STATISTICAL ANALYSIS PLAN
FOR CLINICAL PROTOCOL FPA008-003

A PHASE 1A/1B STUDY OF CABIRALIZUMAB IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH SELECTED ADVANCED CANCERS

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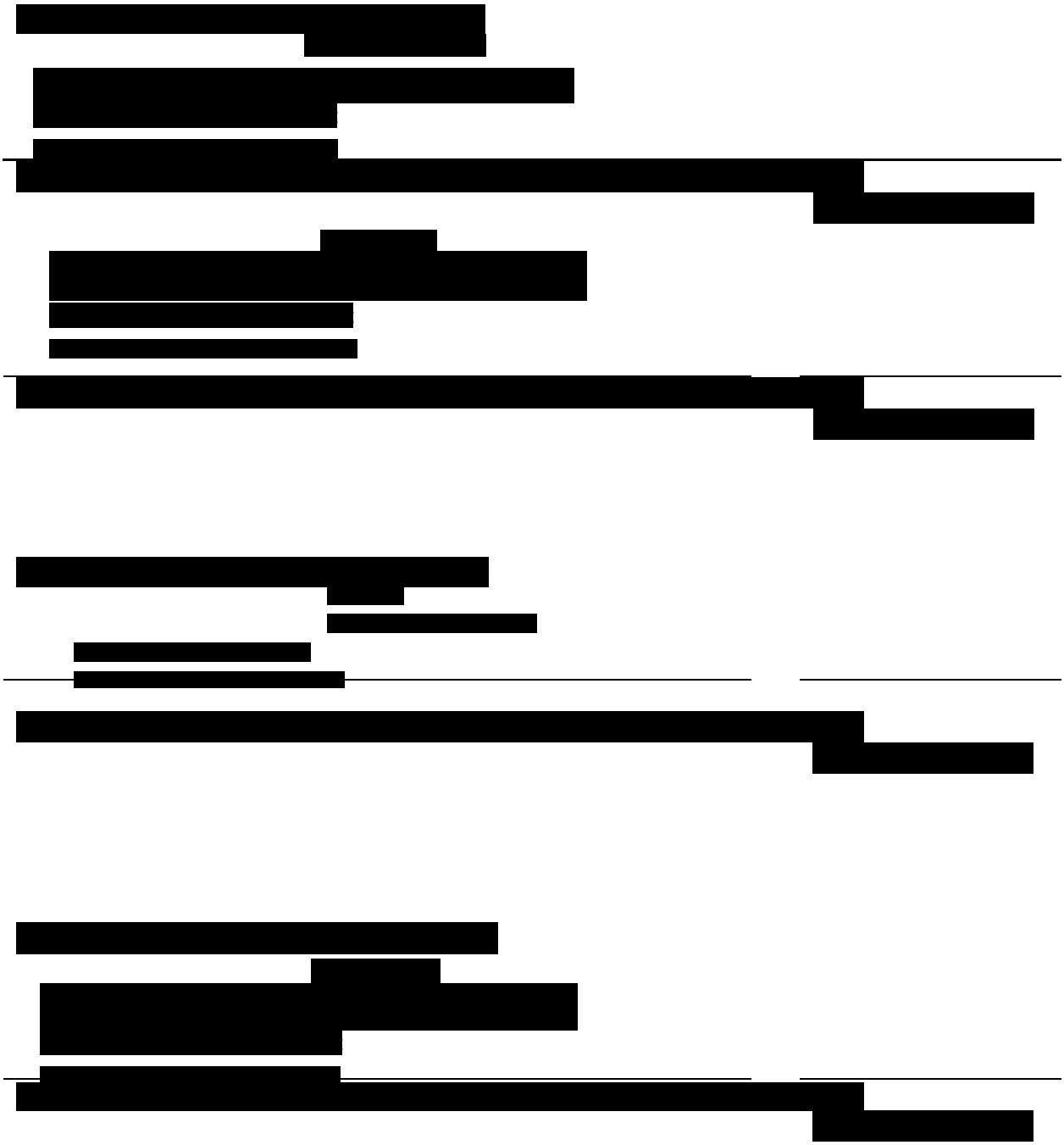

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TABLE OF CONTENTS

SIGNATURE PAGE 2
TABLE OF CONTENTS 4
1 BACKGROUND AND RATIONALE 8
2 STUDY DESCRIPTION 9
2.1 Study Design 9
2.2 Treatment Assignment 10
2.3 Blinding and Unblinding 11
2.4 Protocol Amendments 11
3 OBJECTIVES 11
3.1 Primary 11
3.2 Secondary 11
[redacted]
4 ENDPOINTS 12
4.1 Primary Endpoints 12
4.2 Secondary Endpoints 13
[redacted]
5 SAMPLE SIZE AND POWER 16
6 STUDY PERIODS, TREATMENT REGIMENS 17
6.1 Study Periods 17
6.2 Treatment Regimens 18
7 STATISTICAL ANALYSES 19
7.1 General Methods 19
7.2 Study Population 20
7.3 Study Conduct 20
7.3.1 Subject Disposition 20
7.3.2 Demographics and Baseline Disease Characteristics 21
7.3.3 Medical History 22
7.4 Extent of Exposure 23
7.4.1 Study Therapy 23
7.4.2 Modification of Study Therapy 24

7.4.3 [redacted] 24
7.4.4 Concomitant Procedure, Elective Procedure or Hospitalization 24
7.5 Efficacy 24
7.5.1 Primary Efficacy 25
7.5.2 Secondary Efficacy 26
7.6 Safety 28
7.6.1 Deaths 29
7.6.2 Serious Adverse Events 29
7.6.3 Adverse Events Leading to Discontinuation of Study Therapy 30
7.6.4 Adverse Events 30
7.6.5 Select Adverse Events 31
7.6.5.1 Incidence of select AEs 31
7.6.6 Other Events of Special Interest 31
7.6.7 Clinical Laboratory Evaluations 32
7.6.7.1 Abnormal Hepatic Test 32
7.6.7.2 Abnormal Thyroid Test 34
7.6.7.3 Abnormal Laboratory Test 34
7.6.8 Immunogenicity 35
7.6.9 Vital Sign 35
7.6.10 Electrocardiograms 36
7.6.11 Physical Examinations 36
7.6.12 ECOG 36
7.6.13 Pregnancy Testing 36
7.7 Pharmacokinetics 37
7.8 Pharmacodynamics 41
7.9 Conventions 41
7.9.1 Decimal Places 41
7.9.1.1 Missing data 41
8 DOCUMENT HISTORY 44
9 REFERENCES 45
APPENDIX 1: Major changes to stats analysis in protocol amendments 46
APPENDIX 2: Baseline Disease Characteristics 48
APPENDIX 2: Baseline Disease Characteristics (Continued) 49

LIST of ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-Drug Antibodies
AE	Adverse Event
AEOSI	Events of Special Interest
ALT	Anti-Drug Antibodies
AST	Aspartate Aminotransferase
CI	Confidence Interval
CK	Creatine Kinase
CR	Complete Response
CRF	Case Report Form
CSF1R	Colony Stimulating Factor 1 Receptor
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GBM	Malignant Glioma
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
IHC	Immunohistochemistry
kg	Kilogram
K-M	Kaplan-Meier
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
MDSC	Myeloid-Derived Suppressor Cell
MedDRA	Medical Dictionary For Regulatory Activities
mg	Milligram
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamics
PD	Progressive Disease
PD-1	Programmed Cell Death 1
PFS	Progression Free Survival
PK	Pharmaocokinetics
PR	Partial Response

PR	Pulse Rate
PT	Preferred Term
QRS	QRS Interval of the ECG
QT	QT Interval of the ECG
QTc	Corrected QT Interval
QTcB	Corrected QT Interval Using Bazett’s Formula
QTcF	Corrected QT Interval Using Fridericia's Formula
RCC	Renal Cell Carcinoma
RD	Recommended Dose
RECIST v1.1	Response Evaluation Criteria In Solid Tumors, Version 1.1
RR	RR Interval of the ECG
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCCHN	Squamous Cell Carcinoma of The Head And Neck
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TSH	Follicle Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
WHODD	World Health Organization Drug Dictionary

