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Title: APX005M With Nivolumab and Cabiralizumab in Advanced Melanoma, Non-small Cell Lung Cancer or Renal Cell Carcinoma

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A Phase I/Ib Study of APX005M in Combination with Nivolumab and Cabiralizumab in Patients with Advanced Melanoma, Non-small Cell Lung Cancer or Renal Cell Carcinoma Whose Disease Has Progressed on Anti-PD-1/PD-L1 Therapy

BMS Protocol Number:	CA025-007
Institutional Protocol Number	HIC #2000021757
Investigational Products:	APX005M, Cabiralizumab (FPA008), and Nivolumab
IND Number:	139038
Development Phase:	Phase 1/1b
Indications Studied:	Melanoma, NSCLC, RCC
Protocol Version:	10
Date of Protocol:	21 Mar-2022
Sponsor:	Yale Cancer Center
Industry Collaborators:	Bristol-Myers Squibb, Apexigen, Inc.

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Co-Principal Investigators	Scott Gettinger, MD

Study Synopsis

Title:	A Phase 1/1b Study of APX005M in Combination with Nivolumab and Cabiralizumab in Patients with Advanced Melanoma, Non-small Cell Lung Cancer or Renal Cell Carcinoma Whose Disease Has Progressed on Anti-PD-1/PD-L1 Therapy
Protocol Number:	CA025-007
Clinical Phase:	1/1b
Sponsor:	Yale Cancer Center
Industry Collaborators:	Bristol-Myers Squibb, Apexigen, Inc.
Study Center:	Yale Cancer Center
Background:	New combinatorial therapeutic strategies are needed to overcome resistance to immune checkpoint inhibitors in a number of malignancies. We hypothesize that manipulation of the innate immune system by targeting macrophage activity will assist in reversing local immune suppression and overcome resistance to PD-1/PD-L1 inhibition.
Objectives:	

Phase 1 Objectives

Primary	• To assess the safety and tolerability of APX005M in combination with cabiralizumab • To assess the safety and tolerability of APX005M in combination with cabiralizumab and nivolumab • To determine the recommended phase 2 dose (RP2D) of APX005M in combination with a fixed dose of cabiralizumab and nivolumab
Secondary	• To determine the adverse event (AE) profile of this combination
Exploratory	• To characterize the pharmacokinetic (PK) profile of APX005M when administered in combination with cabiralizumab and nivolumab • To characterize the pharmacodynamic (PD) profile of APX005M when administered in combination with cabiralizumab and nivolumab • To further characterize the PD profile and immunogenicity of APX005M in combination with cabiralizumab and nivolumab by analyses of pre-treatment and on-treatment tumor biopsies and blood collection

Phase 1b Objectives

Primary	• Determine the objective response rate (ORR) using RECIST v1.1 to APX005M in combination with cabiralizumab and nivolumab in patients with advanced melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC) whose tumors are resistant to anti-PD-1/PD-L1 therapy • Evaluate the safety and tolerability of the RP2D of APX005M in combination with cabiralizumab and nivolumab
Secondary	• To determine the progression-free survival (PFS) of patients with melanoma, NSCLC or RCC treated with APX005M in combination with cabiralizumab and nivolumab whose tumors are resistant to anti-PD-1/PD-L1 therapy. • To determine the overall survival (OS) of patients with melanoma, NSCLC or RCC treated with APX005M in combination with cabiralizumab and nivolumab whose tumors are resistant to anti-PD-1/PD-L1 therapy. • To assess the association of selected biomarker measures and clinical efficacy measures using pre-treatment and on-treatment tumor biopsies
Exploratory	• To identify immune correlates that are associated with clinical response or resistance to the triple combination. Biomarker analyses will include study of pre-treatment and on-treatment biopsies as well as analyses of select serum and PBMC markers.
Investigational Products	• APX005M Solution for Intravenous Infusion • Cabiralizumab Solution for Intravenous Infusion • Nivolumab Solution for Intravenous Infusion
Study Design	This trial is a phase 1/1b study to evaluate the safety, efficacy, and tolerability of APX005M in combination with nivolumab and cabiralizumab. The phase 1 dose escalation portion will enroll patients with advanced solid tumors (melanoma, NSCLC, and RCC) to determine the RP2D of APX005M. The phase 1b dose expansion portion will study the triple drug combination in three disease cohorts. APX005M is a humanized IgG1 agonistic monoclonal antibody that binds CD40. Nivolumab is a humanized IgG4 monoclonal antibody directed against PD-1. Cabiralizumab is a humanized IgG4 monoclonal antibody directed against CSF1R.

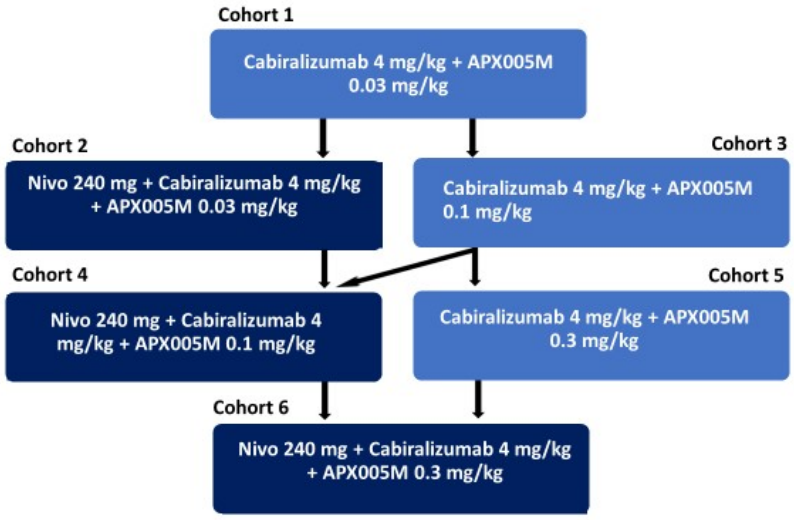
Phase 1: Dose Escalation

Patients with advanced solid tumors will be sequentially enrolled in 6 cohorts using a standard 3 + 3 dose escalation design to determine safety, characterize the AEs, and establish the RP2D of APX005M in combination with nivolumab and cabiralizumab. A minimum of 48 hours observation will be required after each patient is enrolled in cohorts 1-6, before a subsequent patient can be enrolled. Approximately 3 patients will be enrolled per cohort. Cohorts 1, 3, and 5 will include cabiralizumab at 4 mg/kg and dose escalation of APX005M. Cohorts 2, 4, and 6 will include nivolumab at 240 mg, cabiralizumab at 4 mg/kg, and dose escalation of APX005M. Each cycle will be 14 days with anticipated dosing as follows:

Phase 1 Dose Escalation Cohorts

Cohort	**Nivolumab (mg)**	**Cabiralizumab (mg/kg)**	**APX005M (mg/kg)**
1	Not given	4	0.03
2	240	4	0.03
3	Not given	4	0.1
4	240	4	0.1
5	Not given	4	0.3
6	240	4	0.3

If none of the first 3 evaluable patients in a dose cohort experience a dose-limiting toxicity (DLT) in the first two cycles, then the next 3 patients will be treated at the next higher dose cohort. If 1 of 3 patients within a cohort experiences a DLT in the first two cycles, then 3 additional patients will be added to that cohort. If a second patient experiences a DLT at that dose level in the first two cycles, the next cohort will not be initiated, and the dose of one or more drugs will be de-escalated. Patients at each dose level will be evaluated for at least 4 weeks from the start of treatment before additional patients can be treated at a higher dose level. If DLTs are observed in 2 or more patients within a cohort, the maximum tolerated dose (MTD) will have been exceeded and no further patients will be treated at that dose level. At 8 weeks, imaging studies will be performed to assess for response. Of note, 2 sets of cohorts will be conducted simultaneously: Cohorts 2 and 3, and Cohorts 4 and 5, as depicted below.



Dose escalation will be based on the number of DLTs experienced during the DLT evaluation interval as determined by dose escalation meetings attended by the PIs and Industry Collaborators (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.

Algorithm for Dose-Escalation Decisions

Number of Patients with DLT at a Given Dose Level	**Dose Escalation Decision Rule**
0/3	Escalation will occur into the next highest dose cohort
1/3	Enroll 3 additional patients at current dose level
≥2/3	Stop enrolment. Enroll 3 more patients at the lower dose level, if only 3 were previously entered, or at an intermediate dose level.
1/6	Open next cohort
≥2/6	Stop enrolment. Enter 3 more patients at the lower dose level or at an intermediate dose level.

Phase 1b Study

Once a specific dose regimen is determined to be safe as determined by the Sponsors and Industry Collaborators, the phase 1b portion will follow and will enroll additional patients in three disease-specific cohorts, all of whom who have progressed on prior PD-1/PD-L1 therapy: advanced melanoma, NSCLC,

and RCC who have progressed on prior PD-1/PD-L1 therapy. Patients will be treated at the estimated APX005M RP2D in combination with nivolumab 240 mg IV and cabiralizumab 4 mg/kg on day 1 of each 14-day cycle.

Number of Patients

In the Phase 1 dose escalation portion, at least 3 patients with advanced solid tumors will be enrolled per cohort using a standard 3+3 design. There are a total of 6 cohorts. In the Phase 1b portion, a Simon's two-stage design will be used to study 3 disease cohorts: advanced melanoma, NSCLC, and RCC. The null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. In the first stage, 13 patients in each disease cohort will be accrued. If there are 1 or fewer responses in these 13 patients, the enrollement in that disease cohort will be stopped. Otherwise, 21 additional patients will be accrued for a total of 34 patients per disease cohort. The null hypothesis will be rejected if 6 or more responses are observed in 34 patients. This design yield a type I error rate of 0.1 and a power of 80% when the true response rate is 25%.

Study Population

The phase 1 dose escalation portion will include patients with advanced melanoma, NSCLC, and RCC with the same criteria as listed below for the phase 1b portion.

The Phase 1b dose expansion portion of the trial studying APX005M at the RP2D in combination with cabiralizumab and nivolumab will consist of three solid tumor cohorts. All patients in all tumor types are required to have progressed while on anti-PD(L)-1 therapy without any intervening therapy. Additional descriptions are below:

Melanoma:

- Unresectable stage III or stage IV melanoma, irrespective of *BRAF* status, with histologic or cytologic confirmation

RCC:

- Histologic or cytologically documented, locally advanced unresectable or metastatic RCC irrespective of histologic subtype

NSCLC:

- Histologic or cytologically documented, locally advanced or metastatic (i.e. Stage IIIB not eligible for definitive chemoradiotherapy, stage IV, or recurrent) NSCLC.
- Patients known to harbor an ALK rearrangement or EGFR mutation known to be sensitive to FDA-approved tyrosine kinase inhibitors (TKI), are only eligible after experiencing disease progression (during or after treatment) or intolerance to an FDA approved ALK TKI or EGFR TKI, respectively.
- Patients with TKI-treated EGFR mutant NSCLC harboring the secondary EGFR T790M tumor must have received prior osimertinib.
- Patients with crizotinib-treated ALK rearranged NSCLC must have received a next generation ALK inhibitor.

