A Phase 1a/1b Study of Cabiralizumab in Combination with Nivolumab in Patients with Selected Advanced Cancers

Protocol Number:	FPA008-003
Investigational Products:	Cabiralizumab (FPA008) and Nivolumab
IND Number:	126401
Development Phase:	Phase 1a/1b
Indications Studied:	Advanced Cancers
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Sponsor:	Five Prime Therapeutics, Inc. [redacted]
Responsible Medical Officer:	Sandeep Inamdar, MBBS [redacted]

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Protocol Synopsis

Title: A Phase 1a/1b Study of Cabiralizumab in Combination with Nivolumab in Patients with Selected Advanced Cancers

Protocol Number: FPA008-003

Clinical Phase: 1a/1b

Sponsor: Five Prime Therapeutics, Inc.

Study Centers: There will be approximately 50 study centers participating in this study.

Objectives:

Phase 1a Objectives

Primary
- 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

Secondary
- 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 IHC analyses of CD8, CD68, and other selected biomarkers)

[redacted]

Phase 1b Objectives

Primary
- To evaluate the clinical benefit of cabiralizumab in combination with nivolumab in patients 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 patients with selected advanced cancers treated at the RD

Phase 1b Objectives (Cont.)

Secondary

- To evaluate the clinical benefit of cabiralizumab in combination with nivolumab in patients 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

[redacted]

Investigational Products

Cabiralizumab Solution for Intravenous Infusion
Nivolumab Solution for Intravenous Infusion

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 patients 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 the combination arms of the study (except for the 3-week dosing regimen cohort -Cohort 1aD), cabiralizumab and nivolumab will be given on Day 1 of each 14-day treatment cycle. For cohort 1aD, cabiralizumab and nivolumab will be administered on Day 1 of each 21-day treatment cycle. 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.

The study includes Phase 1a and Phase 1b. Patients will be enrolled into either Phase 1a or Phase 1b of the study.

Phase 1a consists of 7 dose escalation cohorts, one 3-week dosing regimen cohort. Phase 1a may also include up to 40 additional patients that will be enrolled for further exploration of safety and PK.

Phase 1b consists of 7 tumor-specific expansion cohorts across 6 cancer types.

Study Design (Cont.)

Phase 1a: Dose Escalation

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.

Dose escalation will be based on the number of DLTs experienced during the DLT evaluation interval as determined by the Investigators and Medical Monitor (see Section 3.1.2.1.1 for DLT criteria). The DLT evaluation interval begins on the first day of treatment and continues for 28 days. Patients who receive at least 2 doses of study drug during the 28-day evaluation interval or patients who discontinue study treatment for drug-related AEs before receiving 2 doses of study drug will be considered evaluable for DLT determination. In consultation with Investigators, the Sponsor has the option to investigate dose levels different than those defined in the protocol.

Dose escalation in Phase 1a proceeds as follows:

- If none of the first 3 evaluable patients in a dose cohort experiences a DLT within the DLT evaluation interval, then the next 3 patients will be treated at the next higher dose cohort.
- If 1 of the first 3 evaluable patients in a cohort experiences a DLT within the DLT evaluation interval, then 3 additional patients will be treated in that dose cohort.
  - If no more than 1 of the first 6 evaluable patients experiences a DLT during the DLT evaluation interval, then the next 3 patients will be enrolled at the next higher dose cohort.
  - If 2 of the first 6 evaluable patients in a cohort experience a DLT, that cohort will be expanded to 9 evaluable patients.
- If 2 of the first 3 evaluable patients experience a DLT within the DLT evaluation interval, then 6 additional patients may be treated in that dose cohort, upon approval of Investigators and the Medical Monitor.
- If the incidence of DLT is > 33% in the overall population up to 9 patients, that dose level has exceeded the MTD and dose escalation will be terminated.

Study Design (cont.)

Phase 1a: Dose Escalation

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

The DLT period is defined as the first 28-days (completion of 2 cycles). Upon the first occurrence of a delayed DLT (defined as any DLT that occurs between 4 to 6 weeks after administration of study drug) in any patient enrolled in Phase 1a dose escalation, all ongoing and subsequent DLT periods will be expanded to 42 days for all remaining and subsequent patients enrolled in Phase 1a dose escalation. If no patient experiences a delayed DLT, the DLT period will remain at 28 days for all patients. AST, CK, or LDH laboratory abnormalities without clinical sequelae are not considered a delayed DLT (see Section 3.1.2.1.1).

In the event that no MTD is identified and drug exposure exceeds those deemed necessary based on nonclinical pharmacology data or the clinical PK and PD data (if available), FivePrime and the Investigators may make a decision to discontinue dose escalation.

Study Design (cont.)

Phase 1a: 3-Week Dosing Regimen	An alternative dosing regimen cohort (1aD) with 10 patients has been added to characterize the PK and safety of cabiralizumab in combination with nivolumab when administered at a 3-week dosing schedule. In this cohort, 4 mg/kg cabiralizumab in combination with 3 mg/kg nivolumab will be administered intravenously every three weeks until disease progression, unacceptable toxicity, or other reason for treatment discontinuation. Patients who enter this cohort will follow eligibility criteria for Phase 1a. Patients will not be evaluated for DLT as the dose frequency is less than Cohort 1aC3 which has cleared the DLT window at the time of this amendment.
Phase 1a: Exploration Cohort	Based on emerging clinical and translational data, up to 40 patients will be included in Phase 1aE to further explore safety, PK, and PD at alternative dose levels or dosing schedules which have already successfully cleared their respective DLT periods. In each cohort, cabiralizumab either as monotherapy or in combination with nivolumab will be administered until disease progression, unacceptable toxicity, or other reason for treatment discontinuation. Patients who enter Phase 1aE will follow eligibility criteria for Phase 1a.
Phase 1b: Dose Expansion	Seven cohorts consisting of approximately 30 patients each in specific tumor types will characterize the safety and evaluate the efficacy at the RD of cabiralizumab in combination with nivolumab. In each cohort, 4 mg/kg cabiralizumab in combination with 3 mg/kg nivolumab will be administered intravenously every 2 weeks until disease progression, unacceptable toxicity, or other reason for treatment discontinuation.

Notable Aspects of Study Conduct:

Study History

- Cohort 1aM1 (2 mg/kg cabiralizumab monotherapy) was enrolled first, followed by enrollment of a cohort of 3 new patients in the 1 mg/kg cabiralizumab and nivolumab combination cohort (1aC1).
- Cohort 1aM2 (6 mg/kg cabiralizumab monotherapy) was opened after the DLT period cleared in the 2 mg/kg cabiralizumab monotherapy cohort (1aM1).
- Cohort 1aM3 (4 mg/kg cabiralizumab monotherapy) was opened after DLTs were observed in Cohort 1aM2.
- Cohort 1aM2 (6 mg/kg cabiralizumab monotherapy) was re-opened after the DLT period cleared in the 1aM3 (4 mg/kg cabiralizumab monotherapy) cohort (See Section 1.4 for the rationale for re-opening Cohort 1aM2)

Study Design (cont.)

Phase 1b: Dose Expansion (cont.)

- Cohort 1aC2 (2 mg/kg cabiralizumab and nivolumab combination) was opened after the DLT period cleared in the 1 mg/kg cabiralizumab and nivolumab combination cohort and 2 mg/kg cabiralizumab monotherapy cohorts (1aC1 and 1aM1, respectively).
- Cohort 1aC3 (4 mg/kg cabiralizumab and nivolumab combination) was opened after the DLT period cleared in the 1 mg/kg and 2 mg/kg cabiralizumab and nivolumab combination cohorts (1aC1 and 1aC2 respectively) and in the respective monotherapy cohorts.

Study Plan

- At least 3 patients will be enrolled into each dose escalation cohort.
- Upon completion of the DLT period, approximately 40 additional patients may be enrolled in Phase 1aE to further characterize safety, PK, and PD.
- Alternative dose levels of cabiralizumab may be tested based on safety, PK and biomarker data.
- Patients in the combination cohorts can be treated beyond disease progression in accordance with protocol specific guidelines (see Section 4.3.8).
- Tumor biopsies will be performed in at least 10 patients in each Phase 1b dose expansion cohort (optional for cohort 1b7 GBM) before treatment, at 1 month post-treatment
- Skin biopsies will be performed in all Phase 1a patients before treatment, at 1 month post-treatment.
- Post-disease response and/or progression tumor biopsy and skin biopsy will be optional for all patients.

Dosing and Cohorts

For patients in the monotherapy cohorts, cabiralizumab infusion will be administered as a 30-minute IV infusion on Day 1 of each 14-day treatment cycle. Patients in combination therapy cohorts will receive nivolumab infusion first at a dose of 3 mg/kg as a 30-minute IV infusion, with a 30 to 60-minute rest, followed by 30-minute IV infusion of cabiralizumab, on Day 1 of each treatment 14-day cycle. Patients in 3-week dosing regimen cohort (1aD) will receive the nivolumab and cabiralizumab infusion on Day 1 of each 21-day treatment cycle.

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 patients for the duration of this study.

Dosing and Cohorts (cont.)

Phase 1aM: Monotherapy Dose Escalation Cohorts

Cabiralizumab monotherapy in patients with advanced solid tumors

- Cohort 1aM1: cabiralizumab 2 mg/kg every 2 weeks
- Cohort 1aM2: cabiralizumab 6 mg/kg every 2 weeks
- Cohort 1aM3: cabiralizumab 4 mg/kg every 2 weeks

Phase 1aC: Combination Dose Escalation Cohorts

Cabiralizumab and nivolumab combination therapy in patients with advanced solid tumors

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

Alternative dose levels of cabiralizumab may be tested based on safety, PK and biomarker data. See Section 1.4 for cohort design and rationale.

Phase 1aD: Combination 3-week Dosing Regimen Cohort

Cabiralizumab and nivolumab combination therapy in patients with advanced solid tumors

Cohort 1aD1: cabiralizumab 4 mg/kg + nivolumab 3 mg/kg every 3 weeks

Phase 1aE: Monotherapy or Combination Exploration Cohorts

Cabiralizumab monotherapy or combination therapy in patients with selected advanced cancers

Up to 40 patients may be enrolled to further characterize safety, PK, and PD at alternative dose levels or dosing schedules (not to exceed the MTD)

Phase 1b: Combination Dose Expansion Cohorts

Cabiralizumab and nivolumab combination therapy in patients with selected advanced cancers

- 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)

Number of Patients

The total number of patients planned for this study is estimated to be 295 in North America.

Study Population

Inclusion Criteria for All Cohorts

For entry into the study, *all* of the following criteria must be met.

1. Patients must have at least one measurable lesion at baseline by computed tomography (CT) or magnetic resonance imaging (MRI) as per RECIST v1.1 criteria.
    a. Tumor sites situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.
    b. Sites for biopsy must be distinct from target lesions used for efficacy assessment.
2. Patients must have had progressive disease on, after, or refused, appropriate approved therapy for their tumor type unless otherwise specified in the cohort specific criteria; for example, all non small-cell lung cancer (NSCLC) patients should have progressed on or after (or deemed to be unsuitable for) platinum doublet chemotherapy, and appropriate approved therapy for patients with EGFR or ALK mutations.
3. All patients in Phase 1a and patients who consent to be biopsied in Phase 1b must have at least 1 tumor site that can be biopsied and be willing to have pre-treatment and on-treatment tumor and skin biopsies (optional for patients in the GBM cohort). Biopsies will be performed according to the treating institution's own guidelines from a minimum of 10 patients in each Phase 1b cohort. If biopsy has been performed and adequate sample collected as part of the patient's standard of care within 28 days prior Cycle 1 Day 1, it does not need to be repeated if the sample is available.
4. Understand and sign an IRB/IEC-approved ICF prior to any study-specific evaluation
5. Age ≥18 years
6. ECOG performance status of 0 or 1
7. Willing and able to comply with all study procedures
8. Prior focal radiotherapy must be completed at least 2 weeks before first dose of study drug administration. No radiopharmaceuticals (strontium, samarium) within 8 weeks before first dose of study drug administration.
9. Prior surgery that requires general anesthesia must be completed at least 1 week before first dose of study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before first dose of study drug administration and patients should have recovered.

Study Population (cont.)

10. Screening laboratory values must meet the following criteria:

    Hematologic

    a. Neutrophils ≥1500 cells/ µL
    b. Platelets ≥100 x 10^3/ µL
    c. Hemoglobin ≥9.0 g/dL

    Serum creatinine ≤1.5x ULN or creatinine clearance of ≥40 mL/minute (using Cockcroft/Gault Formula)

    $$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})}$$

    $$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})}$$

    d. PT/INR ≤ 1.5x ULN and PTT (aPTT) ≤ 1.5x ULN

    Hepatic

    a. AST or ALT ≤3x ULN
    b. Bilirubin ≤1.5x ULN (except patients with Gilbert's syndrome, who must have total bilirubin <3 mg/dL)
    c. Albumin >3.0 g/dL (pancreatic cancer patients only)

11. Women of childbearing potential (WOCBP) must have a negative serum β-human chorionic gonadotropin (β-hCG) at screening and agree to use a reliable form of contraception (e.g., oral contraceptives, intrauterine device, or double barrier method of condom and spermicide) for at least 28 days prior to the dosing of any study drug and for at least 23 weeks after the last dose of any study drug.
12. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus 31 weeks post-treatment completion.

For additional cohort-specific inclusion criteria, refer to Section 3.2.4.

Exclusion Criteria for All Cohorts

Patients who meet ANY of the following criteria will be excluded from study entry.

1. Current or history of clinically significant muscle disorders (e.g., myositis), recent unresolved muscle injury, or any condition known to elevate serum CK levels

Study Population (cont.)

2. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses >10 mg/day prednisone or equivalent daily) must be discontinued at least 2 weeks before study drug administration except in the case of tumor-related AE treatment. Patients with a condition requiring chronic systemic treatment with either corticosteroids (inhaled or topical steroids and adrenal replacement steroid doses >10 mg/day prednisone equivalent) or other immunosuppressive medications within 2 weeks of treatment are permitted in the absence of active autoimmune disease (except for patients with glioma).
3. Decreased cardiac function with NYHA > Class 2
4. Uncontrolled or significant heart disorder such as unstable angina
5. Significant abnormalities on ECG at screening. QTcF >450 msec for males or >470 msec for females at screening
6. History of anti-drug antibodies, severe allergic, anaphylactic, or other infusion-related reaction to a previous biologic agent
7. Known history of sensitivity to infusions containing Tween 20 (polysorbate 20) and Tween 80 (polysorbate 80)
8. Consumption of non-pasteurized milk while on study drug and for 30 days after discontinuing study drug
9. Non-oncology vaccine therapies for prevention of infectious diseases (e.g., HPV vaccine) within 4 weeks of study drug administration. The inactivated seasonal influenza vaccine can be given to patients before treatment and while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (i.e., pneumovax, varicella, etc.) may be permitted, but must be discussed with the Sponsor's Medical Monitor and may require a study drug washout period prior to and after administration of vaccine.
10. Current unresolved infection or history of chronic, active, clinically significant infection (viral, bacterial, fungal, or other) which, in the opinion of the Investigator, would preclude the patient from exposure to a biologic agent or pose a risk to patient safety
11. Positive test for latent tuberculosis (TB) at screening (e.g. T-SPOT or Quantiferon test) or evidence of active TB
12. Patients with abnormal serum chemistry values, which in the opinion of the Investigator is considered to be clinically significant, will be excluded from the study. This will include patients who show clinical signs and symptoms related to their abnormal serum chemistry values as well as patients whose serum chemistry values are asymptomatic but clinically significant (e.g. hypokalemia or hyponatremia).

Study Population (cont.)

13. Lack of peripheral venous or central venous access or any condition that would interfere with drug administration or collection of study samples
14. Any uncontrolled medical condition or psychiatric disorder which, in the opinion of the Investigator, would pose a risk to patient safety or interfere with study participation or interpretation of individual patient results
15. Concomitant use of statins while on study. However, a patient using statins for over 3 months prior to study drug administration and in stable status without CK rise may be permitted to enroll.
16. Pregnant or breastfeeding
17. Active, known, or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism requiring only hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
18. Treatment with any anti-cancer therapy or participation in another investigational drug or biologics trial within 28 days or ≤ 5 half-lives (whichever is shorter) prior to first dose of study drug administration or while on this study
19. Known history of testing positive for human immunodeficiency virus (HIV) 1 or 2 or known acquired immunodeficiency syndrome (AIDS)
20. Positive test for hepatitis B virus surface antigen (HBsAg) or detectable hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection
21. Symptomatic interstitial lung disease or inflammatory pneumonitis
22. Untreated or active central nervous system (CNS) or leptomeningeal metastases. Patients are eligible if metastases have been treated and patients are neurologically returned to baseline or neurologically stable (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to first dose of study drug administration. In addition, patients must be either off corticosteroids, or on a stable dose or decreasing dose of ≤ 10 mg daily prednisone or prednisone equivalent (except for patients with glioma).
23. Evidence of coagulopathy or bleeding diathesis
24. Any uncontrolled inflammatory GI disease including Crohn's Disease and ulcerative colitis
25. Prior exposure to any CSF1R pathway inhibitors
26. Transfusion completed within 72 hours prior to first dose of study drug administration

For additional cohort-specific exclusion criteria, refer to Section 3.2.4.

Dose-Modification Criteria

Dose reductions for cabiralizumab and nivolumab are not permitted.

[redacted]

Withdrawal Criteria

Patients ***must*** discontinue study drugs for any of the following reasons:

- Withdrawal of informed consent (patient's decision to withdraw for any reason)
- Any clinically significant AE, abnormal laboratory test results, or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the patient
- Patients who are required to have prohibited concomitant medications
- Pregnancy
- Termination of the study by the Sponsor
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of a psychiatric or physical (e.g., infectious disease) illness
- Documented disease progression or clinical deterioration while receiving active study therapy
  - Patients who receive cabiralizumab in combination with nivolumab may continue beyond disease progression at the discretion of the Investigator and in consultation with the Sponsor
- Non-compliance by the patient

Study Endpoints

Phase 1a Endpoints

Primary

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

Secondary

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})

Immunogenicity: Defined as an immune response to either cabiralizumab or nivolumab, will be assessed by measurement of total anti-FPA008 antibodies and total anti-nivolumab antibodies from all patients. Immunogenicity testing will consist of screening, confirmation, and titration for both cabiralizumab and nivolumab.

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

[redacted]

Phase 1b Endpoints

Primary

Efficacy

- ORR will be defined as the total number of patients with confirmed responses of either CR or divided by the total number of patients who are evaluable for a response per RECIST 1.1 by investigator assessment

Safety

- The incidence of AEs, 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

Secondary

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})

Immunogenicity: Defined as an immune response to either cabiralizumab or nivolumab, will be assessed by measurement of total anti-FPA008 antibodies and total anti-nivolumab antibodies from all patients. Immunogenicity testing will consist of screening, confirmation, and titration for both cabiralizumab and nivolumab.

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.
  - One-year OS
  - Median OS

Phase 1b Endpoints (cont.)

Secondary (cont.)

- DOR will be defined as the time from response (CR or PR) until the onset of PD.
- PFS will be defined for each patient as the time from the first dose to the first observation of disease progression or death due to any cause.
- ORR by Independent Radiology Review

[redacted]

Schedule of Assessments

See the following appendices for the Schedule of Assessments.