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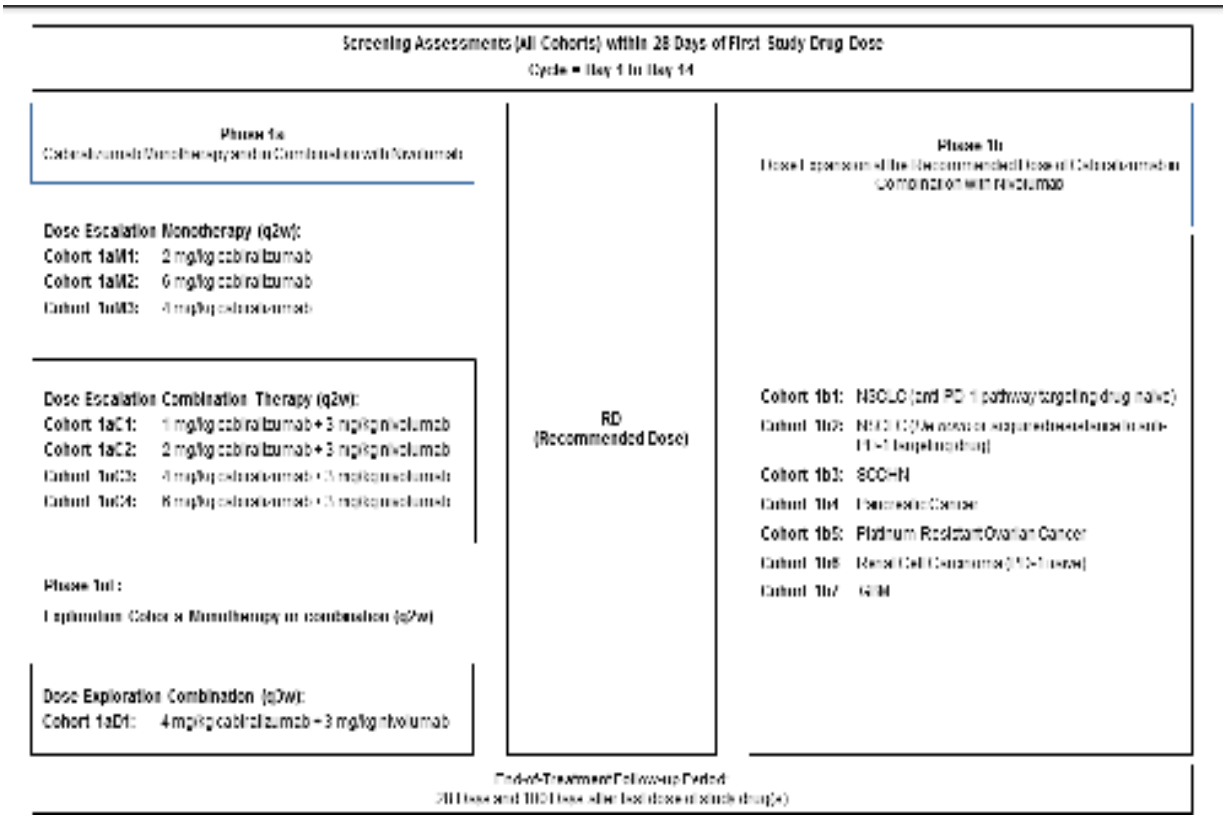
2.1 Study Design

This study is a Phase 1a and 1b, open-label, multicenter, dose escalation and dose expansion study to evaluate the efficacy, safety, tolerability, PK, and PD of cabiralizumab as monotherapy and in combination with nivolumab in subjects with selected advanced cancers. Cabiralizumab is a humanized monoclonal antibody directed against CSF1R, and nivolumab is a fully human monoclonal antibody directed against PD-1. For monotherapy arms of the study, cabiralizumab will be given on Day 1 of each 14-day treatment cycle. For the combination arms of the study, cabiralizumab and nivolumab will be given on Day 1 of each 14-day treatment cycle (except for the 3-week dosing regimen cohort). Nivolumab will be administered as an IV infusion over 30 minutes followed by a 30 to 60-minute rest, and then cabiralizumab will be administered as an IV infusion over 30 minutes. If any Grade 3 or higher infusion reaction is observed during the proposed infusion rate of nivolumab 3 mg/kg over 30 minutes, the infusion rate will be extended to 60 minutes for all current and subsequent subjects for the duration of this study.

The study will include a Phase 1a dose escalation, Phase 1a 3-week dosing regimen, Phase 1a exploration and a Phase 1b dose expansion. Phase 1a dose escalation consists of 3 cabiralizumab monotherapy cohorts (1aM1, 1aM2 and 1aM3) and 4 cohorts of cabiralizumab in combination with nivolumab (1aC1, 1aC2, 1aC3 and 1aC4). Phase 1a 3-week dosing regimen (1aD) consists of 1 cohort which will administer cabiralizumab at 4mg/kg in combination with nivolumab at 3 mg/kg every three weeks instead of every two weeks. The Phase 1a exploration (1aE) is designed to further evaluate the safety, PK, and PD of cabiralizumab as monotherapy and in combination with nivolumab. Phase 1b consists of 7 cohorts (1b1 through 1b7) across 6 cancer types. Subjects will be enrolled into either Phase 1a or Phase 1b of the study.

Figure 1: Study Design Schematic



The total number of subjects planned for this study is estimated to be 295 in North America. By the end of the study, approximately 85 subjects in Part 1a (approximately 20 in monotherapy dose escalation, 15 in combination dose escalation, 10 in an 3-week dose regimen, and up to 40 in exploration cohorts) and 210 subjects in Part 1b (approximately 30 subjects for each of the 7 Phase 1b cohorts) will be enrolled. There will be approximately 50 study centers participating in this study.

2.2 Treatment Assignment

The study includes Phase 1a and Phase 1b. Subjects will be enrolled into either Phase 1a or Phase 1b of the study. Phase 1a consists of 7 dose escalation cohorts and one 3-week dosing regimen cohort. Phase 1a also includes up to 40 additional subjects that will be enrolled for further exploration of safety and PK. In Phase 1a, a modified 3 + 3 + 3 design will be used to assess the safety of cabiralizumab in monotherapy and in combination with nivolumab.

Phase 1b consists of 7 tumor-specific expansion cohorts across 6 cancer types. (Refer figure 1 for study design)

2.3 Blinding and Unblinding

This is an open-label study and there will be no blinding of subjects' treatment during this study.

2.4 Protocol Amendments

This analysis plan reflects revised protocol version 05, amendment 4, and dated 07-JUN-2017. Major changes that are applicable to stats analysis in protocol amendments are described in Appendix 1.

3 OBJECTIVES

3.1 Primary

Phase 1a:

- To assess the safety and tolerability of cabiralizumab as monotherapy
- To assess the safety and tolerability of cabiralizumab in combination with nivolumab
- To determine the recommended dose (RD) of cabiralizumab in combination with a fixed dose of nivolumab

Phase 1b:

- To evaluate the clinical benefit of cabiralizumab in combination with nivolumab in subjects with selected advanced cancers through the analysis of objective response rate (ORR)
- To evaluate the safety and tolerability of cabiralizumab in combination with nivolumab in subjects with selected advanced cancers treated at the RD

3.2 Secondary

Phase 1a:

- To characterize the PK profile of cabiralizumab
- To characterize the PK profile of nivolumab when administered in combination with cabiralizumab
- To characterize the immunogenicity of cabiralizumab and nivolumab
- To characterize the PD profile of cabiralizumab and nivolumab by analyses of biopsies (including immunohistochemistry (IHC) analyses of CD8, CD68, and other selected biomarkers)

Phase 1b:

- To evaluate the clinical benefit of cabiralizumab in combination with nivolumab in subjects with selected advanced cancers through the analysis of overall survival (OS), duration of response (DOR), and progression free survival (PFS)
- To characterize the PK profile of cabiralizumab when administered in combination with nivolumab
- To characterize the PK profile of nivolumab when administered in combination with cabiralizumab
- To characterize the immunogenicity of cabiralizumab and nivolumab
- To characterize the PD profile of cabiralizumab and nivolumab by analyses of biopsies (including IHC analyses of CD8, CD68, and other selected biomarkers)
- To assess the association of selected biomarker measures and clinical efficacy measures using pre-treatment and on-treatment tumor biopsies

4 ENDPOINTS

4.1 Primary Endpoints

Phase 1a

- **Safety**
  - The incidence of Grade 3 and Grade 4 AEs and clinical laboratory abnormalities defined as DLTs
  - The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities

Phase 1b

- **Efficacy**

- ORR is defined as the total number of subjects with confirmed responses of either complete response (CR) or partial response (PR) divided by the total number of subjects in the response-evaluable population (as defined in section 7.2) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) by investigator assessment

- **Safety**
  - The incidence of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, and ECG abnormalities
  - The incidence of treatment discontinuations, modifications, and interruptions due to adverse events
  - Grade 3 and Grade 4 AEs and clinical laboratory abnormalities

4.2 Secondary Endpoints

Phase 1a

- **Pharmacokinetic:** The following PK parameters will be derived from concentration-time data for cabiralizumab when appropriate and applicable. Accumulation ratio of C_{max} and C_{min} for nivolumab may be calculated if the data are available.
  - Area under serum concentration-time curve (AUC)
  - Maximum serum concentration (C_{max})
  - Minimum serum concentration (C_{min})
  - Clearance (CL)
  - Volume of distribution at steady state (V_{ss})
  - Accumulation ratio
  - Elimination half-life ($t_{1/2}$)
- **Immunogenicity**: Defined as an immune response to either cabiralizumab or nivolumab, will be assessed by measurement of total anti-cabiralizumab antibodies and total anti-nivolumab antibodies from all subjects. Immunogenicity testing will consist of screening, confirmation, and titration for both cabiralizumab and nivolumab. To classify the ADA status of a subject using data from an in vitro test method, each sample from a subject is categorized based on the following definitions:

Table 1. Sample ADA Status

Sample ADA Status	Definition
Baseline ADA-positive sample	ADA is detected in the last sample before initiation of treatment
Baseline ADA-negative sample	ADA is not detected in the last sample before initiation of treatment
ADA-positive sample	1) an ADA detected (positive seroconversion) sample in a subject for whom ADA is not detected at baseline, or (2) an ADA detected sample with ADA titer to be at least *4*-fold or greater (≥) than baseline positive titer
ADA-negative sample	ADA sample that is not deemed ADA-positive

Next, using the sample ADA status, subject ADA status is defined as follows:

Table 1.1 Subject ADA Status

ADA Status	Definition
Baseline ADA-positive	A subject with baseline ADA-positive sample
ADA-positive	A subject with at least one ADA positive-sample relative to baseline at any time after initiation of treatment
ADA-negative	A subject with no ADA-positive sample after the initiation of treatment

- **Pharmacodynamic Biomarkers**
    - Changes in whole blood monocyte subsets by flow cytometry
    - Changes in cytokine levels by multiplex analysis
    - Change in macrophage and T-cell levels in tumor biopsy samples

Phase 1b

- **Pharmacokinetic**: The following PK parameters will be derived from concentration-time data for cabiralizumab when appropriate and applicable. Other parameters, such as dose dependency and accumulation ratio, may also be calculated. Accumulation ratio of C_{max} and C_{min} for nivolumab may be calculated if the data are available.
    - Area under serum concentration-time curve (AUC)
    - Maximum serum concentration (C_{max})
    - Minimum serum concentration (C_{min})
    - Clearance (CL)
    - Volume of distribution at steady state (V_{ss})

- Accumulation ratio
- Elimination half-life ($t_{1/2}$)

- **Immunogenicity**: Defined as an immune response to either cabiralizumab or nivolumab, will be assessed by measurement of total anti-cabiralizumab antibodies and total anti nivolumab antibodies from all subjects. Immunogenicity testing will consist of screening, confirmation, and titration for both cabiralizumab and nivolumab. ADA status of a subject will be classified by following the rule in Table 1.
- **Pharmacodynamic Biomarkers**
  - Changes in whole blood monocyte subsets by flow cytometry
  - Changes in cytokine levels by multiplex analysis
  - Change in macrophage and T-cell levels in tumor biopsy samples
- **Efficacy**
  - OS will be defined as the time between the first dose of study drug and death.
  - DOR will be defined as the time from first confirmed response (CR or PR) until the first objectively documented disease progression per RECIST v1.1 or death due to any cause by investigator assessment
  - PFS will be defined for each subject as the time from the first dose to the first objectively documented disease progression per RECIST v1.1 or death due to any cause by investigator assessment.
  - ORR per RECIST v1.1 by Central Imaging Review

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

Approximately 85 subjects will be enrolled in Phase 1a. In dose escalation, between 3 and 9 subjects are expected to be treated at each dose escalation cohort according to the algorithm outlined in Table 1. There will also be up to 40 subjects enrolled into the exploratory dose cohorts to further explore safety, PK, and PD, and approximately 10 subjects enrolled into the 3-week dosing regimen cohort to characterize the PK and safety profile at a 3-week dosing schedule. In Phase 1b, approximately 210 subjects will be enrolled.

Table 2: DLT evaluation and enrollment decisions will follow the below guidance

Algorithm for Dose-Escalation Decisions

6 STUDY PERIODS, TREATMENT REGIMENS

6.1 Study Periods

The study will consist of 3 periods including screening (up to 28 days), treatment, and follow-up.

Screening: Subjects who have fully consented to participation in the study will undergo screening assessments within 28 days (4 weeks) prior to administration of the first infusion of study treatment.

Treatment cycles: (including end of the DLT period and Phase-1a extended treatment period.)

For subjects in the monotherapy cohorts: cabiralizumab infusion administered as a 30-minute IV infusion on Day 1 of each 14-day treatment cycle.

For the combination therapy: nivolumab administered first as a 30-minute IV infusion, with a 30- to 60-minute rest, followed by a 30-minute infusion of cabiralizumab on Day 1 of each 14-day treatment cycle.

For cohort 1aD (Subjects in 3-week dosing regimen cohort): Study drugs on Day 1 of each 21-day treatment cycle.

End-of-Treatment Follow-up Period: All subjects should return to the clinic 28 (±7) days and 100 (±7) days from their last dose of study drug to complete the End-of-Treatment Follow-up

Period, irrespective of whether a subject is discontinued from the study drug at a planned visit or mid-cycle. Subjects should continue onto Long-Term Follow-up after completing the End-of-Treatment. Subjects will be followed every 12 (±2) weeks for survival, or more frequently as needed.

6.2 Treatment Regimens

Phase 1a Monotherapy Cohorts and Combination Dose Escalation Cohorts (1aM and 1aC)

Phase 1a consists of three cabiralizumab monotherapy cohorts and four dose-escalation cohorts of cabiralizumab in combination with nivolumab with a minimum of 3 subjects enrolled in each cohort. The planned dose levels and schedules for the Phase 1a cohorts are as follows:

- Cohort 1aM1: 2 mg/kg cabiralizumab, every 2 weeks
- Cohort 1aM2: 6 mg/kg cabiralizumab, every 2 weeks
- Cohort 1aM3: 4 mg/kg cabiralizumab, every 2 weeks
- Cohort 1aC1: 1 mg/kg cabiralizumab + 3 mg/kg nivolumab, every 2 weeks
- Cohort 1aC2: 2 mg/kg cabiralizumab + 3 mg/kg nivolumab, every 2 weeks
- Cohort 1aC3: 4 mg/kg cabiralizumab + 3 mg/kg nivolumab, every 2 weeks
- Cohort 1aC4: 6 mg/kg cabiralizumab + 3 mg/kg nivolumab, every 2 weeks

Phase 1a 3-week Dosing Regimen Cohort (1aD):

- 4 mg/kg cabiralizumab + 3 mg/kg nivolumab, every 3 weeks (Cohort 1aD1)
  (To characterize the PK profile and safety of cabiralizumab in combination with nivolumab when administered as an alternative dosing schedule.)