Inclusion Criteria

1. Biopsy proven metastatic melanoma, NSCLC or RCC whose disease has progressed on a prior regimen containing a PD-1 or PD-L1 inhibitor, without intervening therapy. Progression will be determined by the investigator based on clinical and/or radiographic features.

2. At least 1 site of disease must be accessible to provide repeat biopsies for tumor tissue. This site may be a target lesion as long as it will not be made unmeasurable by the biopsy procedure

3. Age ≥18, able to understand and sign the informed consent form

4. ECOG performance status < 2

5. Any number of previous treatments. Other prior systemic therapies must have been administered at least 4 weeks before administration of the study drugs; the exception to this is small molecule inhibitors, which must be

stopped at least 2 weeks or after five half-lives of the drug, whichever is shorter, prior to the start of the study drugs.

6. Life expectancy of at least 6 months

7. A history of previously treated brain metastases is allowed, provided that they are stable for at least 4 weeks.

8. Willingness to undergo mandatory tumor biopsy prior to initiation of therapy and before the fifth cycle.

9. Willingness to provide an archival specimen block, if available, for research.

10. Patients must have normal organ and marrow function (as outlined in Section 3.2.2)

11. Female subject of childbearing potential should have a negative urine or serum pregnancy within 24 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

12. Female subjects of childbearing potential should be willing to use a highly effective contraception (hormonal or IUD) or be surgically sterile, or abstain from heterosexual activity for a period of at least 5 months after the last dose of study drug. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

13. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through at least 7 months after the last dose of study drug.

14. 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.

15. Prior focal radiotherapy is allowed. Radiation to brain, pulmonary or intestinal sites must be completed at least 4 weeks prior to study Day 1. There is no time restriction prior to study Day 1 for patients who have received radiation to bone, soft tissue or other sites. No radiopharmaceuticals (strontium, samarium) within 8 weeks before first dose of study drug administration.

16. Major surgery must be completed at least 4 weeks prior to the 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. Wounds must be healed.

Exclusion Criteria

1. Untreated brain metastases.

2. A patient who has had prior immune therapy or chemotherapy, within 4 weeks prior to study Day 1, or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent will be excluded. The exception is targeted therapy that must have been completed at least 2 weeks or after 5 half-lives, which ever is shorter, prior to study Day 1. Patients who have had prior ipilimumab must have received their last dose no less than 4 weeks prior to study Day 1.
    a. Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
    b. Note: Toxicity that has not recovered to ≤ Grade 1 is allowed if it meets the inclusion requirements for laboratory parameters.

3. Has had prior treatment with any other CSF1R inhibitor or CD40 agonist
4. Use of corticosteroids to control immune related adverse events at enrollment will not be allowed, and patients who previously required corticosteroids for symptom control must be off steroids for at least 2 weeks. Low-dose steroid use (≤10 mg of prednisone or equivalent) as corticosteroid replacement therapy for primary or secondary adrenal insufficiency is allowed.
5. Has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to prior treatments with the exception of clinically insignificant adverse events such as alopecia, clinically insignificant laboratory abnormalities, clinically insignificant rash and Grade 2 neuropathy.
6. History of grade 3-4 neurologic or cardiac toxicity or life-threatening liver toxicity poorly responsive to steroids with prior anti-PD-1/anti-PDL1 monotherapy.
7. Presence of leptomeningeal disease.
8. Has active autoimmune disease unrelated to use of immune checkpoint inhibitors that has required systemic treatment in the past year (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
9. Pregnancy or breast feeding. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with nivolumab, cabiralizumab or APX005M, breastfeeding must be discontinued if the mother is enrolled on this trial.

10. Patients may not be receiving any other investigational agents and may not have participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

11. Either a concurrent condition (including medical illness, such as active infection requiring treatment with intravenous antibiotics or the presence of laboratory abnormalities) or history of a prior condition that places the patient at unacceptable risk if he/she were treated with the study drug or a medical condition that confounds the ability to interpret data from the study.

12. Concurrent, active malignancies in addition to those being studied.

13. Active (non-infectious) pneumonitis.

14. Has a known Human Immunodeficiency Virus (HIV), Hepatitis B (HBV), or Hepatitis C (HCV) acute or chronic infection.

15. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

16. History of myocardial infarction or unstable angina within 3 months prior to Cycle 1, Day 1.

17. Prisoners, or subjects who are under compulsory detention

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

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

20. 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

21. Open wounds and active skin infections

22. Uveal melanoma in the Phase Ib dose expansion trial

Concomitant Medications

All medications taken within 28 days before the administration of the first dose of any study drug and all concomitant therapy administered during the study until 100 (±7) days after last dose of any study drug (or use of subsequent anti-cancer therapy) will be collected. All subsequent anti-cancer therapy will be collected in the Long-Term Follow-up Period.

Information on all prior treatments indicated for advanced cancer, including chemotherapy, biochemotherapy, immunotherapy, radiation, surgery, biologic, and experimental therapy will be collected.

No concomitant medication information will be collected following patient discontinuation from the study except for concomitant medication use associated with study drug-related AEs or AEs that lead to discontinuation from the study.

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
- Non-compliance by the patient

List of Key Study Personnel

Sponsor:	Yale Cancer Center
Industry Collaborators:	Bristol-Myers Squibb, Apexigen, Inc.
Principal Investigator:	Harriet Kluger, MD
Co-Principal Investigators:	Scott Gettinger, MD
Co-Investigators:	Anne Chiang, MD Sarah Goldberg, MD Roy Herbst, MD, PhD Michael Hurwitz, MD, PhD Mario Sznol, MD
Serious Adverse Event Reporting:	Bristol-Myers Squibb Apexigen, Inc. FDA

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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 5.0	Common Terminology Criteria for Adverse Events, version 5.0
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

1. Introduction and Study Rationale

1.1 Introduction

Immunotherapies including PD-1/PD-L1 inhibitors have become effective standard therapies in several advanced cancers. Objective response rates (ORR) for advanced melanoma patients treated with dual (ipilimumab and nivolumab) or single agent (nivolumab) immune checkpoint inhibitors have reached up to 57.6% and 43.7%, respectively [1-4]. However, not all patients respond and after 2 years of monotherapy, approximately half of the responders have progressed. Similarly, in advanced non-small cell lung cancer (NSCLC) patients with greater than 50% tumor PD-L1 positivity, pembrolizumab is used in the front-line setting with a 44.8% response rate [5]. Nivolumab and atezolizumab are also approved for NSCLC patients who have progressed on platinum-based chemotherapy and who are not candidates for EGFR or ALK inhibitors [6, 7]. Additionally, nivolumab is approved in second-line treatment of advanced renal cell carcinoma (RCC) with a 25% ORR [8]. In the absence of targetable driver mutations, limited treatment options exist for next-line therapy in patients who do not initially respond to or who develop acquired resistance to PD-1 inhibitors. New combinatorial therapeutic strategies are needed to overcome this resistance.

Proposed mechanisms for resistance to anti-PD-1/PD-L1 therapy include lack of or inactivation of T cells, T cell exhaustion, loss of antigen presentation, or expression of other immunosuppressive molecules. Tumor-associated macrophages (TAMs) comprise up to 30% of innate immune cells in the tumor microenvironment [9] and can serve as both negative (M1) and positive (M2) regulators of tumor growth. M2 macrophages are anti-inflammatory and secrete immunosuppressive growth factors that negatively impact cytotoxic T-cell capabilities [10-13] and promote tumorigenesis, invasion, and metastasis [14, 15]. We hypothesize that manipulation of the innate immune system by targeting macrophage activity will assist in reversing local immune suppression and overcome resistance to PD-1/PD-L1 inhibition.

1.2 Rationale for Combination of APX005M with nivolumab and cabiralizumab

Immunotherapies including CSF1R inhibitors (CSF1Ri) and CD40 agonists (CD40α) target innate immune cells. Researchers including those at Yale have shown these agents to suppress poorly T-cell infiltrated melanomas in a T-cell independent fashion. Macrophage colony-stimulating factor 1 (CSF-1) is chemotactic signal that stimulates monocyte tumor infiltration and differentiation into M2 macrophages [10, 16] and elevated expression of CSF-1 and CSF1R is associated with poor prognosis [17]. For example, in a melanoma mouse model, CSF1Ri improved efficacy of adoptive cell therapy by increasing T-cell tumor infiltration and decreasing immunosuppressive macrophage infiltration [18]. CD40 is similarly expressed on macrophages and other antigen presenting cells, and interacts with its ligand, CD40L, on T cells. CD40α have also been shown to increase tumoricidal activity of macrophages and stimulate maturation of antigen presenting cells. In a pancreatic mouse model, combination PD-1 blockade and CD40α improved anti-tumor immunity compared to either agent alone [19]. Clinical trials of CD40α have shown activity in melanoma, including durable responses [20].

Pre-clinical studies at Yale in the Kaech and Bosenberg laboratories have supported the notion that TAMs may confer resistance to PD-1/PD-L1 inhibition [21]. Using the $Braf^{V600E}/Pten^{-/-}$ genetically engineered mouse melanoma model (GEMM), we have generated a series of cell lines

(YUMM for Yale University Mouse Melanoma) and irradiated derivatives (YUMMER for Yale University Mouse Melanoma Exposed to UVB Radiation). These models are unique in that they are driven by mutations relevant to human melanomas and can be studied in immune competent mice. YUMM tumors tend to be resistant to PD-1/PD-L1 inhibitors, while the YUMMER tumors are less resistant, but do develop resistance over time, mimicking primary and acquired resistance seen in humans. We have found that the predominant immune population present in tumors with poor cytotoxic T cell infiltration are TAMs. TAMs are particularly in abundance relative to CD8+ T cells in YUMM tumors, with the inverse being observed in YUMMER tumors (Figure 1).

