-point progressive disease (PD) assessment(s).

In the secondary analysis, conducted for sensitivity evaluation, an alternative, more conservative approach will be used. BOR will be evaluated only over time-point assessments until first observed PD, as initially proposed in RECIST 1.0 (Therasse et al 2000).

Confirmation of objective response (complete response [CR] or partial response [PR]) is required for respective BOR of CR or PR. Confirmation must be obtained at a subsequent assessment at least 4 weeks apart. In case of CR, the confirmatory assessment must be performed at a consecutive assessment, except for intercurrent non-evaluable assessments.

In case of PR, confirmatory assessment after initial CR/PR may be obtained a) in the primary analysis any time at least 4 weeks apart from the initial assessment, without restrictions on intercurrent assessment b) in the secondary analysis, any time after 4 weeks and after at most 1 intercurrent assessment of non-evaluable (NE) or SD.

For patients who did not fulfill requirements for BOR of CR or PR as described above, BOR of SD is defined, in the primary analysis, as i) initial time point assessment(s) of SD, PR, CR without PD at a minimum interval of 39 days (6 weeks-3 days), disregarding NE assessments and/or ii) unconfirmed PR or CR any time at initial evaluation, without PD at a minimum interval of 39 days and/or iii) durable SD following transient PD: at least 2 assessment(s) of SD, PR, CR (ignoring intercurrent NE assessments) at least 39 days (6 weeks-3 days) apart and without new PD within 84 days, counting time from the last transient PD assessment. Subjects who have a response of PR or CR with no subsequent tumor assessments will be assigned a BOR of SD and will be flagged in listings. In the secondary analysis, BOR evaluation of SD is only considered based on only criterion i) above. For BOR of SD without confirmation, the stable disease must meet the criterion of minimum time of 39 days.

For patients with time point assessment(s) of PD, excluding any transient PDs (PD followed by confirmed objective response or durable SD) and who do not satisfy criteria for BOR of CR, PR, and SD described above, the BOR assessments in the primary analysis will be PD. In the secondary analysis, a similar definition will be used but without excluding transient PDs.

Finally, BOR of NE will be assigned where there are either no evaluable time point assessments at all or first time point assessment(s) of SD was before minimum interval of 39 days without evaluable assessments preformed after 39 days.

The objective response rate (ORR) is the percentage of subjects with a BOR of PR or CR (i.e., objective response). The analysis of ORR will include confirmed responses and unconfirmed responses for both primary and alternative analyses. Subjects with missing tumor response status assessment will be counted as non-response (that is, subjects without any follow-up assessment) will be counted in the denominator for ORR.

BOR and ORR will be listed for Safety Analysis Set as available using primary and alternative definitions. For confirmed response, duration of response will be listed (see Section 8.7.2). The listings of time-point response will include assessments of target lesion, non-target lesions, and

new lesion data, as well as percentage change from baseline in the sum of diameters of target lesions.

8.7.2 Duration of Response

Duration of response (DOR) will be analyzed only for subjects who responded to the study treatment. DOR is defined as the time from first observation of CR or PR which was subsequently confirmed until the first time of disease progression or death by any cause within 90 days (i.e., 12 weeks+6 days) of last tumor assessment. All assessments performed before initiation of a new anti-cancer therapy will considered for evaluation of DOR. If a patient transitioned to a new anti-cancer therapy, any time point assessment(s) and death(s) that happened after that will be disregarded. Similar to evaluation of BOR, in the primary analysis any transient time-point PD(s) will be disregarded for determination of DOR when followed by confirmed objective response or durable stable disease, as defined in Section 8.7.1. In the alternative (sensitivity) analysis, DOR will be counted using the date of first observed PD, whether transient or not.

The starting event for DOR will be the date of the first objective response. The terminating event will be the date of PD or death within 90 days (i.e., 12 weeks+6 days) of the last tumor assessment, whichever occurs first. The censoring event will be the earliest of the dates of last evaluable assessment, last evaluable assessment performed before initiation of new anti-cancer therapy (if applicable), or last evaluable assessment without any assessment in the following 90 days and then followed by PD or death.