Phase 1a Exploration Cohorts (1aE):

- The Phase 1a exploration consists of up to 40 additional subjects to further evaluate the safety, PK, and PD of cabiralizumab as monotherapy and in combination with nivolumab in melanoma (Cohort 1aE2), anaplastic thyroid cancer (Cohort 1aE3), and pancreatic cancer (Cohort 1aE4).

Phase 1b Expansion Cohorts:

- Phase 1b will enroll up to 7 expansion cohorts in 6 advanced cancer types (1b1 through 1b7). Enrollment in Phase 1b will begin when an RD has been identified based on overall safety, tolerability, PK, and PD data.
- Cohort 1b1: NSCLC (PD-1 naive)

- Cohort 1b2: NSCLC
  (De novo or acquired resistance to anti-PD-1 targeting drug)
- Cohort 1b3: Squamous Cell Carcinoma of the Head and Neck (SCCHN)
- Cohort 1b4: Pancreatic Cancer
- Cohort 1b5: Advanced Ovarian Cancer
- Cohort 1b6: Renal Cell Carcinoma
- Cohort 1b7: Malignant Glioma (GBM)

7 STATISTICAL ANALYSES

7.1 General Methods

The statistical analysis will be conducted following the principles specified in the International Conference on Harmonisation (ICH) Topic E9 Statistical Principles for Clinical Trials (CPMP/ICH/363/96).

All statistical tabulations and analyses will be done using SAS®, Version 9.3 or higher.

Unless otherwise noted, continuous variables will be summarized using number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum, and maximum; categorical variables will be summarized using the frequency count and the percentage of subjects in each category.

In the data listings, study day relative to first dose of study drug may be presented. Study day relative to first dose will be calculated as: event date – first dose date in the study (+ 1 if event date ≥ first dose date in the study).

When appropriate, baseline is defined as the last non-missing result with a collection date-time less than the date-time of the first dose of study medication. If time is missing, unless otherwise specified, baseline is the last non-missing result prior to or equal to the date of first dose of study drug.

Unless otherwise specified, non-efficacy analyses except for biomarker and PK parameters, will be presented by:

- Overall monotherapy cohorts; overall combination cohorts
- individual or combined cohort by different dose and regimen

For efficacy and biomarker analyses, unless otherwise specified, the summary will be presented by:

- Pancreatic cancer cohort subjects dosed with 4 mg/kg cabiralizumab + 3 mg/kg nivolumab every 2 weeks, i.e., cohort 1aE4+1b4
- Pancreatic 6mg/kg cohort, i.e., cohort 1aC4
- Other individual cohort

PK analyses will be presented by individual or combined cohort by different dose and regimen.

7.2 Study Population

- Enrolled Population: All subjects who signed the ICF and are approved for enrollment with a study subject number assigned by sponsor or designee.
- Response-Evaluable Population based on investigator assessment: Subjects who have a measurable lesion at baseline and one of the following: 1) at least 1 post-baseline tumor assessment, 2) clinical progression, 3) death.
- Response-Evaluable Population based on central review assessment: Subjects who have one of the following: 1) at least 1 post-baseline tumor assessment, 2) clinical progression, 3) death.
- Safety Population: All subjects who receive any dose of cabiralizumab and/or nivolumab. This is the population of primary interest for the summaries of demographics, baseline characteristics, prior therapy, exposure, and safety. Summaries of OS, PFS, and ORR will also be provided for this population.
- PK Concentration Population: All subjects who receive at least one dose of cabiralizumab and/or nivolumab and have at least one available serum concentration data.
- PK Evaluable Population: Subjects in the PK Concentration Population who have adequate PK assessments to reliably derive at least one PK parameter. This is the population of primary interest for the summaries of the PK parameters and exploratory analyses of the association of PK data with efficacy measures.
- Biomarker Subjects: All subjects who receive at least one dose of cabiralizumab and/or nivolumab and have available biomarker data.
- Immunogenicity Subjects: All subjects who receive at least one dose of cabiralizumab and/or nivolumab and have available ADA data.

7.3 Study Conduct

7.3.1 Subject Disposition

Summary 1:

Number (%) of subjects will be presented for the following analysis population:

- Enrolled population
- Safety population
- Response-Evaluable population
- PK concentration population
- PK Evaluable population
- Biomarker subjects
- Immunogenicity subjects

The number of enrolled subjects will serve as the denominator for the percentage calculation.

Summary 2:

Subject disposition will be presented for enrolled population. Number (%) of subjects will be presented for the following:

- Enrolled in study
- Received treatment (yes/no)
- Discontinued from treatment
- Reason for treatment discontinuation
- Discontinued from study
- Reason for study discontinuation
- Participated in long-term follow-up (yes/no)

Denominator for 'Received treatment (yes/no)' will be based on the number of enrolled subjects. For all others, percentages will be based on the number of subjects in safety population.

Summary 3:

Number (%) of enrolled subjects who have specified protocol deviation and summary for a given category or subcategory of the protocol deviation.

Listing:

- Analysis population and subject disposition for each enrolled subject.
- Subjects with protocol deviations

7.3.2 Demographics and Baseline Disease Characteristics

Summary:

- Descriptive summary statistics will be provided for the safety population. The included demographic characteristics are: age, sex, race, and ethnicity. Two age categories in years will be summarized: <65, 65-85, >=85, or <65, 65-75, >=75. Additionally, summary for pancreatic cancer cohort subjects dosed with 4 mg/kg cabiralizumab + 3 mg/kg nivolumab every 2 weeks, i.e., cohort 1aE4+1b4, will be included along with other cohorts specified in section 7.1. Descriptive statistics of baseline physical measurements will be provided for safety population. Included measurements are height, weight, and ECOG performance status.
- Descriptive statistics of baseline disease characteristics for safety population by tumor type, associated individual cohort and overall within the given tumor type.
- Descriptive statistics of selected baseline disease characteristics for safety population with Melanoma.
- Descriptive statistics of selected baseline disease characteristics for safety population with NSCLC.
- Descriptive statistics of selected baseline disease characteristics for safety population with ovarian cancer.
- Descriptive statistics of selected baseline disease characteristics for safety population with SCCHN.
- Descriptive statistics of selected baseline disease characteristics for safety population with pancreatic cancer.
- Descriptive statistics of selected baseline disease characteristics for safety population with RCC.
- Descriptive statistics of selected baseline disease characteristics for safety population with GBM.

Please refer to Appendix 2 for the baseline disease characteristics summarized for different tumor type.

Listing:

Demographic characteristics and baseline physical measurements will be displayed for enrolled population. Baseline variables such as tumor tissue collection details (biopsy site, location of biopsy, lymph node location), and tumor markers (type of tumor marker, result) will be listed.

7.3.3 Medical History

Summary:

Medical history will be summarized by the incidence of subjects in safety population with reported Medical Dictionary for Regulatory Activities (MedDRA® Version 18.0) by system organ class (SOC) and preferred terms (PTs).

Listing:

Medical history will be listed for enrolled population.

7.4 Extent of Exposure

The extent of exposure will be characterized according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed.

7.4.1 Study Therapy

Summary:

Descriptive statistics will be provided by treatment for the following:

- Exposure to cabiralizumab (weeks)
- Exposure to nivolumab (weeks)

Exposure (weeks) is defined as the (number of days between start date of first injection and stop date of last injection + 21)/ 7 for Cohort 1aD1, and (number of days between start date of first injection and stop date of last injection + 14)/ 7 for all the other cohorts.

- Total cabiralizumab dose administered (mg and mg/kg)
- Total nivolumab dose administered (mg and mg/kg)
- Number of cabiralizumab doses administered
- Number of nivolumab doses administered
- Relative Dose Intensity of cabiralizumab and nivolumab

Relative dose intensity is defined as ([total dose administered in mg/kg]/ [planned total b dose])*100, where planned total dose is the prescribed starting dose in mg/kg times the exposure to study drug divided by 14 and 21 for all the cohorts except for 1aD1 and cohort 1aD1, respectively.