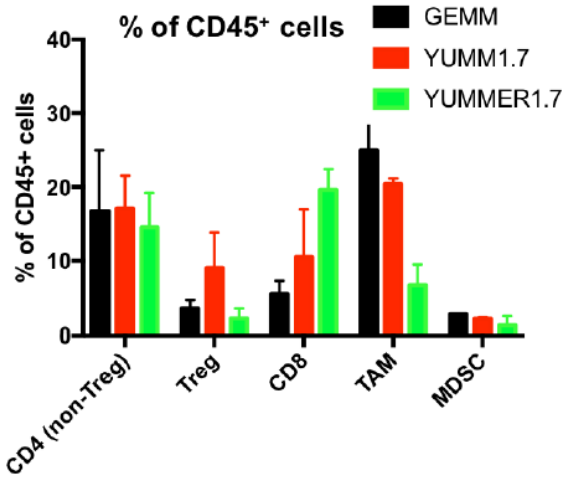
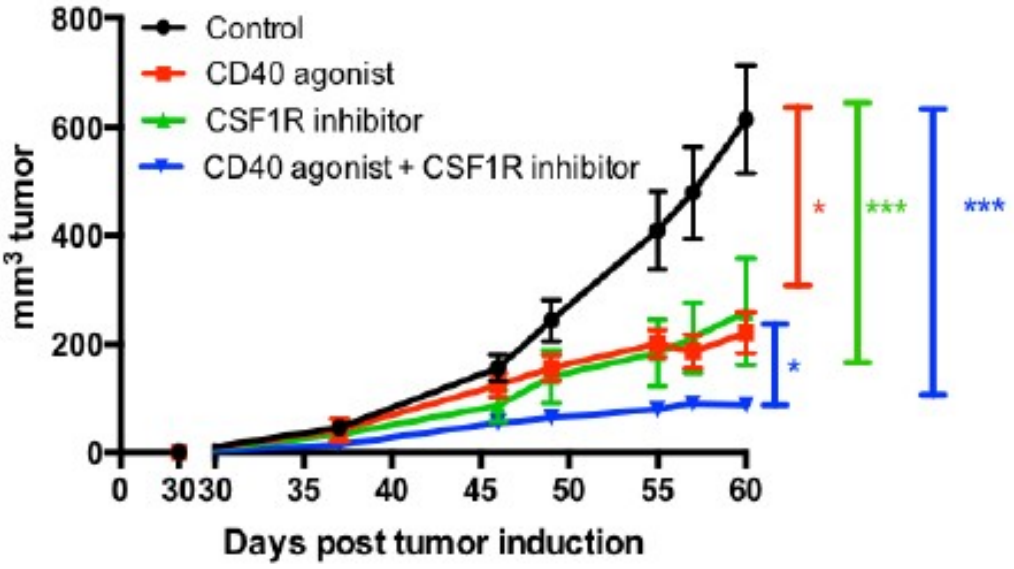


Figure 1. Content of immune infiltrating cells in the $Braf^{V600E}/Pten^{-/-}$ genetically engineered mouse melanoma models (GEMM), a cell line model derived from these GEMM tumors, YUMM 1.7, and a model generated by exposure to UVB radiation (YUMMER1.7), which is more sensitive to PD-1/PD-L1 inhibitors, but develops resistance over time. TAM content is abundant in the former, whereas more CD8 cells are infiltrating the latter.

Tumor infiltrating neutrophils (TINs) and CD4 T cells are present as well, but mostly at the tumor margin. Tumor growth in this model is not responsive to anti-PD-1/PD-L1 treatment alone, but combination therapy with CSF1Ri slows tumor growth significantly compared to the control (data not shown). Treatment with combined CSF1Ri/CD4α slows tumor growth more than either agent alone (Figure 2 upper panel). The combination therapy also resulted in increased tumor infiltrating immune cells, clearly impacting the TAM population (Figure 2 lower panel).



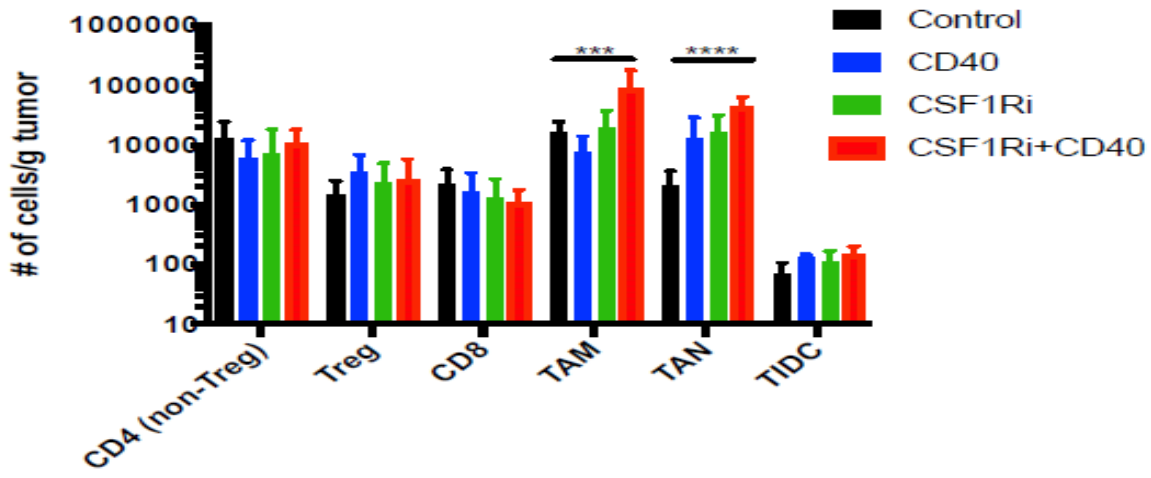


Figure 2. Upper panel: Groups of 12 mice were treated with control vehicle, CD40 agonist alone, CSF1R inhibitor alone, or the combination 30 days after tumor induction. The combination resulted in significant inhibition of tumor growth compared with either drug alone.

Lower Panel: Treatment of mice with CD40 agonists, CSF1R inhibitors or the combination thereof impacted tumor infiltrating immune cells, particularly tumor associated macrophages (TAM) and neutrophils (TAN).

Additional detailed mechanistic studies have been conducted supporting the combination of CD40α and CSF1Ri in these animal models and their role in activating the innate immune system (Perry CJ et al, submitted). Combined treatment with CD40α and CSF1Ri alters the composition of TAMs, increases Type I inflammation and chemokine expression, and enhances CD8 T-cell infiltration and PD-1 expression.

As shown in the flow plots in Figure 3 for example, the expression TNF-α on TAMs significantly increases with combined CSF1Ri/CD40α.

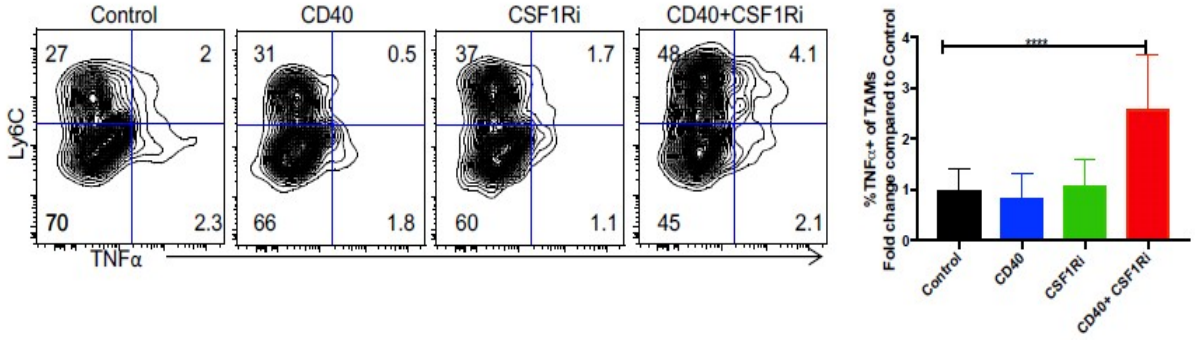
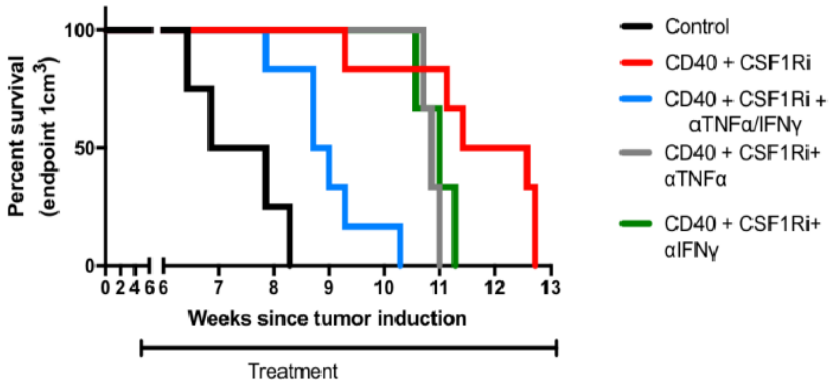


Figure 3. Treatment with CSF1Ri and CD40α in combination alters the macrophage content to a greater degree than either drug alone.

Inflammatory cytokines including TNFα and IFNγ appear to be necessary for anti-tumor immunity provided by combined CSF1Ri and CD4α therapy. As shown in the Kaplan-Meier curves (Figure 4 upper panel) and the associated log-rank p values (Mantel-Cox) (Figure 4 lower panel), TNFα and IFNγ blocking therapy actually interferes with tumor growth suppression from combined CSF1Ri and CD40α therapy. Data are from one experiment (n=3-6), representative of three independent experiments (total n=6-15).



	Two-way comparison	Log-rank P value
Control	CD40+CSF1Ri	0.0011
Control	CD40+CSF1Ri +αTNFα/IFNγ	0.0068
Control	CD40+CSF1Ri +αTNFα	0.0285
Control	CD40+CSF1Ri +αIFNγ	0.0189
CD40+CSF1Ri	CD40+CSF1Ri +αTNFα/IFNγ	0.0177
CD40+CSF1Ri +αTNFα	CD40+CSF1Ri +αTNFα/IFNγ	0.010
CD40+CSF1Ri +αIFNγ	CD40+CSF1Ri +αTNFα/IFNγ	0.010

Figure 4. Kaplan Meier survival curves (upper panel) and associated statistical comparisons (lower panel) show that TNFα and IFNγ are necessary for anti-tumor immunity provided by combined CSF1Ri and CD40α therapy, as blocking them interferes with the inhibition of tumor growth by these drugs.