Appendix A: Schedule of Assessments – Phase 1a Cabiralizumab Monotherapy and Combination

Appendix B: Schedule of Assessments – Phase 1b Cabiralizumab + Nivolumab

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List of Abbreviations and Definitions

ACTH	Adrenocorticotropic hormone
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AT	Aminotransferase
AUC	Area under the concentration-time curve
β-HCG	Beta-human chorionic gonadotropin
BID	Bis in die; twice daily
BMI	Body mass index
BMS	Bristol-Myers Squibb
BOR	Best overall response
BP	Blood pressure
BTLA	B- and T-lymphocyte attenuator
BUN	Blood urea nitrogen
ºC	Degrees Celsius
CBC	Complete blood count
CD	Cluster of differentiation
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	Confidence interval
CK	Creatine kinase
CL	Clearance
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response

CRC	Colorectal cancer
CRF	Case report form, may be paper or electronic
CRO	Contract research organization
CRP	C-reactive protein
CSF1	Colony stimulating factor 1
CSF1R	Colony stimulating factor 1 receptor
CSR	Clinical study report
CT	Computed tomography
CTA	Clinical trials agreement
CTCAE v 4.03	Common Terminology Criteria for Adverse Events, version 4.03
CTLA-4	Cytotoxic T lymphocyte antigen 4
CTX	C-terminal collagen crosslink peptides
CV	Coefficient of variation
DC	Dendritic cell
DILI	Drug-induced liver injury
dL	Deciliter
DLT	Dose-limiting toxicity
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
DOR	Duration of response
dt-TGCT	Diffuse-type tenosynovial giant-cell tumor
EC_{50}	Half-maximal effective concentration
ECG	Electrocardiogram
ECLA	Electrochemiluminescence assay
ECM	Extracellular matrix
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylene diamine tetraacetic acid
e.g.	exempli gratia (for example)
ELISA	Enzyme-linked immunosorbent assay
ePPND	Enhanced pre- and post-natal development

ESR	Erythrocyte sedimentation rate
ºF	Degrees Fahrenheit
FACS	Fluorescent-activated cell sorter
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FISH	Fluorescent *in situ* hybridization
FivePrime	Five Prime Therapeutics, Inc.
$FOXP3^{+}$	Forkhead box p3
FSH	Follicle stimulating hormone
g	Gram
GBM	Malignant glioma
GCP	Good Clinical Practice
GI	Gastrointestinal
h	Hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	Heart rate
HRT	Hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	Half-maximal inhibitory concentration
ICD	Implantable cardioverter defibrillator
ICF	Informed consent form
ICH	International Conference on Harmonization
ICOS	Inducible co-stimulator
i.e.	id est (that is)
IEC	Independent ethics committee
IFN	Interferon
IgG	Immunoglobulin G
IHC	Immunohistochemistry

IL	Interleukin
IM	Intramuscular
IMP	Investigational medicinal product
IND	Investigational new drug
INR	International normalized ratio
I-O	Immuno-oncology
irAE	Immune-related adverse event
IRB	Institutional review board
ITIM	Immunoreceptor tyrosine inhibitory motif
ITSM	Immunoreceptor tyrosine-based switch motif
IU	International unit
IV	Intravenous
IXRS	Integrated voice and web response system
kg	Kilogram
KM	Kaplan-Meier
LAG-3	Lymphocyte-activate gene 3
LDH	Lactate dehydrogenase
LFT	Liver function test
LOQ	Limit of quantitation
MABEL	Minimum anticipated biological effect level
mCRPC	Metastatic castration-resistant prostate cancer
MDSC	Myeloid-derived suppressor cell
mg	Milligram
min	Minute
µL	Microliter
mL	Milliliter
MLR	Mixed lymphocyte reaction
µM	Micrometer
mM	Millimolar
mm^3	Cubic millimeters
mmHg	Millimeters of mercury
MRI	Magnetic resonance imaging

MSD	Meso Scale Discovery
MTD	Maximum tolerated dose
N	Number of patients or observations
NCI	National Cancer Institute
ng	Nanogram
NOAEL	No-observable-adverse-effect level
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
NSAID	Non-steroidal, anti-inflammatory drug
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamics
PD-1	Programmed cell death 1
PDAC	Pancreatic ductal adenocarcinoma
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetics
PO	Per os; by mouth
PPK	Population pharmacokinetics
PR	Partial response
PT	Prothrombin time
PTT (aPTT)	Partial thromboplastin time
PVC	Polyvinyl chloride
q2w	Every two weeks
PVNS	Pigmented villonodular synovitis
qPCR	Quantitative real-time polymerase chain reaction
qRT-PCR	Quantitative reverse-transcription polymerase chain reaction
QTcF	Fridericia's correction formula for QT interval
RA	Rheumatoid arthritis
RBC	Red blood cell

RCC	Renal cell carcinoma
RD	Recommended Dose
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SCCHN	Squamous-cell carcinoma of the head and neck
SD	Stable disease
SkTnI	Skeletal troponin
SOP	Standard operating procedure
Src	Sarcoma homology protein
T_3	Triiodothyronine
T_4	Thyroxine
TAM	Tumor-associated macrophage
TB	Tuberculosis
TCR	T-cell receptor
TIL	Tumor-infiltrating lymphocyte
T_{max}	Time of maximum observed concentration
TNF	Tumor necrosis factor
Trap5b	Tartrate resistant acid phosphatases 5b
ULN	Upper limit of normal
USP	United States Pharmacopeia
V_{ss}	Volume of distribution at steady state
V_z	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

2. Objectives

2.1 Phase 1a Objectives

2.1.1 Primary

- 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

2.1.2 Secondary

- 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 IHC analyses of CD8, CD68, and other selected biomarkers)

[redacted]

2.2 Phase 1b Objectives

2.2.1 Primary

- To evaluate the clinical benefit of cabiralizumab in combination with nivolumab in patients 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 patients with selected advanced cancers treated at the RD

2.2.2 Secondary

- To evaluate the clinical benefit of cabiralizumab in combination with nivolumab in patients 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

[redacted]

3. Investigational Plan

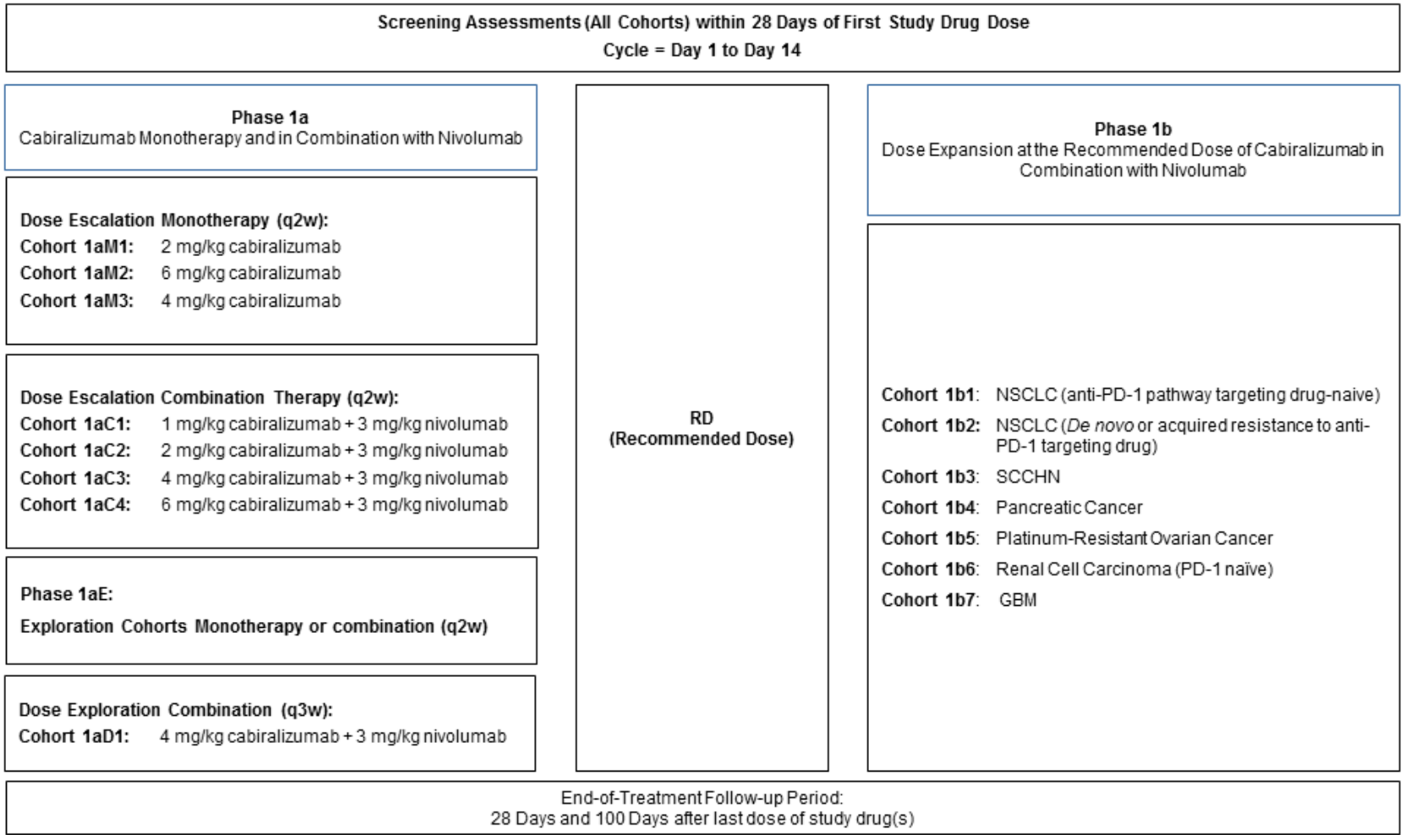
3.1 Study Design and Duration

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 patients 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 patients 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 in combination with nivolumab every three weeks instead of every two weeks. The Phase 1a exploration 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. Patients will be enrolled into either Phase 1a or Phase 1b of the study. The study design is shown in Figure 2.

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

Figure 2: FPA008-003 Study Design



3.1.1 Screening Period

All screening evaluations must be completed and reviewed by the Investigator following the procedure noted in the Study Reference Manual for the enrollment process to confirm that patients meet all eligibility criteria before the first infusion of study drug. Written informed consent for participation in the study must be obtained before performing any study specific screening tests or procedures. Screening assessments will be performed within 28 days prior to the first dose of study drug unless otherwise specified.

Study procedure-related AEs that occur after signing of the ICF and before administration of the first study drug dose will be collected during this period.

3.1.2 Treatment Period

3.1.2.1 Phase 1a Monotherapy Cohorts and Combination Dose Escalation Cohorts

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

- Cohort 1aM1: 2 mg/kg cabiralizumab, q2w
- Cohort 1aM2: 6 mg/kg cabiralizumab, q2w
- Cohort 1aM3: 4 mg/kg cabiralizumab, q2w
  - (Dose was de-escalated to 4 mg/kg after DLT observed in 1aM2 (See Section 1.9)
- Cohort 1aC1: 1 mg/kg cabiralizumab + 3 mg/kg nivolumab, q2w
- Cohort 1aC2: 2 mg/kg cabiralizumab + 3 mg/kg nivolumab, q2w
- Cohort 1aC3: 4 mg/kg cabiralizumab + 3 mg/kg nivolumab, q2w
- Cohort 1aC4: 6 mg/kg cabiralizumab + 3 mg/kg nivolumab, q2w

The 2 mg/kg cabiralizumab monotherapy cohort (1aM1) was enrolled first, followed by enrollment in the 1 mg/kg cabiralizumab and nivolumab combination cohort (1aC1). Both cohorts cleared without any DLTs. The 2 mg/kg cabiralizumab and nivolumab combination cohort (1aC2) started after the DLT period cleared in the 1 mg/kg cabiralizumab and nivolumab combination cohort and 2 mg/kg cabiralizumab monotherapy cohort.

The 6 mg/kg cabiralizumab monotherapy cohort (1aM2) opened after the DLT period cleared in the 2 mg/kg cabiralizumab monotherapy cohort (1aM1). There were two DLTs in patients treated in the 1aM2 cohort, both due to laboratory abnormalities. Subsequently, the dose was de-escalated and Cohort 1aM3 (4 mg/kg cabiralizumab monotherapy) was opened. There were two DLTs in the 1aM3 monotherapy cohort and the protocol was subsequently amended to allow higher cutoffs for these laboratory values (see Section 1.8.1). Additional patients were added to the 1aM3 cohort to evaluate the DLT period under the new criteria.

The 4 mg/kg cabiralizumab and nivolumab combination cohort (1aC3) was opened after the DLT period cleared in the 1 mg/kg and 2 mg/kg cabiralizumab and nivolumab combination cohorts and in the respective cabiralizumab monotherapy cohorts.

The 1aM2 cohort was also re-opened with the new DLT criteria. Upon successful completion of the DLT period the 6 mg/kg cabiralizumab and nivolumab combination cohort (1aC4) may be opened.

Depending on the outcome of the cohorts described above, alternative dose cohorts may be opened. All dose escalation decisions will be based on assessment of DLTs, overall safety, and tolerability. Dose escalation decisions will be agreed upon between the Investigators and Sponsor. Prior to initiating each new dose level or expanding an existing dose level, a safety teleconference will be held wherein the Investigators and Sponsor will review patient data, including but not limited to demographics, dosing, concomitant medications, hematology, serum chemistry, and AEs; and confer and document agreement that dose escalation or expanding an existing dose level is considered appropriate. If the Investigators and Sponsor collectively agree, following review of safety, PK, and PD data (if available), that a different dose escalation scheme (e.g., an alternative dose of cabiralizumab monotherapy or in combination with nivolumab) should be used than the one outlined, this will be permitted. Review of safety, PK, and PD profiles may inform decisions to add cohorts with alternative dose levels or dose regimens (e.g., less frequent dosing) in order to reach an optimal target exposure.

Dose escalation will be based on the number of DLTs experienced during the DLT evaluation interval as determined by the Medical Monitor and Investigators (see Section 3.1.2.1.1 for DLT criteria). The DLT evaluation interval begins on the first day of treatment and continues for 28 days. Patients that receive at least 2 doses of study drug during the 28-day evaluation interval or patients who discontinue study treatment for drug-related AEs before receiving 2 doses of study drug will be considered evaluable for DLT determination. In consultation with Investigators, the Sponsor has the option to investigate alternative dose levels to those defined in the protocol.

Dose escalation in Phase 1a will proceed as follows:

- If none of the first 3 evaluable patients in a dose cohort experiences a DLT within the DLT evaluation interval, then the next 3 patients will be treated at the next higher dose cohort.
- If 1 of the first 3 evaluable patients in a cohort experiences a DLT within the DLT evaluation interval, then 3 additional patients will be treated in that dose cohort.
  - If no more than 1 of the first 6 evaluable patients experiences a DLT during the DLT evaluation interval, then the next 3 patients will be enrolled at the next higher dose cohort.
  - If 2 of the first 6 evaluable patients in a cohort experience a DLT, that cohort will be expanded to 9 evaluable patients.

- If 2 of the first 3 evaluable patients experience a DLT within the DLT evaluation interval, then 6 additional patients may be treated in that dose cohort, upon approval of Investigators and the Medical Monitor.
- If the incidence of DLT will be > 33% in the overall population up to 9 patients, that dose level has exceeded the MTD and dose escalation will be terminated.

[redacted]

Dose escalation will continue in the monotherapy and combination treatment arms until either the MTD or maximum planned dose of cabiralizumab is reached, with a minimum of 3 patients enrolled in each cohort. Dose exploration in Phase 1a may continue beyond identification of a RD and initiation of Phase 1b in order to identify any other dose levels which may be safe and efficacious for Phase 1b.

The MTD is defined as the highest dose associated with DLTs in less than or equal to 33% of patients receiving cabiralizumab or cabiralizumab and nivolumab combination therapy, administered during the DLT period. This will normally be the dose recommended for further study; however, based on review of safety, PK, and PD (if available) data, the RD could be lower than the MTD. If the MTD is not reached, and the highest evaluated cabiralizumab dose alone or in combination with nivolumab is well tolerated, the data will be reviewed to assess whether further dose escalations cabiralizumab are warranted.

If the MTD is not reached during the Phase 1a combination dose escalation, or subsequent cycles of treatment in cleared Phase 1a combination cohorts provide additional insight on the safety profile, an RD may be selected based on overall tolerability, safety, PK, and PD (if available).

Sponsor has the option to expand any cohort previously established to be safe in order to obtain additional data or to investigate alternative dose levels to those defined in the protocol. Upon completion of the DLT period, up to 40 additional patients may be enrolled in Phase 1aE to fully characterize safety, PK, and PD.

If a patient in Phase 1a monotherapy does not receive 2 doses of study drug and does not complete safety assessments and if a patient in one of the Phase 1a combination cohorts does not receive 2 doses of each study drug and does not complete the safety assessment (e.g., safety lab and/or AE reporting) in the DLT period for reasons other than drug-related AEs (e.g., disease progression or withdrawal of consent), then an additional patient will be enrolled into the cohort so that the cohort has at least 3 patients evaluable for the DLT period. All such discussions and decisions will be documented as part of the dose escalation decision-making process.

Upon completion of the DLT period, Phase 1a patients may participate in an Extended Treatment Period following the guidelines in Section 3.1.2.2.

3.1.2.1.1 Dose Limiting Toxicity

A DLT is defined as a study drug-related ≥ Grade 3 AE (using National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v 4.03) occuring during the first 28-days, excluding: Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor), Grade 3 rash, Grade 3 immune-related adverse event (irAE) that resolved to a Grade 1 or less within 14 days, or a transient (resolving within 6 hours of onset) Grade 3 infusion-related AE. Any recurrence of Grade 3 rash, Grade 3 immune-related AE, or Grade 3 infusion-related AE will be considered a DLT. An irAE is defined as a clinically significant AE that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism.

In the absence of clinical symptoms and other accompanying changes in bilirubin or ALT (as noted in appendices F, G, and H), serum elevations of AST/ALT > 12 xULN and ⩽ 20 xULN that last for < 7 days will not be considered a DLT and serum elevations of CK and/or LDH > 15 xULN and ⩽ 20 xULN that last for < 7 days will not be considered a DLT.

Upon the first occurrence of a delayed DLT in any patient enrolled in Phase 1a (defined as any DLT that occurs between 4 to 6 weeks after administration of study drug), all ongoing and subsequent DLT periods will be expanded to 42 days for all remaining and subsequent patients enrolled in Phase 1a dose escalation. If no patient experiences a delayed DLT, the DLT window will remain at 28 days for all patients.

3.1.2.2 Phase 1a Extended Treatment Period

Upon completion of the DLT period, patients from the Phase 1a monotherapy and combination cohorts may participate in an Extended Treatment Period.

Patients from the Phase 1a monotherapy cohorts are allowed to continue to receive cabiralizumab monotherapy at the same cabiralizumab dose level and patients from the Phase 1a combination cohorts are allowed to continue to receive cabiralizumab in combination with nivolumab at the same dose levels until disease progression, unacceptable toxicity, or other reason for treatment discontinuation.

3.1.2.3 Phase 1a 3-week Dosing Regimen Cohort

In protocol amendment 4, a 3-week dose regimen cohort (1aD) is added to characterize the PK profile and safety of cabiralizumab in combination with nivolumab when administered as an alternative dosing schedule. This Phase 1a 3-week Dosing Regimen consists of one cohort evaluating 4 mg/kg cabiralizumab in combination with 3 mg/kg nivolumab, administered intravenously every three weeks until disease progression, unacceptable toxicity, or other reason for treatment discontinuation.

3.1.2.4 Phase 1a Exploration Cohorts

The Phase 1a exploration consists of up to 40 additional patients to further evaluate the safety, PK, and PD of cabiralizumab as monotherapy and in combination with nivolumab.

3.1.2.5 Phase 1b Expansion Cohorts

To further characterize safety and efficacy of cabiralizumab in combination with nivolumab, 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 (if available) data.

During enrollment of any expansion cohort, if the observed number of responses makes it unlikely to achieve a target response rate for that indication, then further recruitment to that cohort may be suspended or terminated.

After initiation of Phase 1b, the dose may be changed based on data from continued dose exploration in Phase 1a. There will be no intra-patient dose modification and any alteration in dose for Phase 1b will only apply to newly enrolled patients in Phase 1b.

3.1.3 End-of-Treatment Follow-up Period

All patients 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 patient is discontinued from the study drug at a planned visit or mid-cycle. AEs will be assessed until resolution, return to baseline, or are stabilized per treating Investigator's assessment. Adverse

event reporting will continue until 100 (±7) days after the last dose of study drug or until initiation of subsequent anti-cancer therapy.

3.1.4 Long-Term Follow-up

Patients should continue onto Long-Term Follow-up after completing the End-of-Treatment Follow-up Period.

Patients will be followed every 12 weeks for survival, or more frequently as needed. Patients who discontinue treatment while showing clinical benefit (complete response [CR], partial response [PR], or stable disease [SD]) should have tumor assessments during these visits for duration of response.

Long-term Follow-up for survival may be conducted by telephone, rather than by an in-person visit, once tumor progression is determined or use of subsequent anti-cancer therapy has been initiated. During the Long-Term Follow-up Period, if the patient undergoes local therapy (e.g., resection, radiation) or new systemic therapy is initiated, this should be documented.

3.1.5 Study Duration

Patients who receive study drug(s) may continue as long as they experience clinical benefit in the opinion of the Investigator or until unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the Investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status, or withdrawal of consent.

3.1.6 Stopping Rules

3.1.6.1 Stopping Rules for All Cohorts

Management of drug-related toxicities will follow the adverse event management tables (Appendix F and Appendix G). Management of drug-related laboratory abnormalities will follow the management tables in Appendix H.

The Sponsor will discuss such cases with the study Investigators as appropriate to determine further enrollment. IRBs may be notified by the Investigators of all cases and decisions regarding continued enrollment, according to applicable regulatory requirements or institution procedures.