In addition, number and percentage will be provided for the subjects with relative dose intensity <50, 50-<70, 70-<90, 90-<110 and >=110.

Listing:

- Study drug administration details will be presented in a listing.
- Calculated exposure parameters for all the subjects

7.4.2 Modification of Study Therapy

Summary:

The following will be summarized for safety population:

- Number (%) of subjects with at least one infusion interruption
- Number of infusion interruptions per subject
- Number (%) of subjects with at least one infusion modification
- Number of infusion modification per subject

The infusion interruption and modification will be summarized separately for cabiralizumab and nivolumab.

[redacted]

7.4.4 Concomitant Procedure, Elective Procedure or Hospitalization

Concomitant procedure, elective procedure or hospitalization will be listed without summary.

7.5 Efficacy

The best overall response will be calculated following RECIST guideline (version 1.1)[1] by using the best response from visits where tumor assessment is performed. For subjects who discontinue from study, experienced progressive disease, died, or had anticancer therapy, tumor-directed radiotherapy, tumor-directed surgery, the tumor assessment up to the earliest date of the above mentioned events will be included in the best overall response calculation. The best overall response will be calculated respectively for the response assessed by investigator and the central review. Complete or partial response requires confirmation at a subsequent time point at least 4

weeks after the initial response is observed. Establishment of stable disease requires a minimum 42 day duration from first dose of study drug.

For this study, the date of investigator assessed timepoint response will be derived as follows:

- If the timepoint response is CR, PR or SD, the latest scan date, either from target or non-target lesion will be used as the timepoint response date.
- If the timepoint response is PD, the scan date of earliest sign of progression, either from target or non-target lesion, or new lesion, is used as the timepoint response date.

Efficacy summaries of objective response rate (ORR) and duration of response (DOR) will be provided for the response-evaluable population for investigator assessment as well as central review assessment. The summaries for OS and PFS will be performed for safety population. Response beyond disease progression will not be included in the analysis. If the sample size is too small to do a certain analysis in a group, number and percent of subjects will be provided. For PFS, DOR, and ORR, the main analysis is based on investigator's assessment; the secondary analysis is based on assessment made by central review committee. Additionally, summary of ORR will be performed for the safety population for investigator assessment.

The by prior line of therapies (<=1 and >=2) subgroup analysis will be performed for PFS and OS for pancreatic cancer subjects.

Time to event distribution (e.g. progression free survival, overall survival, and duration of response) will be estimated using Kaplan-Meier (K-M) method. When appropriate, the median along with 95% CI will be provided using Brookmeyer and Crowley methodology[2](using log-log transformation for constructing the confidence intervals). Rates at fixed timepoints will be derived from the K-M estimate and corresponding confidence interval will be derived based on Greenwood formula. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.

7.5.1 Primary Efficacy

Summary:

- ORR with corresponding 2-sided 95% CI based on Clopper-Pearson method along with each category of BOR for response-evaluable population based on investigator assessment. Time to response will be also included.
- ORR with corresponding 2-sided 95% CI based on Clopper-Pearson method along with each category of BOR for safety population based on investigator assessment.

ORR is defined as total number of subjects with confirmed responses of either CR or PR divided by the total number of subjects in the respective population per RECIST v1.1 by investigator assessment. Time to response will be also included.

7.5.2 Secondary Efficacy

Summary:

- OS by K-M method. The median survival time along with 95% CI as well as OS rate at 4 months, 6 months, and 12 months will be presented by K-M analysis. OS will also be summarized descriptively (mean, standard deviation, median, first and third quartiles, minimum, maximum). The summary is for safety population.

OS is defined as the time (months) between the first dose of study drug and death due to any cause. Subjects will be censored for this endpoint on the date of the last known date alive if they do not die. The subgroup OS summary will be performed for subjects with pancreatic cancer by prior line of therapies (<=1 and >=2).

- PFS by K-M method for safety population based on investigator assessment
- PFS by K-M method for safety population based on central review assessment
- Subgroup PFS analysis by prior line of therapies (<=1 and >=2) for subjects with pancreatic cancer safety population based on central review assessment.

Sensitivity analysis will be performed for the above PFS analyses by treating clinical PD as event as well. Last dose date + 14 days is considered as event date for clinical PD.

PFS will be defined for each subject as the time (months) from the first dose to the first objectively documented disease progression per RECIST v1.1 or death due to any cause in the absence of documented PD. Censoring for the PFS endpoint is summarized in Table 3. PFS rate at specified timepoints (4 months, 6 months, 12 months) will be presented using K-M method.

- Duration of response (DOR) for responders (confirmed CR or PR) for response-evaluable population based on investigator assessment
- Duration of response (DOR) for responders (confirmed CR or PR) for response-evaluable population based on central review assessment

DOR is defined as the time (months) from date of the first documentation of confirmed response (CR or PR) to the first objectively documentation of progressive disease (PD) or to death due to

any cause in the absence of documented PD. The censoring mechanisms for DOR are similar to those for PFS.

- ORR with corresponding 2-sided 95% CI based on Clopper-Pearson method along with each category of BOR for response-evaluable population based on central review assessment. Time to response will also be included.
- ORR with corresponding 2-sided 95% CI based on Clopper-Pearson method along with each category of BOR for safety population based on central review assessment. Time to response will also be included.
- The extent of follow-up defined as the time between first dose date and last known date alive (for subjects who are alive) or death date (for subjects who died) will be summarized descriptively for safety population.

Table 3: Handling of Missing Assessments and Censoring Rules for PFS

Situation	Date of Progression or Censoring	Outcome
No baseline or no evaluable baseline assessment, and no death	Date of first dose	Censored
No post baseline or no evaluable post baseline assessment, and no death	Date of first dose	Censored
No death or disease progression	Date of last evaluable assessment	Censored
Discontinued from study	Date of last evaluable assessment	Censored
New anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without progression reported prior or on the same day	Date of last evaluable tumor assessment prior to the date of initiation of subsequent anticancer therapy	Censored
Disease progression or death	Date of death or first documented progression per RECIST 1.1, whichever is earlier (excludes clinical progression)	Progressed (event)

Figure:

- Percent change from baseline in target lesions over time (spider plot)
- Best Change from baseline in target lesions (waterfall plot)

- K-M plot of DOR for responders based on investigator assessment only when number of responder is not few
- K-M plot of DOR for responders based on central review assessment only when number of responder is not few
- K-M plot of PFS for safety population. Two sets of figures, one based on investigator assessment and the other based on central review assessment, will be provided.
- Subgroup K-M plot of PFS analysis by prior line of therapies (<=1 and >=2) for subjects with pancreatic cancer safety population based on central review assessment
- K-M plot of OS for safety population
- Subgroup K-M plot of OS analysis by prior line of therapies (<=1 and >=2) for subjects with pancreatic cancer safety population

Listing:

The following will be listed for all subjects:

- Tumor lesion measurements
- Tumor evaluation at each visit
- Subject level efficacy for all treated subjects - tumor best overall response (BOR), maximum response in tumor burden, PFS, death indicator
- Duration of response for responders - BOR, time to response, time on therapy, response duration, response duration after treatment discontinuation, reason for treatment discontinuation
- Survival - survival status, first dose date, last dose date, first subsequent anti-cancer therapy date, last known alive date, death date, time to death

For the above listings except for survival, assessment performed by investigator and central review committee will be listed separately.

7.6 Safety

Unless otherwise specified, all analyses will be performed using the safety population.

Adverse events (AEs) will be coded according to the most current version of MedDRA and be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version *4.03*. Treatment-related AEs are those events with relationship to study treatment "Related" as recorded on the CRF. If the relationship to study treatment is missing, the AE will be considered as treatment related.

Listing of adverse events will include all enrolled subjects, as SAEs and deaths are collected pretreatment. Summaries of adverse events will be for treatment-emergent AE (TEAE) that is defined as adverse event starts or severity becomes worse after the first dose and within 100 days of last study therapy. AEs and treatment-related AEs will be tabulated by descending frequency of SOC and descending frequency of PT within each SOC, unless specified otherwise.