In pilot experiments, we have shown that mice (n=11) treated with the triple combination of anti-PD-1/CSF1Ri/CD40α had superior survival compared to treatment with anti-PD-1/CSF1Ri or anti-PD-1/CD40α (Figure 5).

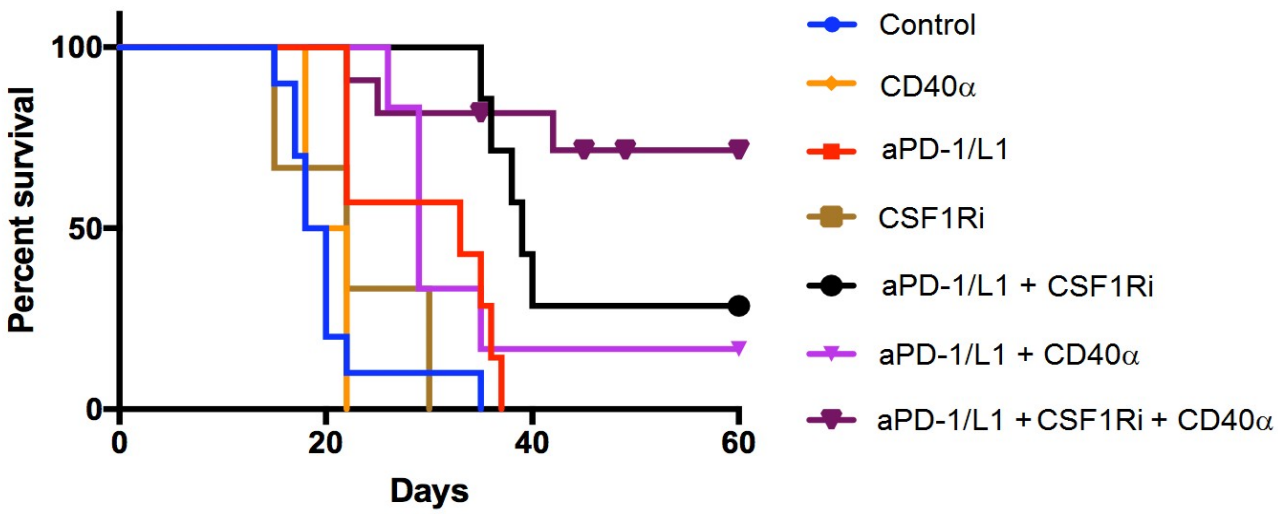


Figure 5. YUMM 1.7 bearing mice were treated with control vehicle, CD40 agonistic antibodies (CD40α), CSF1R inhibitors (CSF1Ri) or anti-PD-1/L1. These tumors are resistant to any of the three monotherapies, and survival was clearly superior with triplet therapy compared with doublets of CSF1Ri or CD40α and PD-1 axis inhibitors.

Thus, based on the above pre-clinical data, we hypothesize that addition of CSF1Ri/CD40α to PD-1 blockade may further disengage T cell suppression and potentiate the anti-tumor immune response. We therefore propose a phase I/Ib clinical trial of the CD40α APX005M in combination with cabiralizumab (CSF1Ri) and nivolumab in advanced solid tumors including melanoma, NSCLC, and RCC. Our preliminary data from immune profiling of murine tumors treated with CSF1Ri and CD40α indicate that biomarkers of response include TNFα, IL-6, CCL3,4,5 and CD8+ T cell/neutrophil recruitment. We aim to identify immune correlates that are associated with clinical response to the triple combination and to develop biomarkers of response using mandatory pre-treatment and on-treatment biopsies.

Seeing that APX005M and cabiralizumab have not been used in combination, and both drugs activate macrophages, we propose an initial cohort of the APX005M and cabiralizumab. This cohort will be followed by the addition of fixed dose nivolumab. APX005M will then be slowly dose escalated in combination with cabiralizumab, with and without nivolumab, to establish safety and to establish the RP2D of APX005M in combination with nivolumab and cabiralizumab.

1.3 Target Receptor Background

1.3.1 Tumor-Associated Macrophages and Colony Stimulating Factor 1 Receptor

Macrophages are myeloid-derived cells that carry out a variety of functions in the human body. They can colonize tissues and tumors through two distinct mechanisms: hematogenous seeding from circulating monocytes or local self-renewal in the form of tissue-resident macrophages [22]. Recent studies have shown that macrophages exert their physiological effect within, and play roles unique to, the tissues in which they are active [23]. Macrophage regulation is complex as these cells actively secrete and respond to multiple cytokine and chemokine gradients within their local environment.

Macrophages are among the most abundant immune cell types in the tumor microenvironment. Based on their opposing functions, macrophages can be classified into two major phenotypes, M1 and M2. M1 macrophages are immunostimulatory and tumor suppressive, while M2 macrophages are immunosuppressive and tumor promoting. Substantial evidence suggests that tumor-associated macrophages (TAMs) are polarized towards an anti-inflammatory M2 phenotype [24]. Consistent with this, increased levels of TAMs are associated with a poor prognosis in the majority of cancers [25]. Based on their tumor-promoting phenotype TAMs have become an attractive therapeutic target.

Colony stimulating factor 1 receptor (CSF1R) signaling plays a fundamental role in the differentiation, maintenance, and function of macrophages [26]. There are two ligands for CSF1R: CSF1 and IL34. These agonists bind to overlapping regions of CSF1R with similar affinity (reviewed in Masteller and Wong [27]). Mice lacking CSF1R, CSF1, or IL34 have deficiencies in macrophages, underscoring the essential role of the CSF1R pathway in the biology of this cell type [27, 28]. Pharmacologic treatments that block CSF1R in cancer settings are expected to reduce or reprogram M2 TAMs and reduce immune suppression. Following treatment with anti-CSF1R agents, the remaining macrophage compartment may be repolarized from an M2 immunosuppressive state to an M1 anti-tumor state, which would support T-cell responses. This conversion associated with concurrent treatment modalities, such as anti-PD-1 treatment, could have an increased effect on reduction of tumor growth [29].

Support for targeting CSF1R in cancer comes from animal studies in which antibody or small molecule inhibition of CSF1R decreases M2 TAMs resulting in decreased immune suppression and a more robust cytotoxic T-cell response [30-32]. Cabiralizumab is a recombinant, humanized immunoglobulin G4 (IgG4) monoclonal antibody that binds to human CSF1R. The interaction of cabiralizumab and CSF1R antagonizes the binding of both CSF1 and IL34 to CSF1R, thereby preventing receptor activation. *In vitro*, cabiralizumab inhibits CSF1 and IL34-induced proliferation and survival of peripheral blood monocytes. *In vivo,* cabiralizumab inhibits the survival of subsets of monocytes and macrophages.

Taken together, these and other emerging data suggest that blocking CSF1R with cabiralizumab treatment may reduce immunosuppression in the tumor environment generated by TAMs and enhance the efficacy of immune-based anti-cancer therapies.

1.3.2 Programmed Cell Death-1 (PD-1; CD279)

PD-1 is a cell surface signaling receptor that delivers inhibitory signals to regulate the balance between T-cell activation and tolerance by interacting with its ligands, PD-L1 (CD274; B7-H1) and PD-L2 (B7-DC/CD273). It is a 55 kDa type I transmembrane protein that is a member of the CD28 family of T-cell costimulatory receptors, which also includes inducible co-stimulator (ICOS), cytotoxic T lymphocyte antigen-4 (CTLA-4), and B- and T-lymphocyte attenuator (BTLA) [33]. PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells [34]. Its ligands, PD-L1 and PD-L2, have been shown to down-regulate T-cell activation upon binding to

PD-1 in both murine and human systems [35, 36]. PD-1 delivers a negative signal by the recruitment of Src homology region 2 domain-containing phosphatase-2 (SHP-2) to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region [37, 38].

Evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice, which develop various autoimmune phenotypes, including dilated cardiomyopathy and a lupus-like syndrome with arthritis and nephritis [39-41]. The emergence of these autoimmune phenotypes is dependent on the genetic background of the mouse strain; many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes [42-44]. Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

The PD-1 targeting agent, nivolumab has been investigated clinically in several tumor types including non-small cell lung cancer (NSCLC), melanoma, and renal cell carcinoma (RCC), Classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, and urothelial carcinoma as a single agent or in combination with other treatments. A selection of efficacy data is described in the Nivolumab Investigator's Brochure)**.**. As a single agent, nivolumab shows remarkably durable efficacy in responding patients.

Nivolumab is currently approved in the US for the following indications [45]:

- BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent.
- BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent.
- Unresectable or metastatic melanoma, in combination with ipilimumab.
- Metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations.
- Advanced renal cell carcinoma for patients who have received prior anti-angiogenic therapy.
- Classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin or 3 or more lines of therapy that includes autologous HSCT.
- Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.
- Locally advanced or metastatic urothelial carcinoma who:
  - have disease progression during or following platinum-containing chemotherapy

– have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

1.3.3 CD40

Apexigen has developed the mAb APX005M, which binds and activates CD40, a costimulatory molecule expressed by antigen presenting cells (APC). As such, APX005M is a CD40 agonistic antibody. The cell surface molecule CD40, a member of the tumor necrosis factor receptor (TNFR) superfamily, plays an important role in induction of tumor apoptosis and regulation of immune activation, especially in crosstalk between T cells and APCs [46]. CD40 is expressed by dendritic cells (DC), B cells, monocytes, and some non-lymphoid cells [47]. The natural ligand (CD40L) for CD40 is CD154, which is expressed on activated T cells and provides a major component of T cell "help" for immune response. Agonistic CD40 antibodies can substitute for the function of CD154 on T cells to boost immunity. Signaling through CD40 on APCs, including dendritic cells (DCs), monocytes, and B cells, can, in turn, enhance the T cell response via improvement in antigen processing and presentation and through the release of cytokines from activated APCs [48, 49]. Therefore, an agonistic CD40 antibody can activate and stimulate both innate and adaptive immunity.

CD40 is also expressed on many tumor cells and can mediate a direct cytotoxic effect. In addition to B cell lymphoma, CD40 expression has been reported in 30−70% of primary human solid tumor samples including melanoma and carcinomas [50]. Activation of CD40 on tumor cells results in tumor cell apoptosis and inhibition of tumor growth [12]. Due to its action on both immune and tumor cells, CD40 has been studied as a target for novel cancer immunotherapy; agonistic anti-CD40 antibodies have been demonstrated to be potent stimulators of tumor immune responses in both animal models and cancer subjects [50-53].