3.1.6.2 Stopping Rules for Clinical Deterioration

Accumulating clinical evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses may follow delayed kinetics of weeks or months, and can be preceded by initial apparent progression of disease with the appearance of new lesions or some enlarging of lesions while certain index lesions are regressing (“mixed response”). Therefore, it is reasonable to allow patients who experience apparent progression to continue to receive treatment until progression is confirmed at the next imaging assessment. These

considerations should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression and is unlikely to reverse with continued study treatment and therefore indicates that the patient is not benefiting from study treatment and cannot be managed by the addition of supportive care. The decision to continue treatment should be discussed with the Sponsor's Medical Monitor or designee. Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include but are not limited to the following:

- Eastern Cooperative Oncology Group (ECOG) score increase of at least 2 points from baseline (e.g. from 0 to 2).
- Habitual changes such as changes in activities and symptoms including reduction in appetite and/or sleep, altered awareness, and increased pain-related symptoms due to cancer.
- Progression of disease confirmed by the treating Investigator.
- Any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the patient even in the absence of any such documented clinical events.

3.2 Study Population

3.2.1 Planned Number of Patients and Study Centers

The total number of patients planned for this study is estimated to be 295 in North America. By the end of the study, approximately 85 patients 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 patients in Part 1b (approximately 30 patients for each of the 7 Phase 1b cohorts) will be enrolled. There will be approximately 50 study centers participating in this study.

3.2.2 Inclusion Criteria for All Cohorts

For entry into the study, ***all*** of the following criteria must be met.

1. Patients must have at least one measurable lesion at baseline by computed tomography (CT) or magnetic resonance imaging (MRI) as per RECIST v1.1 criteria.
    a. Tumor sites situated in a previously irradiated area, or in an area subjected to other loco-reginal therapy, are not considered measurable unless there has been demonstrated progression in the lesion.b. Sites for biopsy must b*e distinct from target lesions used for efficacy assessment.*
2. Patients must have had progressive disease on, or refused, appropriate approved therapy for their tumor type unless otherwise specified in the cohort specific criteria; for example, all

NSCLC patients should have progressed on platinum doublet chemotherapy, and appropriate approved therapy for patients with EGFR or ALK mutations.

3. All patients in Phase 1a and patients who consent to be biopsied in Phase 1b must have at least 1 tumor site that can be biopsied and be willing to have pre-treatment and on-treatment tumor and skin biopsies (optional for patients in the GBM cohort). Biopsies will be performed according to the treating institution's own guidelines from a minimum of 10 patients in each Phase 1b cohort. If biopsy has been performed and adequate sample collected as part of the patient's standard of care within 28 days prior Cycle 1 Day 1, it does not need to be repeated if the sample is available.

4. Understand and sign an IRB/IEC-approved ICF prior to any study-specific evaluation

5. Age ≥18 years

6. ECOG performance status of 0 or 1

7. Willing and able to comply with all study procedures

8. Prior focal radiotherapy must be completed at least 2 weeks before first dose of study drug administration. No radiopharmaceuticals (strontium, samarium) within 8 weeks before first dose of study drug administration.

9. Prior surgery that requires general anesthesia must be completed at least 1 week before first dose of study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before first dose of study drug administration and patients should have recovered.

10. Screening laboratory values must meet the following criteria:

Hematologic

a. Neutrophils ≥1500 cells/ μL

b. Platelets ≥100 x 10^3/ μL

c. Hemoglobin ≥9.0 g/dL

Serum creatinine ≤1.5x ULN or creatinine clearance of ≥40 mL/minute (using Cockcroft/Gault Formula)

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})}$$

d. PT/INR ≤ 1.5 x ULN and PTT (aPTT) ≤ 1.5 x ULN

Hepatic

a. AST or ALT ≤3 x ULN

b. Bilirubin ≤1.5 x ULN (except patients with Gilbert's syndrome, who must have total bilirubin <3 mg/dL)

c. Albumin >3.0 g/dL (pancreatic cancer patients only)

11. Women of childbearing potential (WOCBP) must have a negative serum β-human chorionic gonadotropin (β-hCG) at screening and agree to use a reliable form of contraception (e.g., oral contraceptives, intrauterine device, or double barrier method of condom and spermicide) for at least 28 days prior to the dosing of any study drug and for at least 23 weeks after the last dose of any study drug.

12. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus 31 weeks post-treatment completion.

3.2.3 Exclusion Criteria for All Cohorts

Patients who meet ANY of the following criteria will be excluded from study entry.

1. Current or history of clinically significant muscle disorders (e.g., myositis), recent unresolved muscle injury, or any condition known to elevate serum CK levels

2. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses >10 mg/day prednisone or equivalent daily) must be discontinued at least 2 weeks before study drug administration except in the case of tumor-related AE treatment. Patients with a condition requiring chronic systemic treatment with either corticosteroids (inhaled or topical steroids and adrenal replacement steroid doses >10 mg/day prednisone equivalent) or other immunosuppressive medications within 2 weeks of treatment are permitted in the absence of active autoimmune disease (except for patients with glioma).

3. Decreased cardiac function with NYHA > Class 2

4. Uncontrolled or significant heart disorder such as unstable angina

5. Significant abnormalities on ECG at screening. QTcF >450 msec for males or >470 msec for females at screening

6. History of anti-drug antibodies, severe allergic, anaphylactic, or other infusion-related reaction to a previous biologic agent

7. Known history of sensitivity to infusions containing Tween 20 (polysorbate 20) and Tween 80 (polysorbate 80)

8. Consumption of non-pasteurized milk while on study drug and for 30 days after discontinuing study drug

9. Non-oncology vaccine therapies for prevention of infectious diseases (e.g., HPV vaccine) within 4 weeks of study drug administration. The inactivated seasonal influenza vaccine can be given to patients before treatment and while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (i.e., pneumovax, varicella, etc.) may be permitted, but must be discussed with the Sponsor's Medical Monitor and may require a study drug washout period prior to and after administration of vaccine.

10. Current unresolved infection or history of chronic, active, clinically significant infection (viral, bacterial, fungal, or other) which, in the opinion of the Investigator, would preclude the patient from exposure to a biologic agent or pose a risk to patient safety

11. Positive test for latent tuberculosis (TB) at screening (e.g. T-SPOT or Quantiferon test) or evidence of active TB

12. Patients with abnormal serum chemistry values, which in the opinion of the Investigator is considered to be clinically significant, will be excluded from the study. This will include patients who show clinical signs and symptoms related to their abnormal serum chemistry values as well as patients whose serum chemistry values are asymptomatic but clinically significant (e.g. hypokalemia or hyponatremia).

13. Lack of peripheral venous or central venous access or any condition that would interfere with drug administration or collection of study samples

14. Any uncontrolled medical condition or psychiatric disorder which, in the opinion of the Investigator, would pose a risk to patient safety or interfere with study participation or interpretation of individual patient results

15. Concomitant use of statins while on study. However, a patient using statins for over 3 months prior to study drug administration and in stable status without CK rise may be permitted to enroll

16. Pregnant or breastfeeding

17. Active, known, or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism requiring only hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

18. Treatment with any anti-cancer therapy or participation in another investigational drug or biologics trial within 28 days or $\leq$ 5 half-lives (whichever is shorter) prior to first dose of study drug administration or while on this study

19. Known history of testing positive for human immunodeficiency virus (HIV) 1 or 2 or known acquired immunodeficiency syndrome (AIDS)

20. Positive test for hepatitis B virus surface antigen (HBsAg) or detectable hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection

21. Symptomatic interstitial lung disease or inflammatory pneumonitis

22. Untreated or active central nervous system (CNS) or leptomeningeal metastases. Patients are eligible if metastases have been treated and patients are neurologically returned to baseline or neurologically stable (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to first dose of study drug administration. In addition, patients must be either off corticosteroids, or on a stable dose or decreasing dose of ≤10 mg daily prednisone or prednisone equivalent (except for patients with glioma).

23. Evidence of coagulopathy or bleeding diathesis

24. Any uncontrolled inflammatory GI disease including Crohn's Disease and ulcerative colitis

25. Prior exposure to any CSF1R pathway inhibitors

26. Transfusion completed within 72 hours prior to first dose of study drug administration

3.2.4 Additional Inclusion and Exclusion Criteria for Selected Cohorts

3.2.4.1 Phase 1a

Includes Phase 1a Dose Escalation, Phase 1a Exploration and Phase 1a 3-week Dosing Regimen cohorts

3.2.4.1.1 Cabiralizumab Monotherapy Cohorts

Inclusion

1. Histologically or cytologically confirmed solid tumor that is locally recurrent or metastatic and has progressed following standard treatment or is not appropriate for standard treatment

2. Patients with squamous NSCLC must have documented progression on nivolumab in order to enroll in the monotherapy cohorts of the study.

3.2.4.1.2 Cabiralizumab + Nivolumab Combination Cohorts

Exclusion

1. Prior exposure to any PD-1 pathway targeting drug
   a. This will not apply to additional patients enrolled in Phase 1a after completion of the DLT period to fully characterize safety, PK, and PD.
2. Subjects with history of life-threatening toxicity related to prior immune therapy (e.g., anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (e.g., Hormone replacement after adrenal crisis)

3.2.4.2 Phase 1b

Exclusion

1. Subjects with a history of life-threatening toxicity related to prior immune therapy (e.g., anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to recur with standard countermeasures (e.g., Hormone replacement after adrenal crisis)

3.2.4.2.1 Cohort 1b1: Non-Small Cell Lung Cancer (PD-1 Naïve)

Inclusion

1. Patients with histologically or cytologically documented non-small cell lung cancer (NSCLC) who present with Stage IIIB locally advanced or Stage IV metastatic disease (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology) or with recurrent or progressive disease following multi-modal therapy (radiation therapy, surgical resection, or definitive chemoradiation)
2. Objective evidence of disease progression during or after at least one ALK-targeting agent (if ALK mutation positive) or after at least one EGFR-targeting agent (if EGFR mutation positive) unless patient has refused these diagnostic tests or specific therapies.
3. Disease progression or recurrence during/after a platinum doublet-based chemotherapy regimen for advanced or metastatic disease
    a. Maintenance therapy following platinum doublet-based chemotherapy is not considered a separate therapy regimen.
    b. Patients who received platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, and developed recurrent (local or metastatic) disease within 6 months of completing therapy are eligible.
    c. Patients with recurrent disease > 6 months after platinum-containing adjuvant, neoadjuvant or definitive chemo-radiation therapy given for locally advanced disease, who also subsequently progressed during or after a platinum doublet-based regimen given to treat the recurrence, are eligible.

Exclusion

1. Has received prior therapy immune cell-modulating antibody regimens, such as, but not limited to anti-PD-1, anti-PD-L1, anti PD-L2, anti-CTLA-4, anti-CD137, anti-KIR, and/or anti-OX40 antibodies.

3.2.4.2.2 Cohort 1b2: Non-Small Cell Lung Cancer (De novo or Acquired Resistance to Anti-PD-1 Targeting Drugs)

Inclusion

1. Patients with histologically or cytologically documented NSCLC who present with Stage IIIB locally advanced or Stage IV metastatic disease.

2. Patient has radiological evidence of disease progression after receiving at least 2 doses of an anti-PD-1 targeting drug (e.g. nivolumab,pembrolizumab) in either of the following settings: progressive disease as the initial best objective response (de novo resistance), ***or*** progressive disease after an initial response of either CR, PR or SD (acquired resistance).

3. Objective evidence of disease progression during or after at least one ALK-targeting agent (if ALK mutation positive) or after at least one EGFR-targeting agent (if EGFR mutation positive) unless patient has refused these diagnostic tests or specific therapies.

4. Disease progression or recurrence during/after a platinum doublet-based chemotherapy regimen for advanced or metastatic disease.
    a. Maintenance therapy following platinum doublet-based chemotherapy is not considered a separate therapy regimen.
    b. Patients who received platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, and developed recurrent (local or metastatic) disease within 6 months of completing therapy are eligible.
    c. Patients with recurrent disease > 6 months after platinum-containing adjuvant, neoadjuvant or definitive chemo-radiation therapy given for locally advanced disease, who also subsequently progressed during or after a platinum doublet-based regimen given to treat the recurrence, are eligible.

Exclusion

1. Intolerance to any PD-1 targeting drug.

    Intolerance is defined as any treatment-related Grade 4 AE, or any treatment-related Grade 2 or Grade 3 AE that is unacceptable to the patient and persists despite standard countermeasures.
2. Prior treatment with an mTOR inhibitor (including, but not limited to, everolimus, temsirolimus, sirolimus, and ridaforolimus).

3.2.4.2.3 Cohort 1b3: Squamous Cell Carcinoma of the Head and Neck

Inclusion

1. Patients with histologically or cytologically documented recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) (oral cavity, pharynx, larynx), stage III or IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).

2. Tumor progression or recurrence within 6 months of the last dose of platinum therapy in the adjuvant (i.e. with radiation after surgery), primary (i.e., with radiation), recurrent, or metastatic setting or patients that are intolerant to platinum chemotherapy.

Exclusion

1. Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx and any salivary gland or non-squamous histology.

2. Has received prior therapy immune cell-modulating antibody regimens, such as, but not limited to anti-PD-1, anti-PD-L1, anti PD-L2, anti-CTLA-4, anti-CD137, anti-KIR, and/or anti-OX40 antibodies.

3.2.4.2.4 Cohort 1b4: Pancreatic Cancer

Inclusion

1. Histologically or cytologically documented unresectable localized, borderline resectable, locally advanced or metastatic adenocarcinoma of the pancreas, which has failed, or is not indicated for standard therapy, or for which the patient has refused standard therapy

2. Patients who may have received prior surgery, radiation therapy for the management of locally advanced or metastatic adenocarcinoma of the pancreas providing that disease progression has been documented. All toxicities should be resolved, and the last fraction of radiation treatment was completed at least 4 weeks prior to first study drug administration

Exclusion

1. Patients with islet cell neoplasms, neuroendocrine or other primary tumors in the pancreas
2. Patients with active pancreatitis
3. Has received prior therapy immune cell-modulating antibody regimens, such as, but not limited to anti-PD-1, anti-PD-L1, anti PD-L2, anti-CTLA-4, anti-CD137, anti-KIR, and/or anti-OX40 antibodies
4. Ascites of Grade 2 or higher
5. Albumin <3.0 g/dL

3.2.4.2.5 Cohort 1b5: Advanced Ovarian Cancer

Inclusion

1. Patients with histologically or cytologically confirmed epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer.
2. Patients who have received at least three prior regimens of treatment.

Exclusion

1. Has received prior therapy immune cell-modulating antibody regimens, such as, but not limited to anti-PD-1, anti-PD-L1, anti PD-L2, anti-CTLA-4, anti-CD137, anti-KIR, and/or anti-OX40 antibodies.

3.2.4.2.6 Cohort 1b6: Renal Cell Carcinoma

Inclusion

1. Patients with histologically or cytologically confirmed advanced or metastatic renal cell carcinoma with a clear-cell component.

2. Must have received at least one prior anti-angiogenic therapy regimens (including, but not limited to, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab) in the advanced or metastatic setting. Prior cytokine therapy (eg, IL-2, IFN-α), vaccine therapy, or treatment with cytotoxics is also allowed.

Exclusion

1. Has received prior therapy immune cell-modulating antibody regimens, such as, but not limited to anti-PD-1, anti-PD-L1, anti PD-L2, anti-CTLA-4, anti-CD137, anti-KIR, and/or anti-OX40 antibodies.

3.2.4.2.7 Cohort 1b7: Malignant Glioma

Inclusion

1. Histologically or cytologically documented advanced World Health Organization (WHO) Grade IV malignant glioma (glioblastoma or gliosarcoma).
2. Previous treatment with radiotherapy and temozolomide.
3. Documented first recurrence of GBM by diagnostic biopsy or contrast-enhanced MRI performed within 28 days of first study drug administration per Response Assessment in Neuro-oncology (RANO) criteria.
4. If on steroids, dose must be stable or decreased for a minimum of 5 days prior to baseline MRI.

Exclusion

1. Prior treatment with bevacizumab or another VEGF- or VEGFR-targeting agent.
2. Recent evidence of more than Grade 1 CNS hemorrhage on baseline MRI scan.
3. History or evidence upon physiological/neurological exam of CNS disease (e.g., seizures) unrelated to cancer unless adequately controlled by medication or potentially interfering with the study treatment.
4. Patients unable to have a head contrast-enhanced MRI due to a pre-existing medical condition including a pacemaker or implantable cardioverter defibrillator (ICD) device.

5. Has received prior therapy immune cell-modulating antibody regimens, such as, but not limited to anti-PD-1, anti-PD-L1, anti PD-L2, anti-CTLA-4, anti-CD137, anti-KIR, and/or anti-OX40 antibodies.

3.2.5 Women of Childbearing Potential

Women of childbearing potential (WOCBP) include any females who have experienced menarche and who have not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), and who are not post-menopausal. Post-menopause is defined as:

- Amenorrhea ≥12 consecutive months without another cause, and a documented serum follicle stimulating hormone (FSH) level >35 mIU/mL, ***or***
- Women with irregular menstrual periods and a documented serum FSH level >35 mIU/mL (***Note***: FSH level testing is not required for women ≥62 years old with amenorrhea of ≥1 year), ***or***
- Women on hormone replacement therapy (HRT).

Women who are using oral or other hormonal contraceptives, such as vaginal products, skin patches, or implanted or injectable products, or mechanical products, such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or who are practicing abstinence or who have a sterile (e.g., vasectomy) partner should be considered to be of childbearing potential (Gabbay 2008, Kestelman 1991).

3.4 Discontinuation of Patients following any Treatment with Study Drug

Patients ***must*** discontinue study drugs for any of the following reasons:

- Withdrawal of informed consent (patient's decision to withdraw for any reason)
- Any clinically significant AE, abnormal laboratory test results, or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the patient
- Patients who are required to have prohibited concomitant medications

- Pregnancy
- Termination of the study by the Sponsor
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of a psychiatric or physical (e.g., infectious disease) illness
- Documented disease progression or clinical deterioration while receiving active study therapy
- Non-compliance by the patient

All patients who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 5.2.4. The only exception to this requirement is when a patient withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of a psychiatric or physical illness).

If a patient was discontinued, the reason for discontinuation must be entered on the appropriate CRF. The date and reason for cessation of cabiralizumab and/or nivolumab will be documented, and the Investigator must make every effort to perform the End-of-Treatment Visits. Adverse event reporting will continue until 100 (±7) days after the last dose of study drug or until initiation of subsequent anti-cancer therapy. Patients with ongoing SAEs will be followed until resolution or stabilization.

3.5 Long-Term Follow-up

Patients who discontinue treatment while still receiving clinical benefit (i.e., CR, PR or SD) should get follow-up tumor scans every 12 (±2) weeks until disease progression or use of subsequent anti-cancer therapy to determine the duration of response, unless consent is withdrawn.

Long-Term Follow-up for survival may be conducted by telephone, rather than by an in-person visit, once tumor progression is determined or use of subsequent anti-cancer therapy has been initiated.

4. Study Drugs

In this study, both study drugs, cabiralizumab and nivolumab, are considered Investigational Medicinal Products (IMP).

4.1 Investigational Products

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already having a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. In this protocol, the investigational products are cabiralizumab and nivolumab.

4.2 Handling and Dispensing

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to Patients. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The applicable site personnel should ensure that the study drugs are stored in accordance with the environmental conditions (temperature, light, and humidity) determined by the Sponsor. If concerns regarding the quality or appearance of the study drugs arise, do not dispense the study drugs and contact the Sponsor or designee immediately.

Study drug documentation including all processes required to ensure drug is accurately administered must be maintained. This includes documentation of drug storage and administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g. required diluents, administration sets).

4.2.1 Cabiralizumab

The investigational supply of cabiralizumab will be provided to the study centers by the Sponsor (or designee) and will be administered to patients in the clinical study by a trained healthcare professional.

Cabiralizumab drug product is supplied for IV administration as a sterile, aqueous, colorless to pale yellow liquid, clear to slightly opalescent pyrogen-free solution in 5 mL glass vials stoppered with coated stoppers, and equipped with aluminum seals. Light (few) particulates (consistent in appearance to proteinaceous particles) may be present. Each vial contains a minimum of 5 mL of a 20 mg/mL solution of cabiralizumab (approximately 100 mg per vial). Storage Conditions: 2–8°C (36–46°F). The vials will be provided in a carton. Both vials and cartons will be labeled per local regulations. Refer to the pharmacy manual for more specific information on the drug product.

4.2.2 Nivolumab

The investigational supply of nivolumab will be provided to the study centers by the Sponsor or designee. Refer to the Nivolumab Investigator's Brochure for preparation and storage conditions of nivolumab.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservatives or bacteriostatic agents. No incompatibilities between nivolumab and polyolefin bags have been observed.