When reporting adverse events by CTC grade, summary tables will be provided based on the event with worst CTC grade (independent of relationship to study medication). Subjects will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the 'Total subject' row at their worst CTC grade, regardless of SOC or PT.

The analysis of laboratory results will be based on safety population with data. Laboratory results will be categorized according to NCI CTCAE (version *4.03*) grade. Baseline is defined as the last non-missing measurement prior to the first dosing date and time.

7.6.1 Deaths

All deaths during the study will be summarized for cause of deaths. All recorded deaths for enrolled population will be listed.

Summary:

- All deaths, reasons for death
- Deaths within 30 days of last dose received, reasons for death
- Deaths within 100 days of last dose received, reasons for death

7.6.2 Serious Adverse Events

Overall summary of SAEs and treatment-related SAEs by worst CTC grade will be presented by SOC/PT. By-subject SAE listing will be provided for the enrolled population.

Summary:

- Summary of SAEs by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5) presented by SOC/PT
- Summary of treatment-related SAEs by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5) presented by SOC/PT

Summary of treatment-related SAEs include SAEs that are cabiralizumab-related or nivolumab-related.

By-subject listing of SAEs will be provided

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

AEs leading to study treatment discontinuation are AEs with action taken = "Drug permanently discontinued". Overall summary of AEs leading to discontinuation and treatment-related AEs leading to discontinuation by worst CTC grade will be presented by SOC/PT. By-subject AEs leading to discontinuation listing will be provided.

Summary:

- Summary of AEs leading to discontinuation by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5) presented by SOC/PT

AE leading to discontinuation of cabiralizumab or discontinuation of nivolumab will be included.

- Summary of treatment-related AEs leading to discontinuation by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5) presented by SOC/PT

Adverse events summarized are those relate to at least one of the combination therapy and lead to discontinuation of at least one of the combination.

7.6.4 Adverse Events

Overall summary of any TEAEs and treatment-related TEAEs by worst CTC grade will be presented by SOC/PT. All recorded AEs occurring in the pre-treatment, on-treatment, and post-treatment period will be listed.

Summary:

- Summary of any AEs by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5) presented by SOC/PT
- Summary of treatment-related AEs by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5) presented by SOC/PT

7.6.5 Select Adverse Events

The select Adverse Events (select AEs) consist of a list of preferred terms grouped by specific category (e.g. pulmonary events, gastrointestinal events categories, etc.). AEs that may differ from or be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity are included as select AEs. The select AEs and the categories are defined by the Sponsor and the list that is the most current at the time of analysis will be used.

7.6.5.1 Incidence of select AEs

Overall summary of any select AEs, treatment-related select AEs, serious select AEs, treatment-related serious select AEs, select AEs leading to discontinuation, treatment-related select AEs leading to discontinuation, by worst CTC grade will be presented by category or subcategory/PT. By-subject select AE listing will also be provided.

The following analyses will be conducted:

- Summary of any select AEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5) presented by category or subcategory/PT
- Summary of treatment-related select AEs by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5) presented by category or subcategory/PT
- Summary of any serious select AEs by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5) presented by category or subcategory/PT
- Summary of treatment-related serious select AEs by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5) presented by category or subcategory/PT
- Summary of any select AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5) presented by category or subcategory/PT
- Summary of treatment-related select AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5) presented by category or subcategory/PT

7.6.6 Other Events of Special Interest

Other events of special interest (AEOSI) consist of a list of preferred terms grouped by specific category (e.g. Myositis Event, Myocarditis Event, Demyelination Event, Guillain-Barre Syndrome, Pancreatitis Event, Uveitis Event, Encephalitis Event, etc.). The list of MedDRA

preferred terms used to identify AEOSI is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

Other AEs of special interest will be summarized by treatment group for each category.

- Summary of other AEs of special interest by worst CTC grade (Grade 1, 2, 3, 4, 3-4, 5) presented by Category/PT
- Summary of treatment-related other AEs of special interest by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5) presented by Category/PT
- Summary of serious other AEs of special interest by worst CTC grade (grade 1, 2, 3, 4, 3-4, 5) presented by Category/PT

By-subject listing of other AEs of special interest will be provided.

7.6.7 Clinical Laboratory Evaluations

Clinical laboratory data will be analyzed using both US conventional units and international system of units if needed. The on-treatment period starts at first dose and ends at 100 days after last study therapy.

Summary:

The number (%) of subjects with the following will be summarized using the worst CTC grade on-treatment per subject.

- Post-baseline grade (summary of worst toxicity grade)
- Grade change from baseline
- Descriptive statistics of laboratory test result and their changes from baseline at scheduled nominal visit.

Listing:

- A by-subject listing of these laboratory parameters will be provided. Laboratory abnormality criteria and laboratory results outside of normal range will be listed

7.6.7.1 Abnormal Hepatic Test

Summary:

The number (%) of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized:

- Total bilirubin > 2 to ≤ 3 x ULN
- ALT or AST > 3 x ULN, > 5 x ULN, >10 x ULN, > 12 x ULN, and > 20 x ULN
- ALT or AST > 20 x ULN ***or*** Total bilirubin > 3 x ULN
- Concurrent ALT or AST > 3 x ULN ***and*** Total bilirubin > 2 x ULN ***or*** INR > 1.5
- Concurrent ALT or AST > 5 to ≤12 x ULN ***and*** Total bilirubin ≤ 2 x ULN
- Concurrent ALT or AST > 12 to ≤ 20 x ULN ***and*** Total bilirubin ≤ 2 x ULN

A window of ± 3 days is applied to the concurrent abnormality. The days to onset is defined as the date abnormality criteria is first met - first dose date+1. For the concurrent abnormality, this date refers to the latter date when ALT or AST and Total bilirubin meets the abnormality criteria. The days to resolution refers to the resolution date - first abnormality onset date +1, where the resolution date is defined as the date of the visit when the given abnormality criteria is not met and there is no subsequent abnormality coming back. For concurrent abnormality, all lab test listed in the criteria needs to be nonmissing at the resolution visit. All lab assessment record collected in the study database will be used for the resolution evaluation regardless of whether it falls within the on-treatment window.

The definition of normal for the concurrent abnormality resolution definition is defined as:

- Total bilirubin > 2 to ≤ 3 x ULN
  Definition of normal: Total bilirubin ≤1.5 x ULN
- ALT or AST > 3 x ULN, > 5 x ULN, >10 x ULN, > 12 x ULN, and > 20 x ULN
  Definition of normal: ALT and AST < 2 x ULN
- ALT or AST > 20 x ULN or Total bilirubin > 3 x ULN
  Definition of normal: ALT and AST < 2 x ULN and Total bilirubin ≤1.5 x ULN
- Concurrent ALT or AST > 3 x ULN and Total bilirubin > 2 x ULN or INR > 1.5
  Definition of normal: ALT and AST < 2 x ULN, Total bilirubin ≤1.5 x ULN and INR <= 1.5
- Concurrent ALT or AST > 5 to ≤12 x ULN and Total bilirubin ≤ 2 x ULN
  Definition of normal: ALT and AST < 2 x ULN and Total bilirubin ≤1.5 x ULN
- Concurrent ALT or AST > 12 to ≤ 20 x ULN and Total bilirubin ≤ 2 x ULN
  Definition of normal: ALT and AST < 2 x ULN and Total bilirubin ≤1.5 x UL

Figure:

- Scatter plot of Total bilirubin peak vs AST peak
- Scatter plot of Total bilirubin peak vs ALT peak

On-treatment peak total bilirubin and on-treatment peak AST/ALT may or may not happen on the same day of liver testing.

Listing:

A by-subject listing of these specific abnormalities will be provided if needed.