The potential mechanisms of action for an agonistic anti-CD40 antibody, depending on its isotype, include stimulation of immune response by activating antigen processing and presentation, recruitment of immune effectors such as natural killer (NK) cells and macrophages, and direct cytotoxic effects on tumor cells. Thus, the desired therapeutic CD40 agonist antibody should have these functionalities.

1.3.4 Product Development Background

1.3.4.1 Mechanism of Action

1.3.4.1.1 Cabiralizumab

Cabiralizumab is a recombinant, humanized IgG4 monoclonal antibody that binds to human CSF1R. Cabiralizumab contains a single amino acid substitution in the hinge region to prevent hemi-dimer exchange. Binding of cabiralizumab to CSF1R antagonizes its natural ligands, CSF1 and IL34, thereby preventing activation of CSF1R.

Cabiralizumab inhibits both CSF1 and IL34-induced CSF1R phosphorylation in a cell line engineered to overexpress CSF1R (CHO-CSF1R), demonstrating that cabiralizumab blocks the activation of ligand-induced CSF1R signaling pathways. Cabiralizumab also inhibits CSF1 and IL34-induced proliferation and survival of peripheral blood monocytes *in vitro*, demonstrating that cabiralizumab inhibits not only the initiation of CSF1 and IL34 signaling pathways, but also the subsequent physiologic responses of primary human monocytes to these ligands.

CSF1R is expressed on cells of the monocyte/macrophage lineage and signaling through CSF1R via its ligands, CSF1 and IL34, supports differentiation, maintenance, and function of monocytes, macrophages, and osteoclasts. TAMs are among the most abundant immune cell types in the tumor microenvironment. Substantial evidence suggests that TAMs are polarized towards an anti-inflammatory phenotype (M2 TAMs) and through both cell surface inhibitors and soluble factors, such as immunosuppressive cytokines, play a major role in inhibiting anti-tumor immune responses [24]. CSF1 is a major survival factor for TAMs and targeting CSF1R through cabiralizumab should reduce TAM-mediated immune suppression resulting in strengthening the anti-tumor response to immunotherapy. Therefore, a drug that inhibits CSF1R should limit the immune-suppressive influence of TAMs on the tumor microenvironment and could be complementary and augment current cancer therapies.

1.3.4.1.2 Nivolumab

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immuno-surveillance and escape effective innate and adaptive immune responses [54-57]. Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system.

T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR) [58]. Collectively, these signals govern the balance between T-cell activation and tolerance. PD-1 signaling has been shown to inhibit CD28-mediated upregulation of IL2, IL10, IL13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 signaling has also been noted to inhibit T-cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes [59]. These results suggest that PD-1 blockade has the potential to promote anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

In vitro, nivolumab binds to PD-1 with high affinity (EC_{50} 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands, PD-L1 and PD-L2 ($IC_{50} \pm 1$ nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in a mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cells (PBMCs), the effect of nivolumab on antigen-specific recall response is indicative of nivolumab-augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner versus an isotype-matched control. *In vivo* blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02) [60].

1.3.4.1.3 APX005M

The agonistic CD40 mAb, APX005M, a humanized IgG1 mAb with a mutation in the Fc portion, is engineered to enhance interaction with Fc receptors to mediate antibody crosslinking. APX005M has demonstrated biological activity in human subjects and a favorable toxicity profile when given IV at doses up to 1 mg/kg body weight.

Recently, Zippelius and co-authors [61] showed in preclinical models that CD40 engagement with an agonistic mAb leads to a T cell and IFN-γ dependent upregulation of PD-L1 on tumor infiltrating monocytes and macrophages, thereby feeding into a negative feedback loop, which hampers CD40 induced T-cell responses. This resistance mechanism was successfully circumvented by co-administration of PD-1/PD-L1 blocking antibodies.

Similarly, other groups showed in preclinical models of pancreatic cancer that CD40 activation drove T-cell immunity and reversed the complete resistance of pancreatic tumors to checkpoint blockade. Combining a CD40 agonistic antibody with PD-1/PD-L1 blockade enhanced anti-tumor immunity and improved overall survival versus either monotherapy [19, 62, 63].

Studies elucidating the mechanism of APX005M action showed that it activates the CD40 signaling pathway, leading to APC activation, as seen in increased CD80, CD83, and CD86 expression and release of cytokines from human lymphocytes and monocytes. In particular, APX005M induced interleukin (IL)-12 p(70), TNF-α and IL-6 secretion from DCs. The CD40-agonistic activity of APX005M can be further enhanced by a toll-like receptor (TLR) 4 agonist. In comparison with 3 other CD40-agonistic antibody analogs (CP-870,893, SGN-40, and ADC-1013), APX005M is the most potent CD40 agonist. APX005M's CD40-agonistic activity depends on its ability to bind FcγRs. In in vitro cultures with T cells and DCs, APX005M was able to enhance antigen-specific T-cell proliferation and promote IFN-γ secretion. In combination with an antibody against programmed cell death ligand-1 (PD-L1), APX005M synergistically enhances antigen-specific T-cell responses. Upon binding to CD40-expressing tumor cells, APX005M was capable of inducing ADCP and tumor cell apoptosis. APX005M did not appear to have a substantive effect on normal human DC and T-cell counts, but could partially reduce B-cell counts in vitro [64].

1.3.5 Preclinical Summary

1.3.5.1 Cabiralizumab

The PK profile of cabiralizumab is complex and characterized by nonlinear clearance that is likely mediated by binding to CSF1R on cells. As monocyte and macrophage cells are dependent on CSF1R for viability, these target-bearing cells are reduced in number following cabiralizumab treatment, resulting in a decrease of target-mediated clearance. As target-mediated clearance becomes saturated at high or repeat doses, cabiralizumab clearance is similar to other human IgG antibodies.

Three PD biomarkers correlate with cabiralizumab exposure in nonclinical studies: CSF1 serum levels, circulating CD16-positive peripheral blood monocytes ($CD16^+$ monocytes), and serum markers of bone resorption (Trap5b and CTX). CSF1 serum levels rapidly rise and $CD16^+$ monocyte levels rapidly fall in a dose-dependent manner that correlates closely with cabiralizumab plasma concentration. Saturation of the PD response is achieved at a low dose of cabiralizumab (3 mg/kg weekly) in cynomolgus monkeys. The half-maximal response (IC_{50}) for reduction of $CD16^+$ monocytes occurs at a serum concentration of approximately 3 µg/mL and the maximal response occurs at approximately 10 µg/mL. The level of CD16-negative ($CD16^–$) monocytes does not change with exposure to cabiralizumab.

In the *in vivo* toxicology studies in cynomolgus monkeys, cabiralizumab was generally well tolerated. The most prominent clinical observation was reversible periorbital edema, seen after prolonged exposure to cabiralizumab. The onset of the edema did not show a clear relationship to exposure levels, but edema resolved after systemic clearance of the drug. Periorbital edema is a known side effect of drugs affecting the CSF1 pathway [31, 65]. The main hematologic change was a reversible decrease in circulating $CD16^+$ monocytes, which was considered a PD effect.

Cabiralizumab-related clinical chemistry effects included reversibly increased ALT, AST, CK, and LDH serum levels. These laboratory abnormalities were not associated with any histopathological evidence of liver, cardiac, or muscle tissue injury. Additionally, cardiac troponin, skeletal troponin (SkTnI), myoglobin, and aldolase did not show any changes further confirming the lack of any liver or muscle injury. The increased serum levels are attributed to diminished clearance of ALT, AST, CK, and LDH molecules from serum due to a reduced number of liver Kupffer cells. Kupffer cells are the normal clearance mechanism for these serum enzymes so a loss of macrophages leads to an elevation of these serum enzymes [66]. Accordingly, ALT, AST, CK, and LDH elevations are considered non-toxic and an indirect PD effect of cabiralizumab exposure.

One histopathological finding was the reversible expansion of the submucosal collagen fibers by clear space and varying amounts of a blue, granular extracellular matrix (ECM) in a variety of tissues. This change was neither associated with inflammatory cells nor with any sign of degeneration or other alteration of the collagen fibers, fibroblasts, or the smooth muscle cells within the area of expansion. Because it was not associated with clinical signs and was

reversible, it was deemed to be a non-adverse event. A similar observation was also seen in *op/op* mice that lack functional CSF1. The reduction of tissue macrophages is the likely cause of the observed accumulation of ECM due to a decreased clearance of glycosaminoglycans, especially hyaluronic acid, that are prominent in connective tissue and are normally catabolized by macrophages [67]. This change is also considered to be an indirect PD effect of cabiralizumab.

The no-observable-adverse-effect level (NOAEL) for cabiralizumab was determined to be 100 mg/kg when administered for 13 weekly doses to cynomolgus monkeys, which provides a 32-fold safety factor based on body surface area calculation for the starting dose of 1 mg/kg in humans.

For more detailed information or background on cabiralizumab, please refer to the Cabiralizumab Investigator's Brochure.

1.3.5.2 Nivolumab

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family, such as ICOS, CTLA-4, and BTLA(Nivolumab Investigator's Brochure) . Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and IFN- γ release *in vitro*[68] (Nivolumab Investigator's Brochure). Fluorescent-activated cell sorter (FACS) analysis confirmed that nivolumab binds to transfected Chinese hamster ovary (CHO) with human or cynomolgus monkey PD-1, but not to rat or rabbit PD-1 molecules. Nivolumab has also been shown to bind to PD-1 on activated human T cells expressing cell surface PD-1 or on virus-specific $CD8^+$ T cells from chronically infected hepatitis C virus patients [69, 70].

PD-1 inhibition in an MLR resulted in a reproducible concentration-dependent enhancement of IFN-γ release in the MLR up to 50 µg/mL. No effect was observed with a human IgG4 isotype control or $CD4^+$ T cells and dendritic cell (DC) controls [71].

In intravenous repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. Nivolumab-related findings were limited to a reversible decrease of 28% in triiodothyronine (T_3) among the females administered 27 doses of 50 mg/kg nivolumab. No corresponding changes in the level of thyroxine (T_4), thyroid-stimulating hormone (TSH), or histologic changes in the thyroid were observed. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents[45].

Ipilimumab (BMS-734016), an anti-CTLA-4 monoclonal antibody that blocks the downregulation of T-cell activation, was used in combination with nivolumab to investigate the effects of concurrent inhibition of the PD-1 and CTLA-4 receptors in nonhuman primates[68]. Although gastrointestinal (GI) toxicity has not been observed in cynomolgus monkeys treated with nivolumab alone, dose-dependent GI toxicity was evident in cynomolgus monkeys treated

weekly for 4 weeks with a combination of nivolumab and ipilimumab at combinations of 10 mg/kg and 3 mg/kg and 50 mg/kg and 10 mg/kg, respectively. GI effects have also been observed at a low incidence after ipilimumab administration [68].