DOR will be reported in months and summarized by quartiles estimated from Kaplan-Meier curve, as well as Kaplan-Meier estimates at 6, 9, 12, 18 months. Number and percent of censored and non-censored observations and a plot Kaplan-Meier curve will be provided.

In addition, duration of observation of DOR (whether censored or not) will be summarized as "Observed DOR". The shortest and longest observations will be provided with censoring indicator.

8.7.3 Disease Control Rate

Disease control rate (DCR) is defined as proportion of subjects who have a confirmed response (CR or PR) or SD without PD within 81 days (12 weeks – 3 days) at study start, or durable SD following PD. In the alternative analysis, used for sensitivity analysis in parallel with alternative algorithm for BOR, described previously it is defined as proportion of subjects who have a confirmed response (CR or PR) or SD without PD within 81 days at study start.

DCR and number of subjects with disease control will be tabulated.

8.7.4 Efficacy Analysis Plots

The following plots will be provided for Safety and Efficacy Analysis Set, respectively:

- Waterfall plots of the best percentage change in tumor size (i.e., maximum tumor reduction, or minimum increase in the absence of any reduction) (Gillesp et al 2012)
- Swim lane plot for responders

8.7.5 Subgroup Analyses of Efficacy

Summaries of BOR, ORR, DOR, DCR, PFS, OS, and the waterfall plot will be reported in the following subgroups:

- HCC patients, non-HCC and PD-1/PD-L1 refractory patients, and non-HCC and PD-1/PD-L1 naïve patients
- by drug manufacturing process
- by age groups (age < 55 vs ≥ 55, age < 65 vs age ≥ 65, age < 75 vs age ≥ 75)
- by race group including at least 5 subjects and grouping together all categories with < 5 subjects as "Other"
- by tumor burden (sum of baseline target lesions by investigator assessment) ≤ 50 mm vs > 50 mm

8.7.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the interval from the date of first dose of investigational agent until the earliest date of PD per RECIST 1.1 or death due to any cause within 90 days (i.e., 12 weeks+6 days) of last tumor assessment (if no progression is documented). If a patient transitioned to a new anti-cancer therapy, any time point assessment(s) and death(s) that happened after that will be disregarded.

The primary analysis will be performed ignoring transient PDs, using the same definition of transient PDs as in Section 8.7.1. Thus, the terminating event will be a non-transient PD or death, whichever occurs first. Patients who did not experience a non-transient PD or death will be censored on the date of last evaluable tumor assessment, the date of the last evaluable assessment without any assessment in the following 90 days and then followed by PD or death, or the last evaluable assessment performed before initiation of new anti-cancer therapy (if applicable), whichever comes earlier.

The alternative (sensitivity) analysis will be performed for terminating event of death or first observed time-point PD, whichever occurs first. Censoring will be on the date of last evaluable tumor assessment, the date of the last evaluable assessment without any assessment in the following 90 days and then followed by PD or death, or the last evaluable assessment performed before initiation of new anti-cancer therapy (if applicable), whichever occurs first.

PFS will be reported in months. Median PFS will be provided (estimated using K-M estimate, with 95% CI) and Kaplan-Meier curves of PFS will be plotted.

8.7.7 Overall Survival

Overall survival (OS) is defined as the interval from the date of first dose of investigational agent until the date of death.

OS in months is calculated as:

- (date of death, or censoring – date of first dosing + 1) / 30.4375
- Where the censoring rules are specified as following:
- For subjects who have not died, OS will be censored at last contact date.
- Median OS will be provided (estimated using K-M estimate, with 95% CI) and Kaplan-Meier curve of OS will be plotted for Safety Analysis Set.

8.8 Pharmacokinetic Parameters

PK analyses will be conducted according to separate Pharmacokinetic Analysis Plan.

9 REFERENCES

Eisenhauer E.A., Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, et al. "New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1)." *European Journal of Cancer* 45, no. 2 (January 2009): 228–47.

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