7.6.7.2 Abnormal Thyroid Test

Summary:

The number (%) of subjects with abnormal thyroid test will be summarized as follows:

- Elevated TSH value > ULN and one of the below subcategorie is met:
  - with baseline TSH value ≤ ULN
  - with at least one FT3/FT4 test value < LLN within 2-week window after the abnormal TSH test
  - with all FT3/FT4 test values ≥ LLN within 2-week window after the abnormal TSH test
  - with F3/F4 missing within 2-week window after the abnormal TSH test
- Low TSH < LLN and one of the below subcategorie is met:
  - with baseline TSH value ≥ LLN
  - with at least one FT3/FT4 test value > ULN within 2-week window after the abnormal TSH test
  - with all FT3/FT4 test values ≤ ULN within 2-week window after the abnormal TSH test
  - with F3/F4 missing within 2-week window after the abnormal TSH test

The analyses will include lab values up to 100 days after last dose of study drug.

Listing:

A by participant listing of these specific abnormalities will be provided

7.6.7.3 Abnormal Laboratory Test

Summary:

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized:

- CK > 10 x ULN, > 15 x ULN, > 20 x ULN

- LDH > 10 x ULN, > 15 x ULN, > 20 x ULN

Listing:

A by subject listing of these specific abnormalities will be provided

7.6.8 Immunogenicity

Summary:

The number (%) of subjects with the following anti-drug responses will be reported for immunogenicity subjects. The on-treatment period starts at first dose and beyond.

- baseline nivolumab ADA-positive
- baseline nivolumab ADA-negative
- baseline cabiralizumab ADA-positive
- baseline cabiralizumab ADA-negative
- nivolumab ADA-positive
- nivolumab ADA-negative
- cabiralizumab ADA-positive
- cabiralizumab ADA-negative

Listing:

All collected immunogenicity will be listed with flags indicating baseline-positive sample, ADA-positive sample or ADA-negative sample.

Clinical Implications:

Effect of immunogenicity on clearance of cabiralizumab and nivolumab will be explored. The summary of trough concentration of cabiralizumab and nivolumab will be summarized respectively by postbaseline cabiralizumab and nivolumab ADA status.

7.6.9 Vital Sign

For vital sign parameters of heart rate, blood pressure (systolic and diastolic), temperature, respiration rate, pulse oximetry, and weight, descriptive statistics of measured value and their changes from baseline will be summarized for each scheduled assessment. Additionally, the actual value and change from baseline for the maximum value, minimum value, and last available assessment will be summarized with descriptive statistics. The on-treatment period starts at first dose and ends at 100 days after last study therapy.

Vital signs data will be listed by subject at each visit.

7.6.10 Electrocardiograms

For12-lead ECG parameters (HR and PR, RR, QRS, QT, QTc (QTcF, QTcB and other) intervals), the actual value and change from baseline for the maximum value, minimum value, and last available assessment will be summarized. The on-treatment period starts at first dose and ends at 100 days after last study therapy.

Shift tables will be presented for overall ECG result showing the number and frequency of subjects with normal, abnormal clinical significant, and abnormal not clinically significant at the baseline to post-dose scheduled visits.

All recorded electrocardiograms will be listed for all treated subjects.

7.6.11 Physical Examinations

Physical examination findings will be presented in a subject listing.

7.6.12 ECOG

ECOG performance status will be summarized categorically (ECOG grade: 1, 2, 3, and 4) for each scheduled study visit. Shift tables showing baseline ECOG grade and maximum grade on treatment will be provided. The on-treatment period starts at first dose and ends at 100 days after last study therapy.

A by-subject listing of ECOG will also be provided.

Classification of ECOG performance status is provided below.

Grade	Performance Status Criteria
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light sedentary nature (light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

7.6.13 Pregnancy Testing

A listing of pregnancy tests results will be provided for all treated female subjects.

7.7 Pharmacokinetics

7.7.1 Serum cabiralizumab and nivolumab Concentration

Individual and mean serum concentration of cabiralizumab and nivolumab versus time data will be plotted by individual or combined cohort with different dose and regimen. Summary statistics will be tabulated for the serum concentration-time data of cabiralizumab and nivolumab, as appropriate. For the purpose of calculating or plotting mean concentration-time data, below the lower limit of assay quantitation (LLOQ) values will be treated as missing.

7.7.2 PK Parameters

The PK evaluable population will be used for all summaries of the PK parameters. Summary statistics will be tabulated for each PK parameter by individual or combined cohort with different dose and regimen. Geometric means and coefficients of variation will be presented for Cmax, AUC(0-T), AUC(TAU), Cmin, Ctrough, CL, Vss, MRT and AIs. Medians and ranges (minimum and maximum) will be presented for Tmax. Means and standard deviations will be presented for other PK parameters (i.e., t1/2).

Pharmacokinetic parameters of cabiralizumab will be derived from the serum concentration versus time profiles for the intensively sampled Cycle 1, Day 1 and Cycle 8, Day 1 dose administration in both Phase 1a and Phase 1b of the study. Individual PK parameter values will be derived by non-compartmental methods by a validated PK analysis program using actual times.

Parameter	Units	Definition
Cmax	µg/mL	Maximum observed serum concentration
Tmax	h	Time of maximum observed serum concentration
AUC(0-T)	µg.d/mL	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
AUC(TAU)	µg.d/mL	Area under the serum concentration-time curve in one dosing interval
Cmin	µg/mL	Minimum observed serum concentration during a dosing interval (excludes pre-dose concentration before the first dose)
Ctrough	µg/mL	Concentration associated with the sample at the end of each dose interval.
CL	L/d	Total body clearance calculated Dose divided by AUC(TAU) for Cycle 8, Day 1
AI_AUC	-	AUC accumulation index; ratio of AUC(TAU) for Cycle 8, Day 1 to AUC(TAU) after the first dose
AI_Cmax	-	Cmax accumulation index; ratio of Cmax from any cycles to Cmax after the first dose
AI_Cmin	-	Cmin accumulation index; ratio of Cmin for Cycle 8, Day 1 to Cmin after the first dose
AI_Ctrough	-	Ctough accumulation index; ratio of Ctrough from any cycles to Ctrough after the first dose
pAUCe	%	Percent of AUC extrapolated from the last quantifiable concentration to infinity (Cycle 1, Day 1 only)
λz	d^{-1}	Slope of terminal log-linear elimination phase
Adj R^2	-	Adjusted R^2 of terminal elimination phase
Lz_Start	d	The time point starting the log-linear elimination phase defining the terminal half-life
Lz_End	d	The time point ending the log-linear elimination phase defining the terminal half-life

Parameter	Units	Definition
Lz_N	-	Number of time points in the log-linear elimination phase defining the terminal half-life
MRT	d	Mean residence time. MRT = (AUMCinf/AUCinf) – T/2 where AUMCinf=Area under moments curve of the serum concentration-time from time 0 to infinity, AUCinf=Area under the serum concentration-time curve from time 0 to infinity, and T= infusion duration.
t1/2	d	Terminal half-life calculated post first dose. t1/2=ln(2)/λz
Vss	mL/kg	Steady-state distribution volume projected post first dose. Vss= CL*MRT.

Dose-normalized values for AUCs, Cmax, Cmin, and Ctrough will also be presented using the actual dose administered.

7.7.3 Quality Control Methods for PK Data Analysis

The PK analysis will be subject to Quality Control (QC) review and also review by an independent pharmacokinetist at ICON.

7.7.4 Pharmacokinetic Assessments

7.7.4.1 PK analysis Software

Pharmacokinetic (PK) parameters will be calculated from the serum drug concentration-time data and actual elapsed sampling time using a non-compartmental analysis (NCA) method with i.v infusion input in Phoenix WinNonLin (Build 8.0.0.3176 or higher, Certara LP, St. Louis, MO). Alternative PK analysis methods may be considered if necessary, for example, a population PK analysis or compartmental modeling. Data summaries and plots will be produced using SAS Version 9.1 or higher (SAS Institute, Cary, NC).

7.7.4.2 PK Parameter Evaluation

For cabiralizumab, PK parameters including Cmax, AUC, Cmin, Ctrough, CL, Vss, and MRT will be estimated. The cabiralizumab accumulation ratio for Cmax, Cmin, and Ctrough, and AUC will be estimated for different cycles, as data permit.