In addition, an enhanced pre- and post-natal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted [68]. Administration of nivolumab at up to 50 mg/kg every 2 weeks was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at ≥ 10 mg/kg (area under the concentration-time curve [AUC] from time zero to 168 hours [$AUC_{(0\text{-}168\ h)}$] 117,000 µg•h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice [72].

For more detailed information or background on nivolumab, please refer to the Nivolumab Investigator's Brochure.

1.3.5.3 APX005M

Preclinical experiments with APX005M showed that it activates the CD40 signaling pathway, leading to APC activation, as demonstrated by an increased expression of CD80, CD83, and CD86 and by expression and release of cytokines from human DCs and lymphocytes. As a result of APC activation, APX005M enhances T-cell proliferation to alloantigen, triggers production of IFN-γ in response to viral antigens, and enhances T-cell response to tumor antigens. APX005M combined with a TLR 4 agonist or an antibody against programmed death ligand 1 (PD-L1) synergistically enhances T-cell responses.

In comparison with other CD40-agonistic antibodies, such as CP-870,893, SGN-40, and ADC-1013 analogs, APX005M is the most potent CD40 agonist. APX005M did not appear to have a substantive effect on normal human DC and T-cell counts, but could partially reduce B cell counts in vitro. The potential for APX005M to induce expression of cytokines was evaluated with peripheral blood mononuclear cells (PBMC) obtained from normal humans and treatment naïve cynomolgus monkeys, including anti CD3 antibody as a positive control. Cytokine secretion differed significantly between species with much less secretion from monkey PBMCs compared with human PBMCs. These data suggest that APX005M is a strong CD40-agonistic antibody that can activate APCs (DCs, B cells, and monocytes) and in turn stimulate T-cell response.

For more detailed information or background on APX005M, please refer to the APX005M Investigator's Brochure.

1.3.6 Clinical Summary

1.3.6.1 Cabiralizumab

1.3.6.1.1 Clinical Study Summary of Cabiralizumab

The clinical summary is based on three clinical studies:

1. Study FPA008-001 evaluated the safety of cabiralizumab as single or dual escalating doses in 48 healthy volunteers (36 cabiralizumab and 12 placebo). This study also evaluated the safety and efficacy of cabiralizumab administered as two or three doses, 14 days apart, in 18 rheumatoid arthritis patients. This study has been completed.

2. Study FPA008-002 is evaluating the safety and efficacy of cabiralizumab monotherapy for six months in approximately 40 patients with pigmented villonodular synovitis (PVNS).

3. Study FPA008-003 is evaluating the safety and efficacy of cabiralizumab as monotherapy and in combination with nivolumab in approximately 295 patients with advanced cancers.

1.3.6.1.2 Clinical Pharmacology Summary (Pharmacokinetics, Immunogenicity, and Pharmacodynamics) of Cabiralizumab

The available PK, ADA, and nonclassical CD16+ monocyte status following cabiralizumab treatment with either monotherapy or in combination with nivolumab were characterized in three trials: FPA008 001, FPA008-002, and FPA008-003. The PK, ADA, and nonclassical CD16+ monocyte data from Study FPA008-003 are summarized below; data from Studies FPA008 001 and FPA008-002 are presented in the cabiralizumab IB.

The PK profile of cabiralizumab is characterized by linear and nonlinear clearance pathways, with the latter likely mediated by binding to CSF1R on cells. As monocyte and macrophage cells are dependent on CSF1R for viability, these target-bearing cells are reduced in number following cabiralizumab treatment, resulting in a decrease of target-mediated clearance. Once target mediated clearance is saturated at high or repeat doses, cabiralizumab clearance is similar to other human IgG antibodies.

1.3.6.1.3 Clinical Safety Summary of Cabiralizumab

1.3.6.1.3.1 Study FPA008-001 – Healthy Volunteers and Rheumatoid Arthritis

Thirty six healthy volunteers and 18 RA subjects received cabiralizumab in Study FPA008 001. No dose-limiting toxicities (DLTs) were reported and no unexpected treatment related adverse events (AEs) have been reported from RA subjects treated with three doses up to 6 mg/kg.

1.3.6.1.3.2 Study FPA008-002 – Pigmented Villonodular Synovitis

Study FPA008-002 is currently ongoing and is evaluating cabiralizumab as monotherapy in subjects with PVNS. Details relating to safety are included in the latest version of the cabiralizumab IB (FivePrime, 2017).

1.3.6.1.3.3 Study FPA008-003 – Advanced Cancers

As of August 1, 2017, cabiralizumab-related AEs were reported in 169 of 195 subjects (87%) treated Q2W in Phase 1b of Study FPA008-003. The AEs reported in more than 10% of the subjects included: CK increased (77 subjects, 40%); periorbital edema (73 subjects, 73%); AST increased (65 subjects, 33%); fatigue (61 subjects, 31%); ALT increased and pruritus (32 subjects each, 16%); amylase increase and rash (30 subjects each, 15%); lipase increase (29 subjects, 15%); nausea (27 subjects, 14%); and LDH increased (20 subject, 10%).

Cabiralizumab-related Grade 3 AEs in Phase 1b were predominantly enzyme elevations of CK (14 Grade 3 and 14 Grade 4 events), LDH (one Grade 3 and one Grade 4 event), Alkaline phosphate ([ALP] two Grade 3 events), ALT (two Grade 3 events), and AST (10 Grade 3 events). Other related AEs that were Grade 3 and reported in 2 or subjects included 13 events of amylase increased (12 Grade 3 and one Grade 4), 15 events of Grade 3 lipase increased (14 Grade 3 and one Grade 4), 11 events of Grade 3 Fatigue, and three events of Grade 3 hypertension.

Twenty-six of 195 subjects (13%) experienced a cabiralizumab-related SAE in Phase 1b. The SAEs reported in two or more subjects included: CK increased (three subjects, 3%), brain edema, pneumonitis, hyponatremia (two subjects each, 1%). Also SAEs included one event of Grade 4 CK increased (related to cabiralizumab and nivolumab), one event of Grade 3 autoimmune colitis (related to nivolumab), and one event of Grade 3 hypopituitarism (related to cabiralizumab and nivolumab).

Two Grade 5 SAEs prior to study treatment discontinuation have occurred in Phase 1a of Study FPA008-003: one subject had a Grade 5 pulmonary embolus (not related) and a Grade 5 pneumonitis (related to both drugs; refer to Appendix 7 for management recommendations in cases of pneumonitis) and the other subject had a Grade 5 hypoxic respiratory failure secondary to pneumonia (not related). Six Grade 5 SAEs prior to study treatment discontinuation were reported in Phase 1b of this study. These included 1 sudden cardiac death (unrelated), 1 death due to tumor thrombus blocking a major blood vessel (unrelated), 2 patients with respiratory failure (unrelated), 1 patient with acute respiratory distress (related), and 1 patient with acute respiratory failure (related).

Data from the Phase 1 dose escalation study of cabiralizumab +/- nivolumab in advanced solid tumors was presented at the Society for Immunotherapy of Cancer's 2017 Annual Meeting. Cabiralizumab administered at 4 mg/kg every 2 weeks depleted circulating non-classical monocytes and had a tolerable safety profile when administered with or without nivolumab. The most common treatment-related adverse events attributed to cabiralizumab were elevations in LDH, CK, and serum transaminases without elevation of bilirubin. Grade 3-4 serum enzyme elevations occurred in 9/24 (38%) patients on the cabiralizumab monotherapy arm and in 40/205

(20%) patients on the cabiralizumab plus nivolumab arm. All cases of periorbital edema except for one was grade 1-2, occurring in 5/24 (21%) patients on the cabiralizumab monotherapy arm and in 84/205 (41%) patients on the cabiralizumab plus nivolumab arm. In heavily pre-treated patients with pancreatic cancer, durable clinical benefit was observed in 5/31 (16%) patients with a confirmed ORR of 13%. All confirmed responses occurred in patients with MSS disease who historically have not received benefit from anti-PD-1/PD-L1 agents and a study of cabiralizumab plus nivolumab with or without chemotherapy in pancreatic cancer (NCT03336216) is planned.

1.3.6.2 Nivolumab

1.3.6.2.1 Clinical Pharmacology Summary of Nivolumab

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Based on a population pharmacokinetic (PPK) analysis using data from patients with various tumor types, including melanoma, NSCLC, and RCC and a time varying CL model, nivolumab clearance was shown to decrease over time, with a median maximal reduction from baseline values of approximately 25% resulting in a geometric mean steady state clearance (CLss) (% coefficient of variation [CV%]) of 8.2 mL/h [53.9%]. The decrease in CLss is not considered to be clinically relevant. The geometric mean [CV%] volume of distribution at steady state (Vss) is 6.8 L (27.3%), and elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 status, solid tumor type, baseline tumor size, and hepatic impairment.

The effect of renal impairment on the CL of nivolumab was evaluated in subjects with mild (GFR < 90 and ≥ 60 mL/min/1.73 m2; n=379), moderate (GFR < 60 and ≥ 30 mL/min/1.73 m^2; n=179), or severe (GFR <30 and ≥ 15 mL/min/1.73 m2; n=2) renal impairment compared to subjects with normal renal function (GFR ≥ 90 mL/min/1.73 m2; n=342) in the PPK analysis. No clinically important differences in the CL of nivolumab were found between subjects with mild or moderate renal impairment and subjects with normal renal function. Data from subjects with severe renal impairment are too limited to draw conclusions on this population [45].

1.3.6.2.2 Safety Summary of Nivolumab

Overall, the safety profile of nivolumab monotherapy as well as combination therapy is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose (MTD) reached at any dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs to the nivolumab dose level. Most AEs were low-

grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management algorithms provided in the Nivolumab Investigator's Brochure.

A total of 39 and 306 patients with selected recurrent or treatment-refractory malignancies have been treated in a completed Phase 1 single-dose study (CA209001) and an ongoing Phase 1 multi-dose study (CA209003), respectively. As the safety profile from CA209003 to date is consistent with that observed for CA209001, only data from the larger and more recent study, CA209003, are presented below.