4.3 Study Drug Dosing and Dose Modification

4.3.1 Dosing

For patients in the monotherapy cohorts, cabiralizumab infusion may be administered as a 30-minute IV infusion on Day 1 of each 14-day treatment cycle. For the combination therapy, nivolumab should always be administered first as a 30-minute IV infusion, with a 30- to 60-minute rest, followed by a 30-minute infusion of cabiralizumab (patients in 3-week dosing regimen cohort will receive study drugs on Day 1 of each 21-day treatment cycle). 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 patients for the duration of this study. Patients may be dosed no less than 12 days from the previous dose.

For Cohort 1aM2, 6 mg/kg cabiralizumab monotherapy, and dose escalation Cohorts 1aC2 and 1aC3, cabiralizumab and nivolumab combination therapy, the dose interval between the first and second patients in each cohort should be at least 24 hours for safety monitoring.

Dosing calculations should be based on the body weight assessed at Cycle 1 Day 1 prior to the first dose of study drug administration. It is not necessary to recalculate subsequent doses if the patient's weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded to the nearest milligram.

Patients should be carefully monitored for infusion reactions during study drug administration. If an acute infusion reaction is noted, patients should be managed according to the guidelines in Section 4.3.10 [redacted]

Doses of study drugs may be interrupted, delayed, or discontinued depending on how the patient tolerates the treatment.

All vials are for single use only. Further instructions on study drug preparation and administration are provided in the Pharmacy Manual.

4.3.1.1 Nivolumab Dosing

Patients in combination therapy cohorts will receive the nivolumab infusion first at a dose of 3 mg/kg as a 30-minute IV infusion, on Day 1 of each 14 or 21 day treatment cycle depending on

treatment cohort. 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 patients for the duration of this study.

There will be no dose escalations or reductions of nivolumab allowed. Patients may be dosed no less than 12 days from the previous dose. There are no premedications recommended for nivolumab on the first cycle. Refer to the Pharmacy Manual for nivolumab preparation instructions.

4.3.1.2 Cabiralizumab Dosing

For patients in the combination therapy cohorts, the cabiralizumab infusion will be administered 30 minutes IV infusion, after the end of the nivolumab infusion and a 30- to 60-minute rest, on Day 1 of each 14 or 21day treatment cycle depending on treatment cohort. For patients in the monotherapy cohorts, the cabiralizumab infusion can be initiated at any time as a 30-minute IV infusion on Day 1 of each 14-day treatment cycle.

Cabiralizumab dosing may be modified based on toxicities noted during the treatment period. If necessary, the dose will be adjusted [redacted]) and Sections 4.3.2, 4.3.4, 4.3.5, and 4.3.10.

A research pharmacist (or other responsible personnel) will prepare the solution for administration. After calculating the number of vials, based on the patient's weight, the study drug product will be diluted with 0.9% Sodium Chloride Injection, USP. Prepared cabiralizumab should be administered within 6 hours after preparation (ambient temperature). The IV administration setup for cabiralizumab infusion must contain a 0.2 or 0.22 µm in-line filter or a 0.2 or 0.22 µm syringe filter. Cabiralizumab will be administered under medical supervision as a 30 minute (± 5 minutes) IV infusion via a peripheral vein or central venous catheter. No incompatibilities between cabiralizumab infusion and polyvinyl chloride (PVC), ethylene/propylene IV components, or glass bottles have been observed.

4.3.2 Dose Delay for Cabiralizumab and Nivolumab

Administration of cabiralizumab and/or nivolumab in combination therapy should be delayed for the following:

- Any Grade 3 fatigue which does not resolve to Grade 1 or baseline before the next treatment visit
- Any drug-related laboratory abnormalities would not require a dose delay unless clinically indicated or specified in the protocol or abnormal laboratory management table (Appendix H). Please discuss with the Sponsor's Medical Monitor or designee as needed.
- [redacted]

Patients who require a dose delay of cabiralizumab or cabiralizumab /nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume study drug dosing when re-treatment criteria are met.

If a patient experiences an infusion reaction to cabiralizumab, or nivolumab, or both study drugs, the infusion reaction should be treated following the infusion reaction treatment guidelines [redacted]

If the causality of the AE requiring a dose delay is confirmed to be due to one of the study drugs of the combination therapy, the non-offending drug may be continued per protocol taking into account the safety and clinical benefit to the patient.

4.3.3 Criteria to Resume Treatment with Cabiralizumab and Nivolumab

Patients may resume treatment with cabiralizumab and/or nivolumab when the drug-related AE resolves [redacted] The Sponsor's Medical Monitor or designee can be contacted at any time if further clarification is needed.

4.3.4 Dose Reduction with Cabiralizumab and Nivolumab

Dose reduction for cabiralizumab and nivolumab are not permitted.

4.3.5 Dose Discontinuation Criteria for Cabiralizumab and Nivolumab

Discontinuation rules may be different for monotherapy and combination therapy and not all rules will apply to both arms of the study. [redacted]

Treatment of cabiralizumab in monotherapy or cabiralizumab in combination with nivolumab should be discontinued in the following cases unless otherwise specified:

- Any Grade 3 or higher uveitis ***or*** any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 within the second re-treatment period ***or*** that requires systemic treatment
- Any Grade 3 or higher infusion-related reactions and hypersensitivity requiring discontinuation. Any re-initiation of therapy in this circumstance would require consultation with the Sponsor's Medical Monitor or designee.
- Any Grade 3 non-skin, drug-related AE lasting >7 days, including drug-related uveitis, pneumonitis, hypoxia, bronchospasm, and endocrinopathies with the following exceptions:
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment

discontinuation except:

- Grade 3 drug-related thrombocytopenia >7 days or associated with Grade ≥2 bleeding requires discontinuation

- Any drug-related liver function test (LFT) abnormality that meets any one of the following criteria requires discontinuation:
  - ALT or AST >3x ULN ***and*** total bilirubin >2x ULN ***or*** INR > 1.5 xULN (in the absence of anticoagulation).

    [redacted]
  - ALT or AST > 20x ULN (with or without concurrent liver metastases)
  - Total bilirubin >3x ULN (>5x ULN with concurrent liver metastases)
- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia <7 days
  - Grade 4 lymphopenia or leukopenia <7 days
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The Sponsor's Medical Monitor or designee should be consulted for Grade 4 amylase or lipase abnormalities.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone (ACTH) deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Sponsor's Medical Monitor or designee.
  - Grade 4 CK up to 20 xULN (in the absence of clinical sequelae)
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a patient with a dosing delay lasting > 6 weeks from the previous dose, the Sponsor's Medical Monitor or designee must be consulted. Tumor assessments should continue as per-protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue per protocol, or more frequently if clinically indicated during such dosing delays or per the Investigator's discretion.

  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Sponsor's Medical Monitor or designee. Prior to re-initiating treatment in a patient with a dosing delay lasting > 6 weeks, the Sponsor's Medical Monitor must be consulted. Tumor assessments should continue per protocol every 8 weeks (±7 days) even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue per-protocol or more frequently if clinically indicated during such dosing delays or per the Investigator's discretion.

- Any AE, laboratory abnormality, or intercurrent illness which, in the opinion of the Investigator, presents a substantial clinical risk to the patient with continued cabiralizumab and/or nivolumab dosing
- Any drug-related Grade 3 or higher neurological toxicity
- Any Grade 3 or higher periorbital edema and persistent Grade 2 periorbital edema requiring 2 missed doses unless approved by Sponsor's Medical Monitor
- Any Grade 3 or higher drug-related diarrhea or colitis, which does not resolve to Grade 1 or baseline within 28 days.
- Any Grade 4 skin toxicity
- Any Grade 4 renal toxicity
- Any drug-related Grade 3 or higher pulmonary toxicity

If the causality of the adverse event requiring discontinuation is confirmed to be due to one of the study drugs in the combination therapy, the other drug may be continued per protocol schedule under the following scenarios:

- Timely resolution of the adverse event based on the treatment modification table
- Clinical benefit is shown by the patient based on Investigator assessment

4.3.6 Infusion Delays and Missed Doses with Cabiralizumab and Nivolumab

In case an infusion cannot be administered at a scheduled visit, it must be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed. If the delay is more than 7 days, the infusion at the original scheduled visit will be considered a missed dose and the procedures at the next visit should be performed. If the delay is longer than 7 days, subsequent visits will follow a 2-week (or 3-week in Phase 1a 3-week dosing regimen cohort) dosing interval. If the delay is less than 7 days, the original dosing schedule should be followed. The time between two treatment cycles should be no less than 12 days.

Patients may miss up to up to 6 weeks between doses and may resume the study drug if the event returns to baseline or ≤ Grade 1 within 6 weeks of treatment interruption. Omission of additional dosing longer than 6 weeks for AEs will necessitate the patient's discontinuation from the study unless allowed by the Sponsor's Medical Monitor or designee. Patients may miss doses in the

course of participation in the study, including missed doses for scheduled vacations or other personal reasons as needed, but not more than 6 weeks unless approved by the Sponsor's Medical Monitor or designee.

4.3.7 Intra-Patient Dose Escalation with Cabiralizumab and Nivolumab

Intra-patient dose escalation is not allowed for nivolumab or cabiralizumab.

4.3.8 Treatment beyond Disease Progression with Cabiralizumab and Nivolumab

Accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease [redacted]

Patients treated with cabiralizumab and nivolumab combination therapy will be permitted to continue cabiralizumab and nivolumab treatment beyond initial RECIST v1.1 defined progressive disease, assessed by the Investigator, as long as the following criteria are met:

- Patients who will be treated beyond disease progression must review and sign an ICF before continuing on study drug
- The patient demonstrates investigator-assessed clinical benefit, and do not have rapid disease progression
- Tolerance of study drugs
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)

A radiographic assessment/scan should be performed approximately 8 weeks (±7 days) after initial Investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued progressive disease. The assessment of clinical benefit should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment with cabiralizumab and nivolumab.

If the Investigator feels that any patient receiving cabiralizumab and nivolumab will obtain clinical benefit by continuing treatment, the patient may remain on the trial and continue to receive monitoring according to the time and event schedules per protocol.

For the patients who continue cabiralizumab and nivolumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial progression. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial progression. cabiralizumab and nivolumab treatment should be discontinued permanently upon documentation of further progression.

4.3.9 Dose Modification Algorithms for Immuno-Oncology Agents

Immuno-oncology agents are associated with AEs that can differ in severity and duration compared to AEs caused by other therapeutic classes. Cabiralizumab and nivolumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist Investigators in assessing and managing the following classes of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological
- Infusion reaction
- Periorbital edema
- Uveitis
- Laboratory abnormalities

[redacted]

4.3.10 Treatment of Cabiralizumab and Nivolumab-Related Infusion Reactions

Cabiralizumab and nivolumab may induce infusion or hypersensitivity reactions. If such a reaction were to occur, it may manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypo- or hypertension, bronchospasm, or other symptoms.

Infusion reactions should be graded according to CTCAE v4.03 guidelines. Any Grade 3 or Grade 4 infusion reaction should be reported within 24 hours to the Sponsor's Medical Monitor or designee, and reported as an SAE if it meets the criteria.

The nivolumab 30-minute infusion will be administered first, with a 30- to 60-minute rest, followed by the cabiralizumab 30-minute infusion. It may be unclear if an infusion reaction is due to cabiralizumab, nivolumab, or to both study drugs. Therefore, one set of treatment recommendations (based on the most conservative treatments for infusion reactions due to either study drug) is provided below and may be modified based on clinical judgment, local treatment standards and guidelines, and/or specific symptoms, as appropriate:

For Grade 1 symptoms: Mild reaction (e.g., localized cutaneous reactions including mild pruritus, flushing, rash), requires infusion rate to be decreased; intervention may be indicated.

- Decrease the rate of the study drug infusion until recovery from symptoms.
- Remain at bedside and monitor the patient's vital signs until resolution of symptoms. Diphenhydramine 50 mg may be administered at the discretion of the treating physician.
- When symptoms resolve, restart the infusion at the original infusion rate.
- If a patient has an infusion reaction with nivolumab, cabiralizumab can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes, cabiralizumab infusion may be given the next day. Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.
- If a patient has an infusion reaction with cabiralizumab, prophylactic pre-infusion medications should be given prior to all subsequent cabiralizumab and nivolumab infusions.
- The following prophylactic pre-infusion medications are recommended prior to future infusions of cabiralizumab and nivolumab: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 to 1000 mg at least 30 minutes before additional study drug administrations.

For Grade 2 symptoms: Moderate reaction (i.e., any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic blood pressure >80 mmHg), requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids); prophylactic pre-infusion medications indicated for ≤24 hours.

- Interrupt the study drug infusion.
- Begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol (acetaminophen) 325 to 1000 mg.
- Remain at bedside and monitor the patient's vital signs until resolution of symptoms. Corticosteroid therapy may be administered at the discretion of the treating physician.
- When symptoms resolve, restart the infusion at 50% of the original infusion rate; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate.
- Monitor the patient closely. If symptoms recur, immediately discontinue the infusion; no further study drug will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms.
- If a patient has an infusion reaction with nivolumab infusion, cabiralizumab infusion can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes, the cabiralizumab infusion may be given the next day.

Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.

- If a patient has an infusion reaction with cabiralizumab, prophylactic pre-infusion medications should be given prior to all subsequent cabiralizumab and nivolumab infusions.
- The following prophylactic pre-infusion medications are recommended prior to future infusions of cabiralizumab and nivolumab: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 to 1000 mg should be administered at least 30 minutes before additional study drug administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.
- The amount of study drug infused must be recorded.

For Grade 3 or Grade 4 symptoms: Severe reaction such as bronchospasm, generalized urticaria, systolic blood pressure <80 mmHg, or angioedema; Grade 3 symptoms including prolonged symptoms, which require 6 or more hours to respond to symptomatic medication and/or discontinuation of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae, such as renal impairment, pulmonary infiltrates; Grade 4: life-threatening; pressor or ventilation support indicated.

- Immediately discontinue the study drug infusion. No further study drug will be administered. The amount of study drug infused must be recorded on the CRF.
- Begin an IV infusion of normal saline, and treat the patient as follows: Recommend bronchodilators, epinephrine 0.2 to 1.0 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.
- Remain at bedside and monitor the patient's vital signs until recovery from symptoms.
- The patient should be monitored until the Investigator is comfortable that the symptoms will not recur.
- Investigators should follow their institutional guidelines for the treatment of anaphylaxis.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

4.4 Method of Assigning Patient Identification

Patients must be able to provide written informed consent and meet all eligibility criteria. No waivers of inclusion or exclusion criteria will be granted by Sponsor or its designee for any patient enrolled in the study. Before enrolling a patient, all eligibility criteria must be satisfied.

Patients who qualify for Phase 1a dose esclation of the study will be enrolled as follows:

- The 2 mg/kg cabiralizumab monotherapy cohort was enrolled first, followed by enrollment to the 1mg/kg cabiralizumab /nivolumab combination cohort. Patients in these cohorts will be treated for a total of two 14-day treatment cycles within the DLT period.
- Enrollment into the 4 mg/kg cabiralizumab monotherapy cohort will proceed once the DLT period is cleared in preceding monotherapy cohorts.
- Dose escalation into increasing dose levels of cabiralizumab in combination with nivolumab may proceed until DLTs are observed either in the cabiralizumab monotherapy or the cabiralizumab in combination with nivolumab cohorts after discussion and agreement by the Cohort Review Committee.

In 3-week dosing regimen Cohort (1aD), approximately 10 patients will be enrolled into the 4 mg/kg cabiralizumab in combination with nivolumab cohort. These patients will receive study treatment every three weeks.

The Phase 1a exploration consists of six cohorts of approximately 10 patients each. These cohorts are further evaluating the safety, PK, and PD of cabiralizumab as monotherapy and in combination with nivolumab.

In Phase 1b, approximately 30 patients will be enrolled per cohort. Enrollment will be open for all cohorts in parallel and will continue until the enrollment target is reached. Once a cohort is filled, further enrollment will be restricted to the cohort(s) that have not been filled. A total of approximately 210 patients will be enrolled in the Phase 1b arm of the study.

The Investigator may repeat qualifying lab tests and vitals/ECGs prior to enrollment if a non-qualifying finding is considered an error or an acute finding is likely to meet eligibility criteria upon repeat testing.

4.5 Blinding/Unblinding

This is an open-label study and there will be no blinding or unblinding of patients during this study.

4.6 Treatment Compliance

Study drug will be administered by qualified trained site personnel in the clinical facility. The Investigator or their designated study personnel will maintain a log (Drug Accountability Log) of all study drugs received dispensed and destroyed. The Investigator and the study personnel will ensure that each patient receives the calculated dose of the study drug based on body weight.

Drug supplies will be inventoried and accounted for throughout the study. The Drug Accountability Log will be reviewed by the study monitor during site visits and at the completion of the study. Any discrepancy should be brought to the attention of the Sponsor. Records of study medication administration (date, start and stop time, and dose administered relative to time of preparation) will be recorded on the patient's CRF.

4.7 Destruction of Study Drug

Any unused study drugs can only be destroyed on site after being inspected and reconciled by the responsible site monitor unless study drug vials must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics).

- On-site destruction is allowed provided the following minimal standards are met:
- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's Standard Operating Procedures (SOPs) and a copy provided to the Sponsor upon request.
- Records are maintained that allow for traceability of each vial, including the date disposed of, quantity disposed, and identification of the person disposing of the containers. The method of disposal (i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must also be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study drug (Section 4.8).

It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures and provided that appropriate records of disposal are kept.

4.8 Return of Study Drug

If study drug will not be destroyed on site upon completion or termination of the study, all unused and/or partially used study drug that was supplied must be returned. The return of study drug will be arranged by the responsible Study Monitor.

5. Study Assessments and Procedures

5.1 Schedule of Assessments

The schedule of assessment tables are attached to the protocol as Appendix A, Appendix B, and Appendix C.

5.2 Study Procedures by Visit

5.2.1 Phase 1a Monotherapy

5.2.1.1 Screening Period (Day –28 to Day 0)

Patients 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 cabiralizumab (unless otherwise stated). To determine if the patient meets all inclusion criteria and does not violate any exclusion criteria, the following procedures will be performed (Appendix A).

- Written, signed informed consent must be collected prior to any study-specific procedures
- If available, collect a formalin fixed, paraffin-embedded (FFPE) tissue block or 10 slides of archival tumor sample
- Complete medical and disease history including prior HPV status
- Demographic and baseline characteristics
- Complete physical examination including height and weight
- Photo of periorbital region (required at screening, and if clinically indicated during the study)
- Vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest)
- ECOG performance status evaluation
- Screening labs (as described in Appendix A)
- Clinical safety labs (as described in Appendix A)
- Collect sample if the patient is being followed for a tumor marker (e.g. CA-125, or others)
- 12-lead ECG (required at screening, and if clinically indicated during the study)
- Radiological imaging: CT or MRI is to be performed within 28 days prior to Cycle 1 Day 1. If the CT or MRI is performed as part of the patient's standard of care within 28 days of Cycle 1 Day 1, it does not need to be repeated if the documentation of results is provided and is adequate for RECIST v1.1.