For nivolumab, Ctrough will be reported and accumulation will be evaluated for different cycles, as data permit.

Dose-proportionality will be assessed based on available cabiralizumab PK parameters if applicable.

Only data points that describe the terminal elimination log-linear decline will be used in the regression equation for calculation of λ_z. C_{max} and any data point in the distribution phase will not be included in the calculation of λ_z. A minimum of 3 points will be used for determination of the terminal elimination phase rate constant. A value of adjusted r^2 >0.80 will be considered acceptable for the calculation of the terminal elimination phase rate constant. If adjusted r^2 falls below 0.80, or the above conditions are not met, then the terminal elimination phase rate constant and the associated values of t1/2, AUC(INF), CL and Vss will be flagged. If pAUCe is more than 20%, then AUC(INF) and CL will be flagged. Flagged values will not be included in the calculation of descriptive statistics.

7.7.4.3 Treatment of Outliers

Individual serum concentration-time points, if considered anomalous, may be excluded from the analysis at the discretion of the pharmacokineticist following a review of the available documentation. Any such exclusion will be discussed with the Sponsor's Clinical Pharmacologist and clearly outlined in the CSR.

Entire individual treatment profiles for a subject may be excluded following review of the available documentation and discussion with the Sponsor. However, results of analysis with and without the excluded profiles may be presented in the CSR. Any such exclusion will be clearly listed in the CSR along with justification for exclusion.

Any anomalous concentration values observed prior to the first dose will be identified and discussed in the CSR.

7.7.4.4 Non-Quantifiable or LLOQ Concentrations

For the calculation of PK parameters, predose concentration values prior to the first quantifiable concentration that are below LLOQ values will be assigned a value of zero and thereafter any LLOQ values will be set to missing.

[redacted]

7.9 Conventions

7.9.1 Decimal Places

The number of decimal places displayed in all listings will be determined by the number of decimal places in the raw data.

Unless otherwise specified, minimum and maximum will be reported to the precision as the data collected, one more decimal place for the mean and median, and two more decimal places for the standard deviation. Percentages will be reported with one decimal point.

7.9.1.1 Missing data

No imputation of values for other missing data will be performed, unless specified,

Adverse Event:

If due to partial dates or times, it is not possible to definitively conclude that an AE is not treatment emergent, then a conservative approach will be taken into account whereby it will be classified as a TEAE, e.g. if the first dose date is "10June" and the AE starts in "June", then that AE will be classified as a TEAE, unless the AE stop date precludes this (i.e. the AE stop date is definitively prior to the first dose date).

Imputation rules for missing or partial AE start date are defined below:

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date; otherwise, impute the AE start day as 1.
- Otherwise, impute the AE start day as 1.

Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date; otherwise, impute the AE start Month as January and the Day as 1.
- Otherwise, impute the AE start MONTH as January and the DAY as 1.

Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date then the AE should be considered as a pretreatment AE. Otherwise, the AE will be considered as TEAE.

[redacted]

8 DOCUMENT HISTORY

Version	Summary of Changes
1.0	Original version
2.0	• Added that PK analyses will be presented by individual or combined cohort by different dose and regimen • Removed PFS, ORR, and DOR analysis for colon rectum cancer • Corrected '1aD' to '1aD1' in calculation of exposure and relative dose intensity • Removed Screened Population from the analysis • Changed window of concomitant medication from 100 (±7) days to 100 days after last dose of any study drug (or until use of subsequent anticancer therapy in long-term follow-up period) • Italicized 'and' / 'or' in the concurrent hepatica abnormality criteria for clarification • Changed immunogenicity on-treatment period • Added baseline nivolumab ADA-negative and baseline cabiralizumab ADA-negative in immunogenicity summary • Changed subgroup summary of trough concentration of cabiralizumab and nivolumab from by baseline ADA status to by postbaseline ADA status • Reference of 'CLT' was changed to 'CL" in SAP text • Reference of 'T HALF' was changed to 't1/2' in SAP text • Added definition for MRT, t1/2, and Vss. • Updated version of Phoenix WinNonLin • Clarified MedDRA version

9 REFERENCES

10 APPENDIX

APPENDIX 1: Major changes to stats analysis in protocol amendments

I. Protocol Version 2 Amendment 1, 14 July 2015

None.

II. Protocol Version 3 Amendment 2, 02 October 2015

1. Changed the definition of "Enrolled Population" as "All patients who sign the ICF and are approved for enrollment by sponsor or designee, and for Phase 1b patients only, are registered in IXRS"
2. Added new analysis population "Evaluable Population: Patients who have a measureable lesion at baseline and have at least 1 post-baseline tumor assessment."
3. Section 7.4.2 Efficacy analysis, the definition of Overall Response Rate (ORR) is updated as "defined as the ratio of the number of patients that achieve an objective response to total number of patients who are evaluable for a response."
4. Changed dosing for the : Cohort 1aM2: FPA008 6 mg/kg every 2 weeks
5. Clarified ORR is defined as the ratio of the number of patients that achieve an objective response to total number of patients who are evaluable for a response

III. Protocol Version 4 Amendment 3, 15 April 2016

1. Updated Sample size for the study as "Approximately 70 patients will be enrolled in Phase 1a (dose escalation); between 3 and 9 patients are expected to be treated at each dose escalation cohort according to the algorithm outlined in Table 4 (refer protocol). There will also be up to 40 patients enrolled into completed cohorts to further explore safety, PK, and PD."

IV. Protocol Version 5 Amendment 4, 07 June 2017

1. Updated investigational product FPA008 to cabiralizumab
2. Updated total number of patients for the study
3. Clarified adverse event and concomitant medications follow up period
4. Updated evaluable population for analyses
5. Revised Pharmacodynamic Biomarkers and Immunogenicity endpoints
6. Specified efficacy assessment is based of RECIST v1.1 by investigator assessment
7. Added efficacy assessment by Independent Radiology Review and exploratory end point in Phase 1b
8. Defined objective response and clarified parameter for safety analyses
9. Removed electronic SAE form and Pregnancy Surveillance form

[redacted]

APPENDIX 2: Baseline Disease Characteristics

Baseline Disease Characteristics	MELANOMA	NSCLC	OVARIAN Cancer	SCCHN	PANCREATIC Cancer	RCC	GBM
DISEASE STAGE AT DIAGNOSIS	×	×	×	×	×	×	×
SITEOFMETASTATIC DISEASE	×	×	×	×	×	×	×
PRIORSURGERY	×	×	×	×	×	×	×
PRIORRADIATION THERAPY	×	×	×	×	×	×	×
PRIOR SYSTEMIC THERAPY	×	×	×	×	×	×	×
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1STATUS	×	×	×	×	×	×	×
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOBACCOUSE	×	×	×	×	×	×	×
M STAGE AT STUDY ENTRY	×						
BRAF STATUS	×						
[redacted]	[redacted]						
BASELINEBRAIN METASTATSIS	×	×					
BASELINE LDH	×					×	
ALK STATUS		×					
EGFR STATUS		×					
KRAS STATUS		×					
CELL TYPE		×				×	
BRCASTATUS			×				
HPV STATUS				×			
[redacted]				×			

APPENDIX 2: Baseline Disease Characteristics (Continued)

Baseline Disease Characteristics	MELANOMA	NSCLC	OVARIAN Cancer	SCCHN	PANCREATIC Cancer	RCC	GBM
SITE OF PRIMARY TUMOR-INVESTIGATOR				×			
[redacted]					×		
MSI-H					×		
TUMOR LOCATION – INVESTIGATOR					×		
BASELINE CA19-9					×		
BASELINE ALBUMIN					×		
PRESENCE OF ASCITES					×		
TIME FROM INITIAL DIAGNOSIS TO 1st DOSE						×	
BASELINE HEMOGLOBIN						×	
Baseline ALKALINE PHOSPHATASE						×	
BASELINE CORRECTED CALCIUM						×	
BASELINE MOTZER SCORE						×	
BASELINE MOTZER SCORE						×	
[redacted]							×