In CA209003 (n=306, including 129 patients with NSCLC), as of the 05-Mar-2013 database lock, drug-related AEs of any grade occurred in 75% of patients. The most frequent drug-related AEs occurring in at least 5% of patients included fatigue (28%), rash (15%), diarrhea (13%), pruritus (11%), nausea (9%), decreased appetite (9%), decreased hemoglobin (6%), and pyrexia (6%). The majority of events were low grade, with Grade 3/4 drug-related AEs observed in 17% of patients. The most common Grade 3/4 drug-related AEs occurring in at least 1% of patients were fatigue (2%), pneumonitis (1%), diarrhea (1%), abdominal pain (1%), hypophosphatemia (1%), and lymphopenia (1%). Drug-related SAEs occurred in 14% of patients; 8% were Grade 3/4 including pneumonitis (1%) and diarrhea (1%). The spectrum, frequency, and severity of drug-related AEs were generally similar across the dose levels tested. A review of the safety data by tumor type (RCC, NSCLC, metastatic castration-resistant prostate cancer [mCRPC], colorectal cancer [CRC], and melanoma) also did not show any clinically meaningful differences in the proportion of patients with AEs noted across tumor type.

Select AEs with potential immune-related causality, previously termed "immune-related adverse events" or "adverse events of special interest" were also analyzed taking into account multiple events, with rates adjusted for treatment duration. Most events occurred within the first 6 months of therapy; cumulative or novel toxicities were not observed with prolonged drug exposure. Nineteen of 306 patients (6%) experienced Grade 3/4 treatment-related select AEs. Fifty-two of 230 patients (23%) with drug-related AEs required management with systemic glucocorticoids and/or other immunosuppressive agents. Twenty-one of 52 (40%) resumed nivolumab therapy after toxicity resolved, while the others discontinued therapy.

Although tumor progression was the most common cause of mortality, there were 3 drug-related deaths associated with Grade 3/4 pneumonitis. Pneumonitis (any grade) occurred in 12 of 306 patients (4%), and Grade 3/4 pneumonitis occurred in 4 patients (1%), with clinical presentations ranging from asymptomatic radiographic abnormalities to progressive, diffuse pulmonary infiltrates associated with cough, fever, and/or dyspnea. No clear relationship between the occurrence of pneumonitis and tumor type, dose level, or treatment duration was noted. In 9 of 12 patients, pneumonitis was reversible after treatment discontinuation and/or with immunosuppressive therapy (glucocorticoids, infliximab, or mycophenolate).

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB and Opdivo® package insert [45].

1.3.6.3 APX005M

1.3.6.3.1 Clinical Pharmacology Summary of APX005M

APX005M is an IgG1 humanized mAb with the S267E mutation at the Fc region. APX005M binds with high affinity to human CD40 (Kd = 1.2 × 10-10 M) and monkey CD40 (Kd = 3.5 × 10−10 M), but does not cross-react with mouse or rat CD40. APX005M blocks the binding of CD40 to CD40L. The APX005M binding epitope has been mapped to 2 specific regions on CD40. These are 92TSEACESCVLHRSCSP107 and 125PCPVGFFSNVSSAFEKCHPW144. The region 92TSEACESCVLHRSCSP107 is known as a CD40L binding domain. It has been shown that CD40L-blocking antibodies tend to have more potent CD40 agonistic activities than CD40L-non-blocking antibodies [73].

The direct cytotoxicity effect and the antibody effector functions such as Antibody-dependent cellular phagocytosis (ADCP) of APX005M were determined in CD40 positive human lymphoma xenograft models in mice. In human lymphoma Ramos models, APX005M was capable of inhibiting tumor growth in a dose-dependent manner, and eradicated established tumors at 3 mg/kg and 10 mg/kg. A significant anti-tumor effect was also observed in the rituximab-resistant Namalwa model [64]. These data suggest that APX005M, as a single agent, can induce potent growth inhibition of CD40-expressing human tumors.

Preliminary human data shows that APX005M induces a dose-dependent activation of APCs (as demonstrated by increases in expression of activation markers such as CD54, CD70, CD80, CD86, HLA-DR), T cell activation and increases in circulating levels of IL12, INF-γ, TNF-α and IL6.

1.3.6.3.2 Pharmacokinetics of APX005M

Nonclinical pharmacokinetics (PK) of APX005M were determined in a Good Laboratory Practice (GLP) repeat-dose toxicology study using cynomolgus monkeys. Weekly intravenous (IV) administration of 5 doses of APX005M was well tolerated at 0.3, 3, and 30 mg/kg. The PK properties of APX005M are typical of other mAbs and comprise low clearance (average range of 0.401–7.27 mL/h/kg), small volume of distribution (average range of 57–80.1 mL/kg), and long terminal half-life (average >66 hours at 3 mg/kg and 30 mg/kg). Positive anti-drug antibodies (ADA) titers were observed in all animals in the low-dose group (0.3 mg/kg) but not in the high-dose group (30 mg/kg) [16]. Based on these results, the no observed adverse effect level (NOAEL) was considered 30 mg/kg.

There are limited human PK data with APX005M at this time. Exposures to APX005M at dose levels of 0.03 mg/kg or less were for the most part below the limit of quantitation (BLOQ). IV administration of APX005M at doses between 0.1 and 1 mg/kg lead to rapid increase in serum concentrations, reaching a maximum just after the end of the infusion. Levels declined rapidly thereafter and were for the most part BLOQ between 24 and 168 hours after the start of dosing.

Increases in the dose of APX005M (0.1 mg/kg to 1 mg/kg) led to approximately dose-proportional increases in maximum serum concentration (Cmax) and area under the curve at the last measurable time point (AUC0–t). No accumulation of APX005M was observed with every 21 days dosing.

1.3.6.3.3 Safety Summary of APX005M

Study APX005M-001 is a first in human phase 1 dose escalation study of APX005M with 8 pre-planned dose levels. APX005M was administered to study subjects at doses up to 1 mg/kg. At the 1 mg/kg dose level, 1 out of 6 dose limiting toxicity (DLT)-evaluable subjects experienced a DLT (grade 4 cytokine release syndrome). Two additional subjects at the 1mg/kg dose level experienced serious adverse events (SAE) in later cycles (Grade 3 cytokine release syndrome and Grade 4 thrombocytopenia). On May 2, 2016 Apexigen decided to discontinue dose escalation and enroll up to 6 subjects in dose level 0.6 mg/kg (originally designed as an intermediate de-escalation dose level) and an additional 3 subjects at the previously completed dose level 0.3 mg/kg to better characterize the safety and pharmacodynamics (PDn) of APX005M and to help establish the single agent recommended phase 2 dose (RP2D). The RP2D for APX005M as a single agent every 21 days is 0.3 mg/kg body weight.

As of the data cutoff date of 14 April 2017, 432 AEs have been reported in the 30 subjects enrolled in Study APX005M-001. The majority of AEs (371/432 [85.9%]) were mild or moderate (≤ Grade 2) in severity, 44 events (10.2%) were reported as Grade 3, and 8 events (1.9%) were reported as Grade 4. No Grade 5 events have been reported.

As of 14 August 2017, 17 SAEs had been reported in 6 subjects. With the exception of cytokine release syndrome and thrombocytopenia, all SAEs were considered unrelated to APX005M. Cytokine release syndrome is an expected on-target side effect of CD40 agonists. No thromboembolic or bleeding events have been reported to date for APX005M.

APX005M demonstrated a dose-dependent activation of APCs (as demonstrated by increases in expression of activation markers such as CD54, CD70, CD80, CD86, HLA-DR), T cell activation and increases in circulating levels of IL12, INF-γ, TNF-α and IL6.

For further details on the APX005M-001 study please refer to latest version of the APX005M Investigator's Brochure [64].

Symptoms associated with cytokine release syndrome (including but not limited to flushing, itchiness, chills, fever, rash, tachycardia, hypotension, hypertension, rigor, and myalgia) after administration of APX005M are possible and have been observed in some of the subjects receiving APX005M. Guidance for monitoring and management of cytokine release syndrome are included in this protocol and in the APX005M Investigator's Brochure.

Transient transaminase elevations (≤ Grade 2) have been observed in several subjects with liver metastases, which were not associated with a particular dose of APX005M. Six subjects with

liver metastases enrolled in the study experienced a transient increase in total bilirubin. Liver function test abnormalities tend to resolve to baseline within 7 days from APX005M administration.

Transient decreases in peripheral blood lymphocyte count in general and B-cell count in particular have been observed for APX005M as well as for other CD40-agonistic mAbs and are believed to be a PDn effect. Transient decreases in platelet counts were observed for some of the subjects receiving higher doses of APX005M but were not associated with bleeding or other clinical manifestations.

Other symptoms might also occur, including allergic reactions, which could be severe, pulmonary edema, and rarely, thromboembolic events, myocardial infarction and/or death. In the ongoing Phase 1 study APX005M-001, APX005M demonstrated a dose-dependent activation of APCs, T cell activation and increases in circulating levels of cytokines.

The biological effects and the overall tolerability of APX005M up to 1mg/kg body weight suggest a best in class profile for APX005M and the possibility of a safe and tolerable combination with other immunomodulatory antibodies such as nivolumab.

1.4 Clinical Experience Involving Serum Enzyme Elevations

The safety and preliminary efficacy of cabiralizumab is currently being evaluated in 3 clinical trials. A common feature observed across the clinical trials is an elevation of AST, CK, and LDH after the administration of cabiralizumab. These alterations are the consequence of the direct effect of anti-CSF1R antibodies on the Kupffer cell in the liver that results in a depletion of these cells. Depletion of Kupffer cells allows the enzymes, which are released following normally occurring liver cell turnover, to enter circulation (where they are measured by routine laboratory assessment) rather than being absorbed by the Kupffer cells. Elevated liver enzymes, thus, represent a PD marker rather than a safety signal. The observed elevations were asymptomatic not permanent and not associated with clinical sequelae. Similar effects have been observed across other CSF1R targeted agents (see cabiralizumab IB for additional details). There is a significant body of evidence from the cabiralizumab preclinical and clinical experience as well as from others in the field that suggest elevations of serum enzymes caused by inhibition of the CSF1R pathway are reversible and are not associated with clinical sequelae [66, 74-78].

1.4.1 Serum Enzyme Elevations with Cabiralizumab

In Study FPA008-003, 34 subjects have been dosed as part of Phase 1a dose escalation (24 in cabiralizumab monotherapy and 10 in cabiralizumab + nivolumab combination therapy) and 195 subjects have been dosed as part of Phase 1b dose expansion as of 1 August 2017. In Phase 1a, CK was elevated in 11 of 34 subjects (32%), and 3 events (1%) were Grade 3 or higher. AST was elevated in 16 of 34 subjects (47%), and 10 events (29%) were Grade 3 or higher. ALT was elevated in 4 of 34 subjects (17%), and none of these were Grade 3 or higher. In Phase 1b, CK was elevated in 82 of 195 subjects (42%), and 29 events (15%) were Grade 3 or higher. AST was elevated in 76 of 195 subjects (39%), and 14 events (7%) were Grade 3 or higher. ALT was

elevated in 39 of 195 subjects (20%), and five events (3%) were Grade 3 or higher.
The serum enzyme elevations for Studies FPA008-001 and FPA008-002 follow a similar pattern.