- Serum pregnancy test (β-hCG) for women of childbearing potential
- Skin and tumor biopsy collection (at least 24 hours prior to dosing; analyses described in Appendix D)
- SAE reporting, if applicable
- Document prior and concomitant medications

5.2.1.2 Cycle 1, Day 1

The following procedures will be performed:

- Prior to cabiralizumab infusion (within ≤72 hours unless otherwise stated):
  - Verification of eligibility
  - Update medical and disease history to capture any changes from screening
  - Physical examination including weight
  - Vital signs (blood pressure, pulse, respiratory rate and temperature in resting position after 5 minutes rest)
  - ECOG performance status evaluationClinical safety labs (as described in Appendix A; results must be reviewed before dosing)
  - Collect sample if the patient is being followed for a tumor marker (e.g. CA-125 or others)
  - Serum pregnancy test (β-hCG) for women of childbearing potential
  - Blood collection for:
    - Serum (analyses described in Appendix D, excluding all nivolumab analyses)
    - Whole blood (analyses described in Appendix D)
    - Frozen PBMC (analyses described in Appendix D)
  - AE reporting, if applicable
  - Review of concomitant medications
- Study drug administration: cabiralizumab by IV infusion over 30 minutes (± 5 minutes)
  - Post cabiralizumab administration:
    - Post-dose vital signs (heart rate, blood pressure, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time points after completion of the IV infusion:
      - 10 (±5) minutes, 30 (±10) minutes, and 60 (±15) minutes
      - Blood collection for serum cabiralizumab PK
        - 15 (±5) minutes post-dose
      - Blood collection for serum cabiralizumab PK
        - 4 hours (± 60 minutes) post-dose

5.2.1.3 Cycle 1, Day 2

Patients will return to the study center on Day 2 for 24-hour (± 6 hours) post-dose assessments. No treatment will be administered during this visit, but the following assessments will be completed:

- Blood collection for:
  - Serum (cabiralizumab PK)
- AE reporting, if applicable
- Review of concomitant medications

5.2.1.4 Cycle 1, Day 4

Patients will return to the study center on Day 4 for 72-hour (± 12 hours) post-dose assessments. No treatment will be administered during this visit, but the following assessments will be completed:

- Blood collection for:
  - Serum (cabiralizumab PK)
  - Whole blood (gene expression analyses only)
- AE reporting, if applicable
- Review of concomitant medications

5.2.1.5 Cycle 1, Day 8

Patients will return to the study center on Day 8 for 168-hour (± 24 hours) post-dose assessments. No treatment will be administered during this visit, but the following assessments will be completed:

- Physical examination
- Vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest)
- Clinical safety labs (as described in Appendix A)
- Blood collection for:
  - Serum (cabiralizumab PK)
  - Whole blood (analyses described in Appendix D)
  - Frozen PBMC (analyses described in Appendix D)
- AE reporting, if applicable
- Review of concomitant medications

5.2.1.6 Cycle 2, Day 1

The following procedures will be performed (a ± 2 day window is allowed for Day 1 in subsequent cycles post Cycle 1, Day 1):

- Prior to cabiralizumab infusion (within ≤ 72 hours unless otherwise stated):
  - Physical examination including weight
  - Vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest)
  - ECOG performance status evaluation
  - Clinical safety labs (as described in Appendix A; results must be reviewed before dosing)
  - Blood collection for:
    - Serum (analyses described in Appendix D, excluding all nivolumab analyses)
    - Whole blood (analyses described in Appendix D)
    - Frozen PBMC (analyses described in Appendix D)
  - AE reporting, if applicable
  - Review of concomitant medications
- Study drug administration: cabiralizumab by IV infusion over 30 minutes (± 5 minutes)
  - Post cabiralizumab administration:
    - Post-dose vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time points after completion of the IV infusion:
      - 10 (±5) minutes, 30 (±10) minutes, and 60 (±15) minutes
    - 15 (±5) minutes post-dose
      - Blood collection for serum (cabiralizumab PK)

5.2.1.7 End of the DLT Period (Phase 1a Dose Escalation cohorts only)

For Phase 1a patients in monotherapy dose escalation cohort, if at the end of the DLT period, the Investigator determines that the patient may benefit from continued dosing with cabiralizumab, entry into the Extended Treatment Period may be offered.

If the patient is continuing onto the Extended Treatment Period, proceed to procedures outlined in Section 5.2.1.8.

If the patient does not qualify to receive further doses of cabiralizumab, the patient will return to the clinic for the End-of-Treatment Visits outlined in Section 5.2.1.9.

5.2.1.8 Extended Treatment – Subsequent Cycles, Day 1

Phase 1a extended treatment for patients in monotherapy cohorts (1aM) may begin upon completion of the DLT period. Dosing will be discontinued if the patient experiences either disease progression or unacceptable toxicity.

At each infusion visit, patients are to remain at the study site after each administration of cabiralizumab until completion of all post-dose assessments for safety monitoring. The following assessments will be performed at each visit unless otherwise noted (Appendix A) (a ± 2 day window is allowed for Day 1 in subsequent cycles post Cycle 1, Day 1):

- Prior to each infusion of study drug (within 72 hours unless otherwise stated):
  - Physical examination including weight
  - Vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest)
  - ECOG performance status evaluation
  - Clinical safety labs (as described in Appendix A; results must be reviewed before dosing)
  - Collect sample if the patient is being followed for a tumor marker (e.g. CA-125, or others) on Cycle 3 Day 1, then every other cycle after, or as clinically indicated
  - Radiological imaging: CT or MRI scan performed every 8 weeks (± 7 days) from the first dose for the first 12 months for patients who remain on treatment (and every 12 weeks (± 7 days) thereafter) and 28 days (± 7 days) after the last dose of study treatment.
  - Serum pregnancy test (β-hCG) for women of childbearing potential on Cycle 5, Day 1, then every 8 weeks (every 4 cycles)
  - Skin and tumor biopsy collection (prior to Cycle 3 only, within 7 days prior to Cycle 3 Day 1 and at least 24 hour prior to dosing; for analyses described in Appendix D)
  - Optional skin and tumor biopsy for patients who responded to treatment (within 14 days post tumor assessment; for analyses described in Appendix D)
  - Blood collection for:
    - Serum (for analyses described in Appendix D) as listed below.
      - Cabiralizumab PK for Cycles 3, 4, 5, 8, 9, 13, and 21, then every 6 cycles while on treatment
      - Cabiralizumab ADA for Cycles 3, 4, 5, 9, 13, and 21, then every 6 cycles while on treatment
      - ANA for Cycles 3, 4, 5, 9, 13, 21, then every 6 cycles while on treatment
      - Selected serum markers for Cycles 3, 4, 5, 8, 9, 13, and 21

  - Cytokine multiplex panel for Cycles 3, 4, 5, 8, 9, 13, and 21
- Whole blood (for analyses described in Appendix D) as listed below.
  - $CD14^+/CD16^+$ monocytes for Cycles 3, 4, 5, 8, and 9, 13, and 21, then every 6 cycles while on treatment
  - Gene expression analysis for Cycle 3, 5, 9, 13, and 21, then every 6 cycles while on treatment
  - Frozen PBMC for Cycle 3 (analyses described in Appendix D)
- AE reporting, if applicable
- Review of concomitant medications

- Study drug administration: cabiralizumab by IV infusion over 30 minutes (± 5 minutes)
- Post cabiralizumab administration:
  - Post-dose vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time points after completion of the IV infusion:
    - 10 (±5) minutes, 30 (±10) minutes, and 60 (±15) minutes
    - Blood collection for serum (for analyses described in Appendix D) as listed below.
    - Cabiralizumab PK 15 minutes (±5 minutes) for Cycles 3 and 4
    - Cabiralizumab PK 15 minutes (±5 minutes), 4 hours (±60 minutes), 24 hours (±6 hours), 72 hours (±12 hours) and 168 hours (±24 hours) for Cycle 8 only
    - Selected serum markers 72 hours (±12 hours) and 168 hours (± 24 hours) for Cycle 8 only
    - Cytokine multiplex panel 72 hours (±12 hours) and 168 hours (±24 hours) for Cycle 8 only
    - $CD14^+/CD16^+$ monocytes 72 hours (±12 hours) and 168 hours (±24 hours) for Cycle 8 only

5.2.1.9 End-of-Treatment Follow-up Period

Patients will return to the study center twice, approximately 28 (± 7) days, followed by a subsequent visit 100 (±7) days after their last infusion of cabiralizumab, to complete the End-of-Treatment Follow-up Period.

The following assessments will be performed:

- Physical examination including weight
- Vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest)
- ECOG performance status evaluation

- Clinical safety labs (as described in Appendix A)
- 12-lead ECG (28 [±7] days, post last infusion of cabiralizumab visit only).
- Radiological imaging: CT or MRI scan does not need to be repeated if performed within 8 weeks prior to the End-of-Treatment Visits or if tumor progression was previously determined.
- Serum pregnancy test (β-hCG) for women of childbearing potential
- Optional skin and tumor biopsy for patients who progressed, (28 [±7] days, post last infusion of cabiralizumab visit only) (for analyses described in Appendix D)
- Blood collection
  - Serum (analyses described in Appendix D, excluding all nivolumab analyses)
  - Whole blood ($CD14^+/CD16^+$ monocyte analysis and gene expression analysis only)
- AE reporting, if applicable, until 100 (±7) days after the last dose of study drug or until initiation of subsequent anti-cancer therapy. Patients with ongoing SAEs will be followed until resolution or stabilization.
- Review of concomitant medications

5.2.2 Phase 1a Combination (including 1aC, 1aE, and 1aD cohorts)

5.2.2.1 Screening Period (Day –28 to Day 0)

Patients who have consented to participation in the study will undergo screening assessments within 28 days (4 weeks) prior to administration of the first infusion of cabiralizumab and nivolumab (unless otherwise stated). To determine if the patient meets all inclusion criteria and does not violate any exclusion criteria, the following procedures will be performed (Appendix B):

- Written, signed informed consent must be collected prior to any study-specific procedures
- If available, collect an FFPE tissue block or 10 slides of archival tumor sample
- Complete medical and disease history including prior HPV status
- Demographic and baseline characteristics
- Complete physical examination including height and weight
- Photo of periorbital region (required at screening, and if clinically indicated during the study)
- Vital signs (blood pressure, pulse, respiratory rate, pulse oximetry and temperature in resting position after 5 minutes rest)
- ECOG performance status evaluation

- Screening labs (as described in Appendix B)
- Clinical safety labs (as described in Appendix B)
- Collect sample if the patient is being followed for a tumor marker (e.g. CA-125, or others)
- 12-lead ECG (required at screening, and if clinically indicated during the study)
- Radiological imaging: CT or MRI is to be performed within 28 days prior to Cycle 1 Day 1. If the CT or MRI is performed as part of the patient's standard of care within 28 days of Cycle 1 Day 1, it does not need to be repeated if the documentation of results is provided and is adequate for RECIST v1.1
- Serum pregnancy test (β-hCG) for women of childbearing potential
- Skin and tumor biopsy collection (at least 24 hour prior to dosing; analyses described in Appendix D)
- SAE reporting, if applicable
- Document prior and concomitant medications

5.2.2.2 Cycle 1, Day 1

The following procedures will be performed:

- Prior to cabiralizumab and nivolumab infusion (within 72 hours unless otherwise stated):
  - Verification of eligibility
  - Update medical and disease history to capture any changes from screening
  - Physical examination including weight
  - Vital signs (blood pressure, pulse, respiratory rate, pulse oximetry and temperature in resting position after 5 minutes rest)
  - ECOG performance status evaluation
  - Clinical safety labs (as described in Appendix B; results must be reviewed before dosing)
  - Collect sample if the patient is being followed for a tumor marker (e.g. CA-125, or others)
  - Serum pregnancy test (β-hCG) for women of childbearing potential
  - Blood collection for:
    - Serum (analyses described in Appendix D)
    - Whole blood (analyses described in Appendix D)
    - Frozen PBMC (analyses described in Appendix D)
  - AE reporting, if applicable

  - Review of concomitant medications

- Study drug administration: Nivolumab will be given first, with a 30-minute rest, followed by cabiralizumab.
  - Nivolumab administered by IV infusion over 30 minutes (± 5 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 patients for the duration of this study.)
    - Post-nivolumab administration:
      - Post-dose vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time point after completion of each IV infusion:
        - 10 (±5) minutes
      - Blood collection for serum nivolumab PK
        - 15 (±5) minutes
  - Cabiralizumab administered by 30 minutes IV infusion (± 5 minutes)
    - Post- cabiralizumab administration:
      - Post-dose vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time points after completion of cabiralizumab IV infusion:
        - 10 (±5) minutes, 30 (±10) minutes, and 60 (±15) minutes
      - Blood collection for serum cabiralizumab PK
        - 15 (±5) minutes
        - 4 hours (± 60 minutes)

5.2.2.3 Cycle 1, Day 2

Patients will return to the study center on Day 2 for 24-hour (± 6 hours) post-dose assessments. No treatment will be administered during this visit, but the following assessments will be completed:

- Blood collection for:
  - Serum (cabiralizumab PK)
- AE reporting, if applicable
- Review of concomitant medications

5.2.2.4 Cycle 1, Day 4

Patients will return to the study center on Day 4 for 72-hour (± 12 hours) post-dose assessments. No treatment will be administered during this visit, but the following assessments will be completed:

- Blood collection for:
  - Serum (cabiralizumab PK only)
  - Whole blood ($CD14^+/CD16^+$ monocyte and gene expression analyses)
    - $CD14^+/CD16^+$ monocyte analysis only for patients in Cohort 1aC1 (1 mg/kg cabiralizumab with 3 mg/kg nivolumab)
- AE reporting, if applicable
- Review of concomitant medications

5.2.2.5 Cycle 1, Day 8

Patients will return to the study center on Day 8 for 168-hour (± 24 hours) post-dose assessments. No treatment will be administered during this visit, but the following assessments will be completed:

- Physical examination
- Vital signs (blood pressure, pulse, respiratory rate, pulse oximetry and temperature in resting position after 5 minutes rest)
- Clinical safety labs (as described in Appendix B)
- Blood collection for:
  - Serum (cabiralizumab PK)
  - Whole blood ($CD14^+/CD16^+$ monocyte and gene expression analyses)
  - Frozen PBMC (analyses described in Appendix D)
- AE reporting, if applicable
- Review of concomitant medications

5.2.2.6 Cycle 1, Day 15 (Cohort 1aD only)

Patients will return to the study center on Day 15 for 336-hour (± 24 hours) post-dose assessments. No treatment will be administered during this visit, but the following procedures will be performed:

- Physical examination
- Vital signs (blood pressure, pulse, respiratory rate, pulse oximetry and temperature in resting position after 5 minutes rest)
- Clinical safety labs (as described in Appendix B)
- Blood collection for:
  - Serum (cabiralizumab PK)

- AE reporting, if applicable
- Review of concomitant medications

5.2.2.7 Cycle 2, Day 1

The following procedures will be performed (a ± 2 day window is allowed for Day 1 in subsequent cycles post Cycle 1, Day 1):

- Prior to cabiralizumab and nivolumab infusion (within ≤72 hours unless otherwise stated):
  - Physical examination including weight
  - Vital signs (blood pressure, pulse, respiratory rate, pulse oximetry and temperature in resting position after 5 minutes rest)
  - ECOG performance status evaluation
  - Clinical safety labs (as described in Appendix B; results must be reviewed before dosing)
  - Blood collection for:
    - Serum (analyses described in Appendix D)
    - Whole blood (analyses described in Appendix D)
    - Frozen PBMC (analyses described in Appendix D)
  - AE reporting, if applicable
  - Review of concomitant medications
- Study drug administration: Nivolumab will be given first, with a 30-minute rest, followed by cabiralizumab.
  - Nivolumab administered by IV infusion over 30 minutes (± 5 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 patients for the duration of this study)
    - Post-nivolumab administration during the 30-minute rest:
      - Post-dose vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time point after completion of each IV infusion:
      - 10 (±5) minutes
  - Cabiralizumab administered by 30 minutes IV infusion (± 5 minutes)
    - Post- cabiralizumab administration:
      - Post-dose vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time points after completion of cabiralizumab IV infusion:

- 10 (±5) minutes, 30 (±10) minutes, and 60 (±15) minutes

– Blood collection for serum cabiralizumab PK
  - 15 (±5) minutes

5.2.2.8 End of DLT Period (Phase 1a Dose Escalation cohorts only)

For Phase 1a patients in the combination dose escalation cohorts, if at the end of the DLT period the Investigator determines that the patient may benefit from continued dosing with cabiralizumab and nivolumab, entry into the Extended Treatment Period may be offered.

If the patient continues onto the Extended Treatment Period, proceed to procedures outlined in Section 5.2.2.9.

If the patient does not qualify to receive further study drug, the patient will return to the clinic for the End-of-Treatment Visits outlined in Section 5.2.2.11.

5.2.2.9 Extended Treatment – Subsequent Cycles, Day 1

Phase 1a extended treatment for patients in combination dose escalation cohorts may begin on Cycle 3, Day 1.

At each infusion visit, patients are to remain at the study site after each administration of cabiralizumab and nivolumab until completion of all post-dose assessments for safety monitoring. The following assessments will be performed at each visit unless otherwise noted (Appendix B) (a ± 2 day window is allowed for Day 1 in subsequent cycles post Cycle 1, Day 1):

- Prior to each infusion of study drug (within 72 hours unless otherwise stated):
  - Physical examination including weight
  - Vital signs (blood pressure, pulse, respiratory rate, pulse oximetry and temperature in resting position after 5 minutes rest)
  - ECOG performance status evaluation
  - Clinical safety labs (as described in Appendix B; results must be reviewed before dosing)
  - Collect sample if the patient is being followed for a tumor marker (e.g. CA-125, or others) on Cycle 3 Day 1, then every other cycle after, or as clinically indicated
  - Radiological imaging: CT or MRI scan performed every 8 weeks (± 7 days) from the first dose for the first 12 months for patients who remain on treatment (and every 12 weeks (± 7 days) thereafter) and 28 days (±7 days) after the last dose of study treatment.
  - Serum pregnancy test (β-hCG) for women of childbearing potential on Cycle 5, Day 1, then every 8 weeks (every 4 cycles)
  - Skin and tumor biopsy collection (prior to Cycle 3 only; within 7 days prior to Cycle

3 Day 1 and at least 24 hours prior to dosing; analyses described in Appendix D)

- Optional skin and tumor biopsy for patients who responded to treatment (within 14 days post tumor assessment; for analyses described in Appendix D)
- Blood collection for:
  - Serum (analyses described in Appendix D) as listed below.
    - Cabiralizumab PK for Cycles 3, 4, 5, 8, 9, 13, and 21, then every 6 cycles while on treatment
    - Nivolumab PK for Cycles 3, 4, 5, 8, 9, 13, and 21
    - Cabiralizumab ADA for Cycles 3, 4, 5, 8, 9, 13, and 21, then every 6 cycles while on treatment
    - Nivolumab ADA for Cycles 3, 4, 5, 8, 9, 13, and 21
    - ANA for Cycles 3, 4, 5, 9, 13, and 21, then every 6 cycles while on treatment
    - Selected serum markers for Cycles 3, 4, 5, 8, 9, 13, and 21
    - Cytokine multiplex panel for Cycles 3, 4, 5, 8, 9, 13, and 21
  - Whole blood (for analyses described in Appendix D) as listed below.
    - $CD14^+/CD16^+$ monocytes for Cycles 3, 4, 5, 8, 9, 13, and 21, then every 6 cycles while on treatment
    - Gene expression analysis for Cycles 3, 5, 9, 13, 17, and 21, then every 6 cycles thereafter
    - Frozen PBMC for Cycle 3 (analyses described in Appendix D)
- AE reporting, if applicable
- Review of concomitant medications

- Study drug administration: Nivolumab will be given first, with a 30- to 60-minute rest, followed by cabiralizumab.
  - Nivolumab administered by IV infusion over 30 minutes (± 5 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 patients for the duration of this study)
    - Post-nivolumab administration during the 30- to 60-minute rest:
      - Post-dose vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time point after completion of each IV infusion:
        - 10 (±5) minutes
      - Blood collection for serum (for analyses described in Appendix D) as listed below.
        - 15 minutes (±5 minutes) Nivolumab PK for Cycle 8 only

- Cabiralizumab administered by 30 minutes IV infusion (± 5 minutes)
  - Post- cabiralizumab administration:
    - Post-dose vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time points after completion of cabiralizumab IV infusion:
      - 10 (±5) minutes, 30 (±10) minutes, and 60 (±15) minutes
    - Blood collection for serum (for analyses described in Appendix D) as listed below.
      - Cabiralizumab PK 15 minutes (±5 minutes) for Cycles 3 and 4
      - Cabiralizumab PK 15 minutes (±5 minutes), 4 hours (±60 minutes), 24 hours (±6 hours), 72 hours (±12 hours) and 168 hours (±24 hours) for Cycle 8 only
      - Selected serum markers 72 hours (±12 hours) and 168 hours (± 24 hours) for Cycle 8 only
      - Cytokine multiplex panel 72 hours (±12 hours) and 168 hours (±24 hours) for Cycle 8 only
      - $CD14^+/CD16^+$ monocytes 72 hours (±12 hours) and 168 hours (±24 hours) for Cycle 8 only

5.2.2.10 Cycle 8, Day 15 (Cohort 1aD only)

Patients will return to the study center on Day 15 for 336-hour (± 24 hours) post-dose assessments. No treatment will be administered during this visit, but the following procedures will be performed:

- Physical examination
- Vital signs (blood pressure, pulse, respiratory rate, pulse oximetry and temperature in resting position after 5 minutes rest)
- Clinical safety labs (as described in Appendix B)
- Blood collection for:
  - Serum (cabiralizumab PK)
- AE reporting, if applicable
- Review of concomitant medications

5.2.2.11 End-of-Treatment Follow-up Period

Patients will return to the study center twice, approximately 28 (±7) days, followed by a subsequent visit 100 (±7) days after their last infusion of cabiralizumab and nivolumab, to complete the End-of Treatment Follow-up Period.

The following assessments will be performed:

- Physical examination including weight
- Vital signs (blood pressure, pulse, respiratory rate, pulse oximetry and temperature in resting position after 5 minutes rest)
- ECOG performance status evaluation
- Clinical safety labs (as described in Appendix B)
- 12-lead ECG (28 [±7] days post last infusion of cabiralizumab and nivolumab visit only)
- Radiological imaging: CT or MRI scan does not need to be repeated if performed within 8 weeks prior to the End-of-Treatment Visits or if tumor progression was previously determined.
- Serum pregnancy test (β-hCG) for women of childbearing potential
- Optional skin and tumor biopsy for patients who progressed (28 [±7] days post last infusion of cabiralizumab and nivolumab visit only) (for analyses described in Appendix D)
- Blood collection for:
  - Serum (analyses described in Appendix D)
  - Whole blood ($CD14^+/CD16^+$ monocyte analysis and gene expression analysis)
- AE reporting, if applicable, until 100 (±7) days after the last dose of study drug or until initiation of subsequent anti-cancer therapy. Patients with ongoing SAEs will be followed until resolution or stabilization.
- Review of concomitant medications

5.2.3 Phase 1b Combination Dose Expansion

5.2.3.1 Screening Period (Day –28 to Day 0)

Patients 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 cabiralizumab and nivolumab (unless otherwise stated). To determine if the patient meets all inclusion criteria and does not violate any exclusion criteria, the following procedures will be performed (Appendix B):

- Written, signed informed consent must be collected prior to any study-specific procedures

- If available, collect an FFPE tissue block or 10 slides of archival tumor sample
- Complete medical and disease history including prior HPV status
- Demographic and baseline characteristics
- Complete physical examination including height and weight
- Vital signs (blood pressure, pulse, respiratory rate, pulse oximetry and temperature in resting position after 5 minutes rest;)
- ECOG performance status evaluation
- Screening labs (as described in Appendix B)
- Clinical safety labs (as described in Appendix B)
- Collect sample if the patient is being followed for a tumor marker (e.g. CA-125, or others)
  - CA-125 is required for cohort 1b5
- 12-lead ECG (required at screening, and if clinically indicated during the study)
- Radiological imaging: CT or MRI to be performed within 28 days prior to Cycle 1 Day 1. If the MRI is performed as part of the patient's standard of care within 28 days of Cycle 1 Day 1, it does not need to be repeated if documentation of the results is provided and is adequate for RECIST v 1.1.
- Serum pregnancy test (β-HCG) for women of childbearing potential
- Optional tumor biopsy collection (at least 24 hours prior to dosing; analyses described in Appendix D)
- SAE reporting, if applicable
- Document prior and concomitant medications

5.2.3.2 Cycle 1, Day 1

The following procedures will be performed:

- Prior to cabiralizumab and nivolumab infusion (within 72 hours unless otherwise stated):
  - Verification of eligibility
  - Update medical and disease history to capture any changes from screening
  - Physical examination including weight
  - Vital signs (blood pressure, pulse, respiratory rate, pulse oximetry and temperature in resting position after 5 minutes rest)
  - ECOG performance status evaluation

  - Clinical safety labs (as described in Appendix B; results must be reviewed before dosing)
  - Collect sample if the patient is being followed for a tumor marker (e.g. CA-125, or others)
    - CA-125 is required for cohort 1b5
  - Serum pregnancy test (β-hCG) for women of childbearing potential
  - Blood collection for:
    - Serum (analyses described in Appendix D)
    - Whole blood (analyses described in Appendix D)
    - Frozen PBMC (analyses described in Appendix D)
  - AE reporting, if applicable
  - Review of concomitant medications
- Study drug administration: Nivolumab will be given first, with a 30- to 60-minute rest, followed by cabiralizumab.
  - Nivolumab administered by IV infusion over 30 minutes (± 5 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 patients for the duration of this study)
    - Post-nivolumab administration:
      - Post-dose vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time point after completion of each IV infusion:
        - 10 (±5) minutes
      - Blood collection for serum nivolumab PK
        - 15 minutes (± 5 minutes)
      - Cabiralizumab administered by 30 minutes IV infusion (± 5 minutes)
    - Post- cabiralizumab administration:
      - Post-dose vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time points after completion of cabiralizumab IV infusion:
        - 10 (±5) minutes, 30 (±10) minutes, and 60 (±15) minutes
      - Blood collection for serum cabiralizumab PK
        - 15 minutes (± 5 minutes)
        - 4 hours (± 60 minutes)

5.2.3.3 Cycle 1, Day 2

Patients will return to the study center on Day 2 for 24-hour (± 6 hours) post-dose assessments. No treatment will be administered during this visit, but the following assessments will be completed:

- Blood collection for:
  - Serum (cabiralizumab PK)
- AE reporting, if applicable
- Review of concomitant medications

5.2.3.4 Cycle 1, Day 4

Patients will return to the study center on Day 4 for 72-hour (± 12 hours) post-dose assessments. No treatment will be administered during this visit, but the following assessments will be completed:

- Blood collection for:
  - Serum (cabiralizumab PK only)
  - Whole blood (gene expression analyses only)
- AE reporting, if applicable
- Review of concomitant medications

5.2.3.5 Cycle 1, Day 8

Patients will return to the study center on Day 8 for 168-hour (± 24 hours) post-dose assessments. No treatment will be administered during this visit, but the following assessments will be completed:

- Physical examination
- Vital signs (blood pressure, pulse, respiratory rate, pulse oximetry and temperature in resting position after 5 minutes rest;)
- Clinical safety labs (as described in Appendix B)
- Blood collection for:
  - Serum (cabiralizumab PK)
  - Whole blood ($CD14^+/CD16^+$ monocyte and gene expression analyses)
  - Frozen PBMC (analyses described in Appendix D)
- AE reporting, if applicable
- Review of concomitant medications

5.2.3.6 Cycle 2, Day 1

The following procedures will be performed (a ± 2 day window is allowed for Day 1 in subsequent cycles post Cycle 1, Day 1):

- Prior to cabiralizumab and nivolumab infusion (within ≤72 hours unless otherwise stated):
  - Physical examination including weight
  - Vital signs (blood pressure, pulse, respiratory rate, pulse oximetry and temperature in resting position after 5 minutes rest)
  - ECOG performance status evaluation
  - Clinical safety labs (as described in Appendix B; results must be reviewed before dosing)
  - Blood collection for:
    - Serum (analyses described in Appendix D)
    - Whole blood (analyses described in Appendix D)
    - Frozen PBMC (analyses described in Appendix D)
  - AE reporting, if applicable
  - Review of concomitant medications
- Study drug administration: Nivolumab will be given first, with a 30- to 60-minute rest, followed by cabiralizumab.
  - Nivolumab administered by IV infusion over 30 minutes (± 5 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 patients for the duration of this study)
    - Post-nivolumab administration during the 30- to 60-minute rest:
      - Post-dose vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time point after completion of each IV infusion:
        - 10 (±5) minutes
  - Cabiralizumab administered by 30 minutes IV infusion (± 5 minutes)
    - Post- cabiralizumab administration:
      - Post-dose vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time points after completion of cabiralizumab IV infusion:
        - 10 (±5) minutes, 30 (±10) minutes, and 60 (±15) minutes

  - Blood collection for serum cabiralizumab PK
    - 15 minutes (± 5 minutes)

5.2.3.7 Cycle 3 and Subsequent Cycles, Day 1

At each infusion visit, patients are to remain at the study site after each administration of cabiralizumab and nivolumab until completion of all post-dose assessments for safety monitoring. The following assessments will be performed at each visit unless otherwise noted (Appendix B) (a ± 2 day window is allowed for Day 1 in subsequent cycles post Cycle 1, Day 1):

- Prior to each infusion of study drugs (within ≤72 hours unless otherwise stated):
  - Physical examination including weight
  - Vital signs (blood pressure, pulse, respiratory rate, pulse oximetry and temperature in resting position after 5 minutes rest)
  - ECOG performance status evaluation
  - Clinical safety labs (as described in Appendix B; results must be reviewed before dosing)
  - Collect sample if the patient is being followed for a tumor marker (e.g. CA-125, or others) on Cycle 3 Day 1, then every other cycle after, or as clinically indicated
    - CA-125 is required for cohort 1b5
  - Radiological imaging: CT or MRI scan performed every 8 weeks (± 7 days) from the first dose for the first 12 months for patients who remain on treatment (and every 12 weeks (± 7 days) thereafter) and 28 days (± 7 days) after the last dose of study treatment.
  - Serum pregnancy test (β-hCG) for women of childbearing potential on Cycle 5, Day 1, then every 8 weeks (every 4 cycles)
  - Optional tumor biopsy collection (prior to Cycle 3 only; within 7 days prior to Cycle 3 Day 1 and prior to 24 hours of dosing; analyses described in Appendix D)
  - Optional tumor biopsy for patients who responded to treatment (within 14 days post tumor assessment; for analyses described in Appendix D)
  - Blood collection for:
    - Serum (analyses described in Appendix D) as listed below.
      - Cabiralizumab PK for Cycles 3, 4, 5, 8, 9, 13, and 21, then every 6 cycles while on treatment
      - Nivolumab PK for Cycles 3, 4, 5, 8, 9, 13, and 21
      - Cabiralizumab ADA for Cycles 3, 4, 5, 9, 13, and 21, then every 6 cycles while on treatment
      - Nivolumab ADA for Cycles 3, 4, 5, 8, 9, 13, and 21

  - ANA for Cycles 3, 4, 5, 9, 13, 21, then every 6 cycles while on treatment
  - Selected serum markers for Cycles 3, 4, 5, 9, 13, and 21
  - Cytokine multiplex panel for Cycles 3, 4, 5, 8, 9, 13, and 21
- Whole blood (analyses described in Appendix D) as listed below.
  - $CD14^{+}/CD16^{+}$ monocytes for Cycles 3, 4, 5, 8, 9, 13, and 21, then every 6 cycles while on treatment
  - Gene expression analysis for Cycles 3, 5, 9, 13, and 21, then every 6 cycles while on treatment
  - Frozen PBMC for Cycle 3 only (analyses described in Appendix D)
- AE reporting, if applicable
- Review of concomitant medications

- Study drug administration: Nivolumab will be given first, with a 30- to 60-minute rest, followed by cabiralizumab.
  - Nivolumab administered by IV infusion over 30 minutes (± 5 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 patients for the duration of this study)
    - Post-nivolumab administration during the 30- to 60-minute rest:
      - Post-dose vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time point after completion of each IV infusion:
        - 10 (±5) minutes
      - Blood collection for serum (for analyses described in Appendix D) as listed below.
        - 15 minutes (±5 minutes) nivolumab PK for Cycle 8 only
  - Cabiralizumab administered by 30 minutes IV infusion (± 5 minutes)
    - Post cabiralizumab administration:
      - Post-dose vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest) at the following time points after completion of cabiralizumab IV infusion:
        - 10 (±5) minutes, 30 (±10) minutes, and 60 (±15) minutes
      - Blood collection for serum (for analyses described in Appendix D) as listed below.
        - Cabiralizumab PK 15 minutes (±5 minutes) for Cycles 3 and 4
        - Cabiralizumab PK 15 minutes (±5 minutes), 4 hours (±60 minutes), 24 hours (±6 hours), 72 hour (±12 hours) and 168 hours (±24 hours) Cycle 8 only

- Selected serum markers 72 hours (±12 hours) and 168 hours (± 24 hours) for Cycle 8 only
- Cytokine multiplex panel 72 hours (±12 hours) and 168 hours (±24 hours) for Cycle 8 only
- $CD14^+/CD16^+$ monocytes 72 hours (±12 hours) and 168 hours (±24 hours) for cycle 8 only

5.2.3.8 End-of-Treatment Follow-up Period

Patients will return to the study center twice, approximately 28 (±7) days and 100 (±7) days after their last infusion of cabiralizumab and nivolumab to complete the End-of-Treatment Follow-up Period.

The following assessments will be performed:

- Physical examination including weight
- Vital signs (blood pressure, pulse, respiratory rate, pulse oximetry and temperature in resting position after 5 minutes rest)
- ECOG performance status evaluation
- Clinical safety labs (as described in Appendix B)
- 12-lead ECG (28 [±7] days post last infusion of cabiralizumab and nivolumab visit only)
- Collect sample if the patient is being followed for a tumor marker (e.g. CA-125, or others)
  - CA-125 is require for cohort 1b5
- Radiological imaging: CT or MRI scan does not need to be repeated if performed within 8 weeks prior to the End-of-Treatment Visits or if tumor progression was previously determined.
- Serum pregnancy test (β-hCG) for women of childbearing potential
- Optional tumor biopsy for patients who progressed (28 [±7] days post last infusion of cabiralizumab and nivolumab visit only) (analyses described in Appendix D)
- Blood collection
  - Serum (analyses described in Appendix D)
  - Whole blood ($CD14^+/CD16^+$ monocyte analysis and gene expression analysis)
- AE reporting, until 100 (±7) days after the last dose of study drug or until initiation of subsequent anti-cancer therapy. Patients with ongoing SAEs will be followed until resolution or stabilization.
- Review of concomitant medications

5.2.4 Long-Term Follow-up for All Patients

Patients should continue onto Long-Term Follow-up after completing the End-of-Treatment Follow-up Period.

Patients will be followed every 12 (±2) weeks for survival, or more frequently as needed. Patients who discontinue treatment while showing clinical benefit (complete response [CR], partial response [PR], or stable disease [SD]) should have tumor assessments during these visits for duration of response.

Long-Term Follow-up for survival may be conducted by telephone, rather than by an in-person visit, once tumor progression is determined or use of subsequent anti-cancer therapy has been initiated.

During the Long-Term Follow-up Period, if the patient undergoes local therapy (e.g., resection, radiation) or new systemic therapy is initiated, this should be documented. Patients should be followed until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor.

5.3 Study Assessments

5.3.1 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status (Appendix I), ECG, blood pressure, heart rate, temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen, if applicable) within 28 days prior to first dose.

Safety assessments including serum hematology, chemistry, ECOG, weight and other assessments including ECG (if clinically indicated) will be done as part of standard care during each visit prior to dosing as noted in Appendix A, Appendix B, and Appendix C. Serum chemistry labs will be checked at screening and any abnormalities outside of the normal range will be followed closely with evaluation of symptoms and follow-up laboratory data. Patients will also be monitored for any infusion-related AEs during dosing and followed up accordingly based on protocol guidelines. Pre-medications including steroids, antihistamines or other treatments will be given prior to future dosing if a patient develops infusion reactions per protocol guidelines.

Any patient who has received study drug will be evaluated for safety. Toxicity assessments will be continuous during the treatment phase and End-of-Treatment Follow-up Period clinic visits. Once patients reach the Long-Term Follow-up Period (and tumor progression has been determined or use of subsequent anti-cancer therapy has been initiated), documented telephone calls or email correspondence to assess the patient's status are acceptable.

AEs and laboratory values will be graded according to the NCI CTCAE v 4.03.

Oxygen saturation by pulse oximetry at rest (also the amount of supplemental oxygen, if applicable) should be assessed at each on-study visit prior to dosing. If a patient shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (e.g. dyspnea, cough, fever) consistent with possible pulmonary AEs, the patient should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management table in Appendix G.

Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious AE or SAE page.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (e.g., suspected drug-induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed stable.

Additional testing or assessments may be performed as clinically necessary or as required by institutional or local regulations.

5.3.2 Efficacy Assessments

5.3.2.1 Primary Efficacy Parameters

The primary efficacy parameter is the objective response rate (ORR; number of patients with confirmed response of CR or PR, divided by the total number of patients who are evaluable for a response). Tumor response status will be assessed using RECIST v1.1 by investigator review.

An Independent Radiology Facility will also be established to evaluate imaging data of trial subjects in a central and independent fashion. Board-certified radiologists will determine radiographic response and/or progression following enrollment in according to RECIST v1.1 and/or RANO for Cohort 1b7. Response assesssments by independent review will be a secondary endpoint.

5.3.2.1.1 Tumor Assessment

Tumor assessments will be performed at Screening (within 28 days prior to first dose), then every 8 weeks (± 7 days) from the first dose, for the first 12 months, and then every 12 weeks (±7 days) thereafter. All patients should have tumor response parameters assessed at the End-of-Treatment visit unless a tumor assessment has been performed within 8 weeks prior to an End-of-Treatment Visit or if tumor progression was previously determined. Patients who enter Long-Term Follow-up while showing clinical benefit should have tumor assessments every 12 weeks (±7 days) for duration of response. The same measuring modality should be preferably used by the site to maintain consistency across the study.

Response will be evaluated using RECIST v1.1 for measurable disease. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated both by clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study. These assessments will follow the same schedule as the radiological assessments.

5.3.2.2 Additional Efficacy Parameters

Additional efficacy parameters may include the following: Overall Survival (OS, 1-year OS, and median OS), progression-free survival (PFS), and duration of response (DOR) for those patients with confirmed responses, based on RECIST v 1.1.

CT or MRI will be performed at screening, during treatment, and at the End-of-Treatment Visit per protocol. Measurements of change in tumor burden must be reviewed and documented after each measurement.

5.3.2.3 Tumor Biopsy or Fresh Tumor Tissue Collection

Biopsy at the primary tumor site or metastatic site will be collected at screening (at least 24 hours prior to dosing) and also on-treatment (prior to Cycle 3, Day 1, within 7 days prior to Cycle 3 Day 1 and at least 24 hours prior to dosing) for all Phase 1a patients and 10 patients per cohort in Phase 1b (optional for patients in the GBM cohort). Patients may also have on-treatment biopsy upon documented tumor response and post-treatment biopsy upon documented tumor progression. The post-response and post-progression biopsies will be optional for patients in Phase 1a and Phase 1b (Appendix E). If available, tumor tissue obtained from post-treatment procedures such as surgery may also be collected.

Biopsied lesions may become inflamed, bleed, or change dimensions, which could result in inaccurate tumor measurements. Therefore, it is recommended not to use the biopsied lesion as a target lesion when assessing the response by RECIST v 1.1 criteria.

5.3.2.4 Skin Biopsy Tissue Collection

Skin Biopsy will be collected at screening (at least 24 hours prior to dosing) and on-treatment (prior to Cycle 3, Day 1, within 7 days prior to Cycle 3 Day 1 and at least 24 hours prior to dosing) for all Phase 1a patients. Patients may also have on-treatment skin biopsy upon documented tumor response and post-treatment skin biopsy upon documented tumor progression. The post-response and post-progression skin biopsies will be optional for patients in Phase 1a (Appendix E). It is recommended to biopsy in an area of skin that is devoid of disease (e.g. inflammation, rash, urticaria).

5.3.3 Pharmacokinetic Assessments

Blood samples for the PK evaluation of both cabiralizumab and nivolumab will be collected from all patients.

Patients enrolled in Phase 1a and Phase 1b will have blood drawn for measurement of serum cabiralizumab concentration. Blood samples will be collected during Cycle 1 and Cycle 8 on Days 1, 2, 4, and 8 as well as both before and after infusion for Cycle 2, 3 and 4. In addition, blood samples will be collected before the infusion on Cycles 5, 9, 13, and 21, then every 6 cycles while on treatment. A blood sample will also be collected for PK analysis during the End-of-Treatment Follow-up Period (28 [±7] days and 100 [±7] days post-last dose).

Patients enrolled in the 3-week dosing regimen cohort (1aD) will have additional blood sample drawn on Day 15 of Cycles 1 and 8. See Appendix C for specific collection time points.

Patients enrolled in Phase 1a and Phase 1b combination cohorts will have blood drawn for measurement of serum nivolumab concentration. Blood samples will be collected both before and at the end of infusion for Cycle 1 to Cycle 4. In addition, blood samples will be collected at the end of the infusion for Cycle 8 and before the infusion on Cycles 5, 9, 13, and 21. A blood sample will also be collected during the End-of-Treatment Follow-up Period.

Standard PK parameters will be determined based on serum cabiralizumab concentration-time data, as appropriate. Nivolumab accumulation will be evaluated as appropriate.

5.3.3.1 Pharmacokinetic Collection and processing

Blood samples will be collected and processed for serum according to the instructions provided in a Laboratory Manual.

5.3.3.2 Pharmacokinetic Sample Analysis

Cabiralizumab concentration in serum will be determined in serum using a validated ELISA method. Nivolumab concentration in serum will be determined in serum using a validated ECLA method.

5.3.4 Immunogenicity Assessments

Blood samples will be collected before the infusion on Cycles 1, 2, 3, 4, 5, 9, 13, and 21, and at the 28 (±7) days and 100 (±7) days End-of-Treatment Visits to measure ADA for cabiralizumab and nivolumab. ADA for cabiralizumab in serum will be measured by a validated bridging ECLA that utilizes Meso Scale Discovery (MSD) technology. ADA for nivolumab in serum will be measured by a validated ECLA method.

5.3.5 Biomarker Assessments

A variety of factors that could potentially predict clinical response to the combination of cabiralizumab and nivolumab will be investigated in peripheral blood and in tumor specimens

collected from patients prior to and during treatment. Data from these investigations will be evaluated for associations with response and/or safety (AE) data. In addition, analyses of markers between the treatment arms will provide the necessary data to identify and validate biomarkers with predictive vs prognostic value. Complete instructions on the collection, processing, handling and shipment of all samples described herein will be provided in a Laboratory Manual.

5.3.5.1 Skin Tissue and Tumor Tissue Specimens

Tumor tissue specimens in the form of a paraffin embedded block or unstained slides will be submitted for central IHC assessment. These biopsy samples should be excisional, incisional or core needle as fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses. Tissue samples are being collected to evaluate the PD effect of study drugs on the tumor microenvironment. [redacted]

Skin and tumor biopsy specimens will be obtained before treatment and on-treatment to examine immune infiltrates and expression of selected tumor markers. Optional skin and tumor biopsies may be obtained upon documentation of tumors that have responded and/or progressed on or after treatment to understand mechanisms of resistance.

Samples may be assessed for the expression of immune or disease related genes and/or proteins, as well as for the presence of immune cell populations using a variety of methodologies including but not limited to IHC, qRT-PCR, genetic mutation detection, and *in situ* hybridization (ISH). Other methods of tumor biomarker expression are being evaluated.

5.3.5.2 Serum

[redacted] n addition to the PK and ADA analyses mentioned above, serum samples will be analyzed to determine the PD effect of study drugs on cytokine and CSF1R ligand concentrations. Samples may be assessed by ELISA, seromics, and/or other relevant multiplex-based protein assay methods. Serum marker analyses may also help establish a biomarker signature that may predict benefit or correlate with efficacy that can be used to inform this and future studies. Timings of sample collection are listed in Appendix C and analyses to be performed are described in Appendix D.

[redacted]

[redacted]

5.3.5.4 Flow Cytometry

Pre-treatment and on-treatment whole blood and PBMC samples will be analyzed by flow cytometry to study the effects of cabiralizumab and nivolumab on various peripheral blood immune cell subsets. Whole blood samples will be assessed to confirm the predicted PD effect of cabiralizumab on the reduction of $CD16^+$ monocytes. PBMC samples will be analyzed to determine whether blockade of PD-1 combined with CSF1R targeting will impact peripheral T-cell levels and activation status. [redacted] Timing of sample collection is listed in Appendix C and analyses to be performed are described in Appendix D.

[redacted]

6. Adverse Events

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation, patient-administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by an investigator and should be used to assess all AEs. The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient. (In order to prevent reporting bias, patients should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Collection of Adverse Events

Any new symptoms, injury or worsening of symptoms that occur following signing of the informed consent form (ICF) but prior to first infusion (Cycle 1 Day 1) will be considered pretreatment events and reported on the Medical History page of the electronic case report form (eCRF), unless they directly correlate to a study-related procedure. Adverse event reporting will continue until 100 (±7) days after the last dose of study drug or until initiation of subsequent anti-cancer therapy.

6.2 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- Results in death. Death may occur as a result of the underlying disease process. All events other than progression of underlying disease that result in death during the reporting period up to 100 (±7) days after the last dose of cabiralizumab (or until initiation of subsequent anti-cancer therapy) must be treated as an SAE and reported as such.
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 6.7 for the definition of potential DILIs.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.2.1 for reporting pregnancies).

Note: The following hospitalizations are not considered SAEs in this clinical study:

- Visit to the emergency room or other hospital department <24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., outine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anti-cancer therapy in the absence of any other SAEs
- Hospitalization for an event solely related to disease progression or for an elective or planned procedure to treat a pre-existing condition
- Admission to hospice or care facility to support activities of daily living

6.2.1 Serious Adverse Event Reporting

The Investigator should report any SAE that occurs after the first study drug dose and until 100 (±7) days after the last dose of study drug or until initiation of subsequent anti-cancer therapy. Protocol-specified procedure related SAE will be collected following signing of ICF.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the Investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

- SAEs, related or unrelated to study drug, and pregnancies must be reported to the Sponsor (or designee) within 24 hours of becoming aware of the event. SAEs must be recorded on the SAE Report Form, and pregnancies must be recorded on a Pregnancy Surveillance Form (paper forms). SAE and pregnancy data reporting must be done on the paper SAE/Pregnancy Surveillance Forms provided by the Sponsor (or designee). They are to be transmitted via email or fax [redacted]

If only limited information is initially available, follow-up reports are required.

***Note*:** Follow-up SAE reports should include the same Investigator term(s) initially reported.

If an ongoing SAE changes in intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the Sponsor (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.3 Non-Serious Adverse Events

A ***non-serious adverse event*** is any AE not classified as serious.

6.3.1 Non-serious Adverse Event Reporting

Non-serious AEs should also be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.2.1). Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end-of-study treatment, as appropriate. All identified non-serious AEs must be recorded and described on the appropriate AE page of the CRF.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported during the course of the study.

6.4 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the appropriate CRF page or SAE Report Form as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the patient to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the patient to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting Investigator (e.g., anemia versus low hemoglobin value).

6.5 Pregnancy

If, following initiation of the investigational product, it is discovered that a study patient is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives (90 days) after product administration, the investigational product will be permanently discontinued in an appropriate manner.

The Investigator must immediately notify the Sponsor's (or designee's) Medical Monitor of this event and complete and forward a Pregnancy Form to the Sponsor (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.2.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.6 Overdose

Any dose of study drug in excess of 50% of the dose level specified in the protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as an SAE in the appropriate time frame and documented as clinical sequelae to an overdose. There is no known antidote for a drug overdose to either cabiralizumab or nivolumab. In the event of an overdose, patients should be closely monitored and given appropriate supportive treatment.

6.7 Potential Drug Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

1. ALT or AST elevation >3x ULN

   and

2. Total bilirubin >2x ULN without initial findings of cholestasis (elevated serum alkaline phosphatase) ***or*** INR > 1.5 xULN (in the absence of anticoagulation)

   and

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia including but not limited to viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drugs known to be hepatotoxic.

7. Statistical Considerations

All analyses will be descriptive and will be presented by dose group and overall as appropriate. Data collected in this study will be presented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages.

7.1 Sample Size Determination

Approximately 85 patients will be enrolled in Phase 1a. In dose escalation, between 3 and 9 patients are expected to be treated at each dose escalation cohort according to the algorithm outlined in Table 2 . There will also be up to 40 patients enrolled into the exploratory dose cohorts to further explore safety, PK, and PD, and approximately 10 patients enolled 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 patients will be enrolled.

7.2 Populations for Analyses

- Enrolled Population: 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.
- Evaluable Population: Patients who have a measureable lesion at baseline and have at least 1 post-baseline tumor assessment or patients with the clinical progression or experiencing death event without any post baseline tumor assessment.
- Safety Population: All patients who receive at least one dose of cabiralizumab and/or nivolumab.
- PK Population: All patients who receive at least one dose of cabiralizumab and/or nivolumab and have available serum concentration data.
- Biomarker Patients: All patients who receive at least one dose of cabiralizumab and/or nivolumab and have available biomarker data.
- Immunogenicity Patients: All patients who receive at least one dose of cabiralizumab and/or nivolumab and have available ADA data.

7.3 Endpoints

7.3.1 Phase 1a Endpoints

7.3.1.1 Primary

- 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

7.3.1.2 Secondary

- **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 Cmax and Cmin for nivolumab may be caculated 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})
- **Immunogenicity:** Defined as an immune response to either cabiralizumab or nivolumab, will be assessed by measurement of total anti-FPA008 antibodies and total anti-nivolumab antibodies from all patients. Immunogenicity testing will consist of screening, confirmation, and titration for both cabiralizumab and nivolumab.
- 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

[redacted]

7.3.2 Phase 1b Endpoints

7.3.2.1 Primary

- Efficacy
  - ORR will be defined as the total number of patients with confirmed responses of either CR or PR divided by the total number of patients who are evaluable for a response per RECIST v1.1 by investigator assessment

- Safety
  - The incidence of AEs, 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

7.3.2.2 Secondary

- **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 caculated 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})
- **Immunogenicity:** Defined as an immune response to either cabiralizumab or nivolumab, will be assessed by measurement of total anti-FPA008 antibodies and total anti-nivolumab antibodies from all patients. Immunogenicity testing will consist of screening, confirmation, and titration for both cabiralizumab and nivolumab. The results will be classified into incidence of ADA at baseline and after 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
- Efficacy
  - OS will be defined as the time between the first dose of study drug and death.
    - One-year OS rate
    - Median OS
  - DOR will be defined as the time from response (CR or PR) until the first objectively documented PD per RECIST v1.1
  - PFS will be defined for each patient as the time from the first dose to the first objectively documented of disease progression per RECIST v1.1 or death due to any cause.

– ORR by Central Imaging Review

7.4 Analyses

7.4.1 Demographics and Baseline Characteristics

Demographic data, medical history, other baseline characteristics, concomitant disease, and concomitant medication will be summarized by cohort and overall. To determine whether the criteria for study conduct are met, corresponding tables and listings will be provided. These will include an assessment of protocol deviations, study drug accountability, and other data that may impact the general conduct of the study.

7.4.2 Efficacy Analyses

For each disease type, response to treatment will be summarized for ORR, defined as the ratio of the number of patients that achieve an objective response (a BOR of CR or PR) to total number of patients who are evaluable for a response. Exact confidence interval will be constructed for the response rate. Overall Survival, survival at 1 year, and median survival will be estimated by the Kaplan-Meier method. The corresponding confidence interval will also be presented.

7.4.3 Safety Analyses

Safety analyses will be performed for patients included in the safety population. Incidence of AEs, clinical laboratory information, vital signs, ECOG performance status, weight, and ECGs will be tabulated and summarized.

Incidence of AEs will be summarized overall and with separate summaries for SAEs, AEs leading to discontinuation, AEs leading to death, and NCI-CTCAE v 4.03 Grade 3 or higher AEs.

Weight and vital signs will be summarized descriptively (n, mean, standard deviation, median, minimum, and maximum). ECOG performance status will be summarized categorically and descriptively.

Shift tables displaying patient counts and percentages classified by baseline grade and maximum grade on treatment will be provided for laboratory data by cohort and overall. A marked laboratory change is defined as a shift from a baseline Grade 0 to Grade 3 (non-hematologic) or

Grade 4 (hematologic) on treatment, or a shift from a baseline Grade 1 to Grade 4 on treatment. The number and percentage of patients with marked laboratory changes will be tabulated by cohort and overall.

7.4.4 Pharmacokinetic Analyses

Individual and mean serum concentration of cabiralizumab and nivolumab versus time data will be plotted by dose level. Summary statistics will be tabulated for the serum concentration-time data and estimated PK parameters of cabiralizumab, as appropriate.

For cabiralizumab, PK parameters including C_{max}, AUC, C_{min}, CL, and V_{ss} will be estimated. Other PK parameters as well as inter-patient variability, cabiralizumab accumulation, and dose proportionality will be evaluated when data are available. Nivolumab accumulation will be evaluated as appropriate. PK data (cabiralizumab and/or nivolumab) collected from this study may be used in combination with other studies for exposure-response or population PK modeling, which will be part of a separate report.

7.4.5 Immunogenicity

A listing will be provided of all available immunogenicity data for both cabiralizumab and nivolumab. Additionally, a listing of immunogenicity data from those patients with at least one positive ADA at any time point will be provided by dose level. The frequency of patients with at least one positive ADA assessment, and frequency of patients who develop ADA after a negative baseline assessment will be provided by dose. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status. Associations between pre-dose concentrations of cabiralizumab or nivolumab and corresponding ADA assessments may be explored.

[redacted]

[redacted]

[redacted]

7.5 Interim Analysis

No formal interim analysis is planned.

The Sponsor (and/or designee) and Investigators will review safety data from each dose cohort prior to dose escalation or de-escalation. In addition, an interim data summary may be performed at several times prior to completion of the study in order to facilitate program decisions and to support presentations or publications.

8. Cohort Review Committee

The Cohort Review Committee will consist of representatives from the Sponsor, contract research organization (CRO), as well as one or more designated Investigators from actively participating sites in which cabiralizumab and nivolumab are being evaluated. During Phase 1a, the Cohort Review Committee will assess safety of the study prior to making dose escalation decisions. The Cohort Review Committee will provide guidance on the continuation of the study including the escalation or de-escalation of dose levels. The committee members will review relevant data including AEs, SAEs, laboratory values, and other information. All correspondence during the cohort review meeting will be documented along with any decisions for further expansion, escalation, or discontinuation at the current dose level.

9. Ethical Considerations

9.1 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by GCP guidelines of the ICH and the [redacted] The study also will be carried out in compliance with local legal requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the Informed Consent Form (ICF) will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

9.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, ICF, patient recruitment materials (e.g., advertisements), and any other written information to be provided to patients. The Investigator or Sponsor should also provide the IRB/IEC with a copy of the IB or product labeling information to be provided to patients and any updates.

The Investigator should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

9.3 Informed Consent

All information about the clinical study, including patient information and the ICF, is prepared and used for the protection of the human rights of the patient according to ICH GCP guidelines and the [redacted]

The ICF, prepared by the Investigator with the assistance of the Sponsor, must be approved along with the study protocol by the IEC/IRB and be acceptable to the Sponsor. Before each patient is enrolled on the study, written informed consent will be obtained according to the regulatory and legal requirements. A copy of the signed ICF will be retained by the patient and the original will be filed in the Investigator's site file, unless otherwise agreed. The Investigator

will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must be documented in the source documents and in the CRF.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IRB/IEC, and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

All signed and dated ICFs must remain in each patient's study file and must be available for verification by study monitors at any time.

The rights, safety, and well-being of the patients are the most important considerations and should prevail over interests of science and society.

10. Study Management

10.1 Compliance

10.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, the Sponsor. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to Patients.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Sponsor
- Regulatory Authorities, if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to the Sponsor.

If an amendment substantially alters the study design or increases the potential risk to the patient: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from patients currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new patients prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

10.1.2 Monitoring

During the study, a monitor will perform routine site visits to review protocol compliance, compare CRFs and individual patients' medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. CRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Representatives of the Sponsor will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

All participating centers should take particular care in ensuring that original imaging source data (images, echo images, etc.) are maintained and accessible for monitoring, and that these original source data are then archived on a long-term basis in compliance with ICH GCP

(Section 10.2.1). These images must be stored in a secure location until the Sponsor (or designee) authorizes their destruction, and must be retrievable by study patient number in the event of an audit.

10.1.2.1 Source Documentation

All data obtained during this study should be entered into the CRFs promptly. All source documents from which CRF entries are derived should be placed in the patient's medical records. CRF fields for which source documents will typically be needed include laboratory assessments, physical exam reports, nursing notes, ECG recordings, hospital records, and CT or MRI reports.

The CRFs for each patient will be checked against source documents at the study site by the Site Monitor.

Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

10.1.3 Investigational Site Training

The Sponsor or designee will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, CRFs, study documentation, informed consent, and enrollment of WOCBP.

10.2 Records

10.2.1 Records Retention

The study site will maintain a study file, which should contain, at minimum, the Investigator's Brochure, the protocol and any amendments, the protocol for tissue sampling, drug accountability records, correspondence with the IEC/IRB and the Sponsor (or designee), and other study-related documents.

The Investigator agrees to keep records and those documents that include but are not limited to the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and FivePrime or its designees.

The Investigator shall retain records required to be maintained for a period of 5 years following the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulations or if needed by the Sponsor. In addition, the Investigator must make provision for the patients' medical records to be kept for the same period of time.

No data should be destroyed without the agreement of FivePrime. Should the Investigator wish to assign the study records to another party or move them to another location, FivePrime must be notified in writing of the new responsible person and/or the new location.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

10.2.2 Study Drug Records

It is the responsibility of the Investigator to ensure that a current disposition record of each study drug (supplied by FivePrime) is maintained at each study site where study drugs are inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- Amount received and placed in storage area
- Amount currently in storage area
- Label identification number or batch number
- Amount dispensed to and returned by each patient, including unique patient identifiers
- Non-study disposition (e.g., lost, wasted)
- Amount destroyed at study site, if applicable
- Amount returned to designated parties
- Dates and initials of person responsible for Investigational Product dispensing/accountability as per the Delegation of Authority Form.

The Sponsor will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

10.2.2.1 Case Report Forms

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained.

For sites using the electronic data capture tool, eCRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paperSAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the Sponsor.

The confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The Investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper SAE/pregnancy report forms, must be promptly reviewed, signed, and dated by the Investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For eCRFs, review and approval/signature is completed electronically using the Sponsor's electronic data capture tool.

The Investigator must retain a copy of the CRFs including records of the changes and corrections. Each individual electronically signing eCRFs must meet the Sponsor's training requirements and must only access the Sponsor's electronic data capture tool using the unique user account provided by the Sponsor. User accounts are not to be shared or reassigned to other individuals.

12. Appendices

Appendix A: Schedule of Assessments – Phase 1a Cabiralizumab Monotherapy and Combination

Procedure[a]	Screening	Cycle 1					Cycle 2	Cycle x[s]	Cycle 8	End-of-Treatment Follow-up Period	Long-Term Follow-up Period[u]
	Day –28 to Day 0	Day 1[b]	Day 2	Day 4	Day 8	Day 15[c]	Day 1[b]	Day 1[b]	Days 2, 4, 8 (and 15)[c]	28 (±7) days and 100 (±7) days post-last dose	
Informed Consent	x										
Review/Confirm Eligibility Criteria	x	x									
Medical History / Demographics	x	x									
Physical Examination[d]	x	x			x	x[c]	x	x	x[c]	x	
Height and Weight[e]	x	x					x	x		x	
Vital Signs[f]	x	x			x	x[c]	x	x	x[c]	x	
Photo of Periorbital Region	x										
ECOG Performance Status[g]	x	x					x	x		x	
Screening Labs[h]	x										
Clinical Safety Labs[i]	x	x			x	x[c]	x	x	x[c]	x	
12-Lead ECG[j]	x									x	
CT or MRI Tumor Assessment[k,l]	x							x		x	x
Serum Pregnancy Test[m]	x	x						x		x	
Skin and Tumor Biopsy[n]	x							x		x	
PK Sampling[o,p]		x	x	x	x	x[c]	x	x	x	x	
PD Sampling[o]		x		x	x		x	x	x	x	
ADA Sampling[o]		x					x	x		x	
ANA Sampling[q]		x					x	x		x	
Study Drug(s)[r,s]		x					x	x			
Adverse Events	x———									———x	
[redacted]	[redacted]										
Long-Term Follow-up Contact[u]											x

Notes for Phase 1a Schedule of Assessments

a. Unless specified, prior to infusion procedures are to be completed within 72 hours of scheduled time point and to be synchronized with administration of assigned study drug. Any clinical assessment, laboratory study, or additional non-specified tests may be obtained at any time, if clinically indicated.

b. Each cycle will be 14 days long, with administration of cabiralizumab ± nivolumab on Day 1. In Cohort 1aD, each cycle will be 3 weeks long, with administration of cabiralizumab and nivolumab on Day 1. The first day of treatment in Cycle 1 is defined as Day 1; a ± 2 day window is allowed for Day 1 in subsequent cycles.

c. Day 15 Assessments (Physical Examination, Vital Signs and Clinical Safety Lab) will apply to patients in Cohort 1aD only

d. Standard physical examination will be performed as determined by the Investigator, particularly to follow physical findings to resolution. Targeted physical exams should be conducted at any time to follow up on AE reports.

e. Height is only required to be recorded at screening. Weight is required to be recorded at Day 1 of each cycle. Dose will be adjusted only if weight change is >10% from first dose on Cycle 1 Day 1.

f. Vital signs include pulse, respiratory rate, blood pressure, and temperature in the resting position (sitting or supine). Measure prior to dose and after completion of each IV infusion at the following time points: 10 (±5) minutes, 30 (±10) minutes, and 60 (±15) minutes, 168 hours (±24 hours) [Cycle 1 only] post cabiralizumab administration; 10 (±5) minutes post nivolumab administration. Pulse oximetry is performed at rest prior to dosing for the combination cohorts only.

g. Patient ECOG Status assessments are to be performed within 72 hours prior to dosing (Day 1 of each cycle).

h. Screening labs include serology for Hepatitis B (HBsAg), Hepatitis C (HCV antibody), and test for latent TB (e.g. T-SPOT, Quantiferon).

i. Clinical Safety Labs:
Hematology including CBC with differential, platelets, hemoglobin, hematocrit, RBC, and RBC indices
Chemistry includes CK (creatine kinase), AST (aspartate transaminase), ALT (alanine transaminase), alkaline phosphatase, bicarbonate, bilirubin, (direct and total), BUN (blood urea nitrogen), calcium, chloride, creatinine, glucose, LDH (lactate dehydrogenase), phosphorus, potassium, sodium, and, if applicable, serum pregnancy. Albumin, amylase, lipase, thyroid panel includes TSH, Free T3 and Free T4, PT/INR, and PTT (aPTT) perform at Screening and as indicated. If CK elevation is clinically significant, obtain troponins (cardiac and skeletal), CK isoenzymes, aldolase, and ECG; repeat CK and these additional tests within 48 hours or other interval as clinically indicated, until resolved or stable. If either AST or ALT is elevated, obtain total serum bilirubin, alkaline phosphatase; repeat within 48 hours or other interval, as clinically indicated, until resolved or stable. Additional tests may be obtained at any time, if clinically indicated. If a patient is being followed for a tumor marker (e.g. CA-125, or others), a sample for the tumor marker should be obtained at screening and every other cycle, or if clinically indicated during the study
Urinalysis: Urine dipstick will only be done at screening, and when clinically indicated.

j. Obtain ECG records at Screening and the Day 28 post last infusion End-of-Treatment Visit (after PK blood draw, record exact time). Additional ECGs should be obtained at any time, if serum CK or cardiac troponin is elevated; if abnormal (excluding sinus tachycardia), ECGs should be obtained (if clinically indicated), until the abnormality is resolved or clinically stable. Additional ECGs may be obtained at any time, if clinically indicated. ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for at least 5 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

k. CT or MRI of the Tumor sites measured as per Response Evaluation Criteria in Solid Tumors (RECIST v1.1). If patient terminates prior to scheduled CT or MRI scans, patient should have scans done at End-of-Treatment Visits (does not need to be repeated if performed within 8 weeks prior to End-of-Treatment Visits or if tumor progression was previously determined). Patients who enter Long-Term Follow-up while showing clinical benefit should have tumor assessments q12w for duration of response. The same measuring modality should be used by the site to maintain consistency across the various time points. (Documentation of skin lesions by color photography, including a ruler to measure the size of the lesion, is suggested and should follow the CT or MRI schedule.) Brain scans will be required only if CNS metastasis is suspected, based on Investigator clinical judgment (except for patients in cohort 1b7).

l. Performed every 8 weeks (±7 days) from the first dose for the first 12 months for patients who remain on treatment (and every 12 weeks (±7 days) thereafter) and 28 days (± 7 days) after the last dose of study treatment. CT or MRI scans do not need to be repeated if performed within 8 weeks prior to the End-of-Treatment Visits or if tumor progression was previously determined.

m. All women of childbearing potential will have a serum pregnancy test at screening, Cycle 1 Day 1 and every 8 weeks during treatment, and at the End-of-Treatment Visits.

n. Biopsy at primary tumor or metastatic tumor site and skin biopsy from a site devoid of disease (e.g. rash or urticaira) will be collected at screening [at least 24 hours prior to dosing] and prior to Cycle 3 Day 1 [within 7 days prior to Cycle 3 Day 1 and at least 24 hours prior to dosing]. It is recommended that patients who have documented response receive another biopsy within 28 (±14) days post tumor assessment and/or patient who have progression receive another biopsy at the final End-of–Treatment visit. The post-response and post-progression biopsies are optional. If available, collect an FFPE tissue block or 10 slides of archival tumor sample at Screening.

o. Samples will be collected for PK, PD, and ADA analyses. Not all visits will require collection of all three – see Appendix C for collection schedule.

p. Blood will be collected to evaluate Cmax and/or Cmin on Day 1 of study drugs on Cycles 1, 2, 3, 4, 5, 8, 9, 13, 21, then every 6 cycles while on treatment and End-of-Treatment Follow up Period. Cycles 1 and 8 will have additional samples on days 2, 4, and 8 (and day 15 for patients in Cohort 1aD).

q. Antinuclear antibody (ANA) samples will be collected prior to dose at Cycles 1, 2, 3, 4, 5, 9, 13, 21, then every 6 cycles while on treatment and at End-of-Treatment Visits. Additional ANA reflex samples may be collected upon requested or as clinically indicated. Testing by indirect fluorescent antibody (IFA) will be performed as clinically indicated. If the titer is positive, erythrocyte

sedimentation rate (ESR) and C-reactive protein (CRP) will be tested to confirm the result.

r. Cabiralizumab and nivolumab will both be administered by IV infusion over 30 minutes (± 5 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 patients for the duration of this study. Nivolumab will be given first, with a 30- to 60-minute rest, followed by cabiralizumab as a 30-minute infusion.

s. Cabiralizumab ± nivolumab will be administered every 2 weeks in 14-day cycles. Patients in Cohort 1aD, cabiralizumab and nivolumab will be administered every 3 weeks. The dosing may continue until PD or unacceptable toxicity.

t. These assessments are to be performed prior to each dose (with the exceptions noted in Appendix C) for those patients who continue treatment without signs of progressive disease or toxicity.

u. Patients should be contacted every 12 (±2) weeks for survival status. Patients should have tumor scans every 12 (±2) weeks, if tumor progression was not previously determined and/or use of subsequent anti-cancer therapy has not been initiated. Any new anti-cancer therapy should be documented.

Appendix B: Schedule of Assessments – Phase 1b Cabiralizumab + Nivolumab

Procedure[a]	Screening	Cycle 1				Cycle 2	Cycle x[s]	Cycle 8	End-of-Treatment Follow-up Period	Long-Term Follow-up Period[t]
	Day –28 to Day 0	Day 1[b]	Day 2	Day 4	Day 8	Day 1[b]	Day 1[b]	Days 2, 4, 8	28 (±7) days and 100 (±7) days post-last dose	
	Week 0	Week 1			Week 2	Week 3	Week ≥5			
Informed Consent	x									
Review/Confirm Eligibility Criteria	x	x								
Medical History / Demographics	x	x								
Physical Examination[c]	x	x			x	x	x		x	
Height and Weight[d]	x	x				x	x		x	
Vital Signs[e]	x	x			x	x	x		x	
ECOG Performance Status[f]	x	x				x	x		x	
Screening Labs[g]	x									
Clinical Safety Labs[h]	x	x			x	x	x		x	
12-Lead ECG[i]	x								x	
CT or MRI Tumor Assessment[j,k]	x						x		x	x
Serum Pregnancy Test[l]	x	x					x		x	
Tumor Biopsy[m]	x						x		x	
PK Sampling[n,o]		x	x	x	x	x	x	x	x	
PD Sampling[n]		x		x	x	x	x	x	x	
ADA Sampling[n]		x				x	x		x	
ANA Sampling[p]		x				x	x		x	
Study Drugs[q,r]		x				x	x			
Adverse Events	x———								———x	
[redacted]		[redacted]								
Long-Term Follow-up Contacts[t]										x

Notes for Phase 1b Schedule of Assessments

a. Unless specified, prior to infusion procedure are to be completed within 72 hours of scheduled time point and to be synchronized with administration day of cabiralizumab infusion. Any clinical assessment, laboratory study, or additional non-specified tests may be obtained at any time, if clinically indicated.

b. Each cycle will be 14 days long, with administration of cabiralizumab + nivolumab on Day 1. The first day of treatment in Cycle 1 is defined as Day 1; a ± 2 day window is allowed for Day 1 in subsequent cycles.

c. Standard physical examination will be performed, particularly to follow physical findings to resolution. Targeted physical exams should be conducted at any time to follow up on AE reports.

d. Height is only required to be recorded at screening. Weight is required to be recorded at Day 1 of each cycle. Dose will be adjusted only if weight change is >10% from first dose.

e. Vital signs include pulse, respiratory rate, blood pressure, and temperature in the resting position (sitting or supine). Measure prior to dose and after completion of the IV infusion at the following time points: 10 (±5) minutes, 30 (±10) minutes, and 60 (±15) minutes, 168 hours (±24 hours) [Cycle 1 only] post cabiralizumab administration; 10 (±5) minutes post nivolumab administration. Pulse oximetry is performed at rest prior to dosing only.

f. Patient ECOG Status assessments are to be performed within 96 hours prior to dosing (Day 1 of each cycle).

g. Screening labs include serology for Hepatitis B (HBsAg), Hepatitis C (HCV antibody), and test for latent TB (e.g. T-SPOT, Quantiferon)

h. Clinical Safety Labs:
Hematology including CBC with differential, platelets, hemoglobin, hematocrit, RBC, and RBC indices.
Chemistry includes CK (creatine kinase), AST (aspartate transaminase), ALT (alanine transaminase), alkaline phosphatase bicarbonate, bilirubin, (direct and total), BUN (blood urea nitrogen), calcium, chloride, creatinine, glucose, LDH (lactate dehydrogenase), phosphorus, potassium, sodium, and, if applicable, serum pregnancy. Albumin, amylase, lipase, thyroid panel includes TSH, Free T3 and Free T4, PT/INR, and PTT (aPTT) perform at Screening and as indicated, If CK elevation is clinically significant, obtain troponins (cardiac and skeletal), CK isoenzymes, aldolase, and ECG; repeat CK and these additional tests within 48 hours or other interval as clinically indicated, until resolved or stable. If either AST or ALT is elevated, obtain total serum bilirubin, alkaline phosphatase; repeat within 48 hours or other interval, as clinically indicated, until resolved or stable. Additional tests may be obtained at any time, if clinically indicated. If a patient is being followed for a tumor marker (e.g. CA-125, or others), a sample for the tumor marker should be obtained at screening and every other cycle, or if clinically indicated during the study.
Urinalysis: Urine dipstick will only be done at screening, and when clinically indicated.

i. Obtain ECG records at screening and the Day 28 post last infusion End-of-Treatment Visit (after PK/PD blood draw, record exact time). Additional ECGs should be obtained at any time, if serum CK or cardiac troponin is elevated; if abnormal (excluding sinus tachycardia), ECGs should be obtained (if clinically indicated), until the abnormality is resolved or clinically stable. ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for at least 5 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. Additional tests may be obtained at any time, if clinically indicated.

j. CT or MRI of the Tumor sites measured as per Response Evaluation Criteria in Solid Tumors (RECIST v1.1). If patient terminates prior to scheduled CT or MRI scan, patient should have scans done at End-of-Treatment Visits (does not need to be repeated if performed within 8 weeks prior to End-of-Treatment Visits or if tumor progression was previously determined). Patients who enter Long-Term Follow-up while showing clinical benefit should have tumor assessments q12w for duration of response. Response per CT or MRI will be assessed using RECIST v1.1. The same measuring modality should be preferably used by the site to maintain consistency across the various time points. (Documentation of skin lesions by color photography, including a ruler to measure the size of the lesion, is suggested and should follow the CT or MRI schedule.) Brain scans will be required only if CNS metastasis is suspected, based on Investigator clinical judgment (except for patients in cohort 1b7).

k. Performed every 8 weeks (±7 days) from the first dose for the first 12 months for patients who remain on treatment, and every 12 weeks (±7 days) thereafter. CT or MRI scans do not need to be repeated if performed within 8 weeks prior to an End-of-Treatment Visit or if tumor progression was previously determined.

l. All women of childbearing potential will have a serum pregnancy test at screening, Cycle 1 Day 1 and every 8 weeks while on treatment, and at End-of-Treatment Visits.

m. Biopsy at primary tumor or metastatic tumor site will be collected at screening [at least 24 hours prior to dosing] and prior to Cycle 3, Day 1 [within 7 days prior to Cycle 3 Day 1 and at least 24 hours prior to dosing]. It is recommended that patients who have documented response receive another biopsy within 28 (±14) days post tumor assessment and/or patient who have progression receive another biopsy at the 28-days End-of–Treatment visit. The post-response and post-progression biopsies are optional. If available, collect an FFPE tissue block or 10 slides of archival tumor sample at Screening.

n. Samples will be collected for PK, PD, and ADA analyses. Not all visits will require collection of all three – see Appendix C for collection schedule.

o. Blood will be collected to evaluate Cmax and/or Cmin on Day 1 of study drugs on Cycles 1, 2, 3, 4, 5, 8, 9, 13, 21, then every 6 cycles while on treatment and at the End-of-Treatment visits. Cycles 1 and 8 will have additional samples on days 2, 4, 8, and 15 (Cohort 1aD only)

p. Antinuclear antibody (ANA) samples will be collected prior to dose at Cycles 1, 2, 3, 4, 5, 9, 13, 21, then every 6 cycles while on treatment and at End-of-Treatment Visits. Additional ANA reflex samples may be collected upon requested or as clinically indicated. Testing by indirect fluorescent antibody (IFA) will be performed as clinically indicated. If the titer is positive, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) will be tested to confirm the result.

q. Cabiralizumab and nivolumab will both be administered by IV infusion over 30 minutes (± 5 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 patients for the duration of this study. Nivolumab will be given first, with a 30-to 60-minute rest, followed by cabiralizumab as a 30-minute infusion.

r. Cabiralizumab + nivolumab study drug will be administered every 2 weeks in 14-day cycles and will continue until PD or unacceptable toxicity.

s. These assessments are to be performed prior to each subsequent dose (with exceptions noted in Appendix C) for patients who continue treatment without signs of progressive disease or toxicity.

t. Patients should be contacted every 12 (±2) weeks for survival status. Patients should have tumor scans 12 (±2) weeks, if tumor progression was not previously determined and/or use of subsequent anti-cancer therapy has not been initiated. Any new anti-cancer therapy should be documented.

Appendix C: Schedule of PK and PD Blood Sample Collection for FPA008-003

Study Cycle	Study Day	Time Point	Type of Sample
Screening	Screening (Day –28)	Screening	Biopsy Tissue
Cycle 1	Day 1	Prior to infusion (within 4 hours)	Cabiralizumab and Nivolumab PK (serum)
			Cabiralizumab and Nivolumab ADA (serum)
			Selected serum markers (serum)
			Cytokine multiplex panel (serum)
			ANA (serum)
			$CD14^+/CD16^+$ monocytes (whole blood)
			[redacted]
			[redacted]
		15 (±5) minutes after infusion	Cabiralizumab & Nivolumab PK (serum)
		4 (±1) hours after infusion	Cabiralizumab PK (serum)
	Day 2	24 (±6) hours after infusion	Cabiralizumab PK (serum)
	Day 4	72 (±12) hours after infusion	Cabiralizumab PK (serum)
			$CD14^+/CD16^+$ monocytes (whole blood) (for 1 mg/kg cohort only)
			[redacted]
	Day 8	168 (±24) hours after infusion	Cabiralizumab PK (serum)
			$CD14^+/CD16^+$ monocytes (whole blood)
			[redacted]
			[redacted]
	Day 15 (Cohort 1aD only)	336 (±24) hours after infusion	Cabiralizumab PK (serum)
Cycles 2–4	Day 1	Prior to infusion (within 4 hours)	Biopsy Tissue (prior to Cycle 3 only)
			Cabiralizumab and Nivolumab PK(serum)
			Cabiralizumab and Nivolumab ADA (serum)
			Selected serum markers (serum)
			Cytokine multiplex panel (serum)
			ANA (serum)
			$CD14^+/CD16^+$ monocytes (whole blood)
			[redacted]
			[redacted]
		15 (±5) minutes after infusion	Cabiralizumab PK (serum)
Cycle 8	Day 1	Prior to infusion (within 4 hours)	Cabiralizumab PK (serum)
			Cytokine multiplex panel (serum)
			Selected serum markers (serum)
			$CD14^+/CD16^+$ monocytes (whole blood)

Study Cycle	Study Day	Time Point	Type of Sample
		15 (±5) minutes after infusion	Cabiralizumab PK and Nivolumab PK (serum)
		4 (±1) hours after infusion	Cabiralizumab PK (serum)
	Day 2	24 (±6) hours after infusion	Cabiralizumab PK (serum)
	Day 4	72 (±12) hours after infusion	Cabiralizumab PK (serum)
			Cytokine multiplex panel (serum)
			Selected serum markers (serum)
			$CD14^{+}/CD16^{+}$ monocytes (whole blood)
	Day 8	168 (±24) hours after infusion	Cabiralizumab PK (serum)
			Cytokine multiplex panel (serum)
			Selected serum markers (serum)
			$CD14^{+}/CD16^{+}$ monocytes (whole blood)
	Day 15 (Cohort 1aD only)	336 (±24) hours after infusion	Cabiralizumab PK (serum)
Cycles 5, 9, 13, 21, then every 6 cycles while on treatment	Day 1	Prior to infusion (within 4 hours)	Cabiralizumab and Nivolumab PK (serum)
			Selected serum markers (serum)
			Cytokine multiplex panel (serum)
			ANA (serum)
			$CD14^{+}/CD16^{+}$ monocytes (whole blood)
			[redacted]
			Cabiralizumab and Nivolumab ADA (serum)
End-of-Treatment Follow-up Period (28 [±7] days and 100 [±7] days post-last dose)	Treatment discontinuation/PD	Post completion of treatment course	Biopsy tissue for patients who have documented disease progression (Day 28 post-last dose visit only)
			Cabiralizumab and Nivolumab PK (serum)
			Cabiralizumab and Nivolumab ADA (serum)
			Selected serum markers (serum)
			Cytokine multiplex panel (serum)
			ANA (serum)
			$CD14^{+}/CD16^{+}$ monocytes, (whole blood)
			[redacted]

Note that the nivolumab assessments listed above will not be performed for the Phase 1a monotherapy cohorts.

Appendix D: Sample Collection for PD Analyses

- Tumor biopsy/tumor tissue samples
  - IHC analysis of selected biomarkers
  - Gene expression analysis
  - T-cell receptor clonality
  - Neo-antigen analysis
- Skin biopsy samples
  - IHC analysis of selected biomarkers
- Blood samples
  - Whole blood analyses
    - $CD14^{+}/CD16^{+}$ monocytes
    - [redacted]
    - DNA for SNP analysis
  - Serum analyses
    - PK of cabiralizumab
    - PK of nivolumab
    - ADA of cabiralizumab
    - ADA of nivolumab
    - ANA (if result is positive, check ANA reflex, ESR and CRP to confirm)
    - Selected serum markers
    - Serum cytokine multiplex

[redacted]

Appendix E: Biopsy Requirements

Cohort	Skin Biopsy Time-Point				Tumor Biopsy Time-Point			
	Pre-treatment	On-treatment		Post-progression	Pre-treatment	On-treatment		Post-progression
		Prior to C3D1	Post-response			Prior to C3D1	Post-response	
1aM1	Required	Required	Optional	Optional	Required	Required	Optional	Optional
1aM2	Required	Required	Optional	Optional	Required	Required	Optional	Optional
1aM3	Required	Required	Optional	Optional	Required	Required	Optional	Optional
1aM4	Required	Required	Optional	Optional	Required	Required	Optional	Optional
1aC1	Required	Required	Optional	Optional	Required	Required	Optional	Optional
1aC2	Required	Required	Optional	Optional	Required	Required	Optional	Optional
1aC3	Required	Required	Optional	Optional	Required	Required	Optional	Optional
1aD	Required	Required	Optional	Optional	Required	Required	Optional	Optional
1aE	Required	Required	Optional	Optional	Required	Required	Optional	Optional
1b1	Not Required	Not Required	Not Required	Not Required	Required for ≥ 10 patients	Required for ≥ 10 patients	Optional	Optional
1b2	Not Required	Not Required	Not Required	Not Required	Required for ≥ 10 patients	Required for ≥ 10 patients	Optional	Optional
1b3	Not Required	Not Required	Not Required	Not Required	Required for ≥ 10 patients	Required for ≥10 patients	Optional	Optional
1b4	Not Required	Not Required	Not Required	Not Required	Required for ≥ 10 patients	Required for ≥ 10 patients	Optional	Optional
1b5	Not Required	Not Required	Not Required	Not Required	Required for ≥ 10 patients	Required for ≥ 10 patients	Optional	Optional
1b6	Not Required	Not Required	Not Required	Not Required	Required for ≥ 10 patients	Required for ≥ 10 patients	Optional	Optional
1b7	Not Required	Not Required	Not Required	Not Required	Optional	Optional	Optional	Optional

Pre- and on-treatment C3D1 biopsies are required for a minimum of ten patients per cohort in Phase 1b (optional for Cohort 1b7). If available, tumor tissue obtained from procedures such as surgery may also be collected.

Appendix I: ECOG Performance Status

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.