Please refer to the cabiralizumab IB for more detailed information about these serum enzyme elevations.

1.4.2 Serum Enzyme Elevations with Nivolumab

The hepatic enzyme changes caused by cabiralizumab and nivolumab are due to different mechanisms that should not be additive. For cabiralizumab, the elevations are hypothesized to be due to the on-target effect of Kupffer cell reduction and not to liver cell toxicity. Hepatic AEs, including possible drug induced liver injury (DILI) cases, have been managemable using an established management algorithm and thus do not meaningfully alter the benefit/risk of nivolumab in the advanced malignancy populations. Guidelines for management and safety assessments focused on the liver can be found in Section 4.8 and Section 4.9.

1.4.3 Serum Enzyme Elevations in APX005M

Transient transaminase elevations (≤ Grade 2) with APX005M administration have been observed in several subjects with liver metastases, which were not associated with a particular dose of APX005M. Six subjects with liver metastases enrolled in the study experienced a transient increase in total bilirubin. Liver function test abnormalities tend to resolve to baseline within 7 days from APX005M administration. Elevations of ALT, AST, CK, and LDH were not associated with signs or symptoms of hepatic or muscle injury as demonstrated by concurrent normal total bilirubin, INR, aldolase, and troponin levels.

Please refer to the APX005M Investigator's Brochure for more detailed information about serum liver ezyme elevations and their management, as outlined in Section 4.8 and Section 4.9. Additional laboratory abnormality management algorithms are included to help manage elevations of CK in Section 4.8 and Section 4.9.

2. Objectives

2.1 Phase 1a Objectives

2.1.1 Primary

- To assess the safety and tolerability of APX005M in combination with cabiralizumab
- To assess the safety and tolerability of APX005M in combination with cabiralizumab and nivolumab
- To determine the recommended RP2D of APX005M in combination with a fixed dose of cabiralizumab and nivolumab in advanced melanoma, NSCLC, and RCC

2.1.2 Secondary

- To determine the AE profile of this combination

2.1.3 Exploratory

- To characterize the pharmacokinetic (PK) profile of APX005M when administered in combination with cabiralizumab and nivolumab
- To characterize the pharmacodynamic (PD) profile of APX005M when administered in combination with cabiralizumab and nivolumab
- To further characterize the PD profile and immunogenicity of APX005M in combination with cabiralizumab and nivolumab by analyses of pre-treatment and on-treatment tumor biopsies and blood collection

2.2 Phase 1b Objectives

2.2.1 Primary

- To determine the objective response rate (ORR) using RECIST v1.1 to APX005M in combination with cabiralizumab and nivolumab in 3 separate patient cohorts: advanced melanoma, NSCLC, and RCC whose tumors are resistant to anti-PD-1/PD-L1 therapy
- To evaluate the safety and tolerability of the RP2D of APX005M in combination with cabiralizumab and nivolumab

2.2.2 Secondary

- To determine the PFS of patients with melanoma, NSCLC or RCC treated with APX005M in combination with cabiralizumab and nivolumab whose tumors are resistant to anti-PD-1/PD-L1 therapy.
- To determine the OS of patients with melanoma, NSCLC or RCC treated with APX005M in combination with cabiralizumab and nivolumab whose tumors are resistant to anti-PD-1/PD-L1 therapy.
- To assess the association of selected biomarker measures and clinical efficacy measures using pre-treatment and on-treatment tumor biopsies and blood collection

2.2.3 Exploratory

- To identify immune correlates that are associated with clinical response or resistance to the triple combination. Biomarker analyses will include study of pre-treatment and on-treatment biopsies as well as analyses of select serum and PBMC markers.

3. Investigational Plan

3.1 Study Design and Duration

This study is a Phase 1/1b, open-label, single institution, dose escalation and dose expansion study to evaluate the efficacy, safety, and tolerability of APX005M in combination with nivolumab and cabiralizumab in patients with advanced melanoma, NSCLC, and RCC. Nivolumab is a fully human monoclonal antibody directed against PD-1. Cabiralizumab is a humanized monoclonal antibody directed against CSF1R. APX005M is a humanized IgG1 agonistic monoclonal antibody that binds CD40.

Patients will be sequentially enrolled in the phase 1 dose escalation portion in 6 cohorts using a standard 3 + 3 design to determine safety, characterize the adverse events, and establish the MTD of APX005M in combination with cabiralizumab and nivolumab. A minimum of 48 hours observation will be required after each patient is enrolled in cohorts 1-6, before a subsequent patient can be enrolled. Approximately 3 patients will be enrolled into each cohort. Cohorts 1, 3, and 5 will include cabiralizumab at the fixed RP2D of 4 mg/kg and dose escalation of APX005M. Cohorts 2, 4, and 6 will include nivolumab at 240 mg, cabiralizumab at 4 mg/kg, and dose escalation of APX005M.

All study drugs will will be given on Day 1 of each 14-day treatment cycle. Pre-medications will be given before nivolumab. Nivolumab will be administered as an IV infusion over 30 minutes first followed by a 30-minute break and then cabiralizumab will be administered as an IV infusion over 30 minutes. After another 30-minute break, APX005M will be administered as an IV infusion over 60 minutes. Patients must remain near the vicinity of a hospital with rapid access to an intensive care unit setting during the initial 48 hour period after treatment for the first two treatment cycles.

Dose escalation will be based on the number of DLTs experienced during the DLT evaluation interval as determined by the PI and Industry Collaborators (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.

The phase 1b portion will enroll patients in three cohorts (advanced melanoma, NSCLC, and RCC) to study the RP2D of APX005M in combination with nivolumab and cabiralizumab.

3.1.1 Screening Period

All screening evaluations must be completed and reviewed by the Investigator 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.

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.

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 1 Cohorts and Combination Dose Escalation Cohorts

Phase 1 consists of three dose escalation cohorts of APX005M in combination with cabiralizumab alone, and three dose-escalation cohorts of APX005M in combination with nivolumab and cabiralizumab. A minimum of 3 patients will be enrolled in each cohort. The planned dose levels and schedules for the Phase 1 dose escalation cohorts are as follows in Table 2:

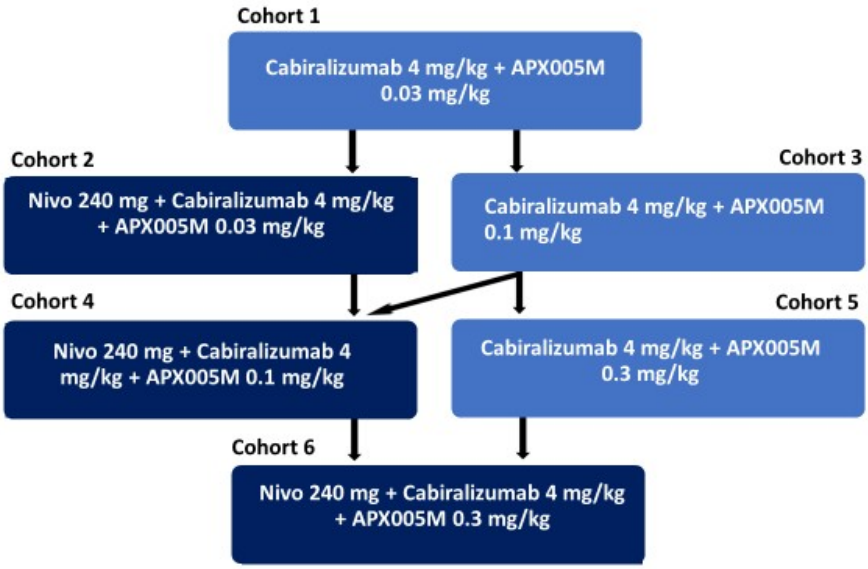
Table 2

Cohort	Nivolumab (mg)	Cabiralizumab (mg/kg)	APX005M (mg/kg)
1	Not given	4	0.03
2	240	4	0.03
3	Not given	4	0.1
4	240	4	0.1
5	Not given	4	0.3
6	240	4	0.3

A minimum of 48 hours observation will be required after each patient is enrolled in cohorts 1-6, before a subsequent patient can be enrolled. As depicted in Figure 6, accrual to cohorts 2 and 3 will only start after the last patient in cohort 1 has been observed for toxicity for at least two 14-day cycles (28 days in total); accrual to cohort 4 will commence when the last patients on cohorts

2 and 3 have been observed for at least two 14-day cycles, accrual to cohort 5 will commence only after the last patient on cohort 3 has been observed for at least two 14 day cycles, and accrual to cohort 6 will accrue once the last patients on cohorts 4 and 5 have been observed for at least two 14-day cycles. Doses will be de-escalated as determined by toxicities.

Figure 6



All dose escalation decisions will be based on assessment of toxicity, overall safety, and tolerability. Dose escalation decisions will be agreed upon by the PIs and study collaborators. Prior to initiating each new dose level or expanding an existing dose level, a safety teleconference will be held wherein the PIs and study collaborators will review patient data, including but not limited to the available 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 PIs collectively agree, following review of safety, PK, and PD data (if available), that a different dose escalation scheme 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.

For the purpose of dose escalation, we will require a 28 day observation period from the time the last patient in a given cohort was treated. For the purpose of calculating the MTD, we will require a minimum of 28 days of observation for each patient.

Dose escalation in Phase 1 will proceed as follows:

If none of the first 3 evaluable patients in a dose cohort experience a DLT in the first two cycles, then the next 3 patients will be treated at the next higher dose cohort. If 1 of 3 patients within a cohort experiences a DLT in the first two cycles, then 3 additional patients will be added to that cohort. If a second patient experiences a DLT at that dose level in the first two cycles, the next cohort will not be initiated, and the dose of one or more drugs will be de-escalated. Patients at each dose level will be evaluated for at least 28 days from the start of treatment before additional patients can be treated at a higher dose level. If DLTs are observed in 2 or more patients within a cohort, the maximum tolerated dose (MTD) will have been exceeded and no further patients will be treated at that dose level.

DLT evaluation and enrollment decisions will follow the guidance in Table 3.

Table 3: Algorithm for Dose-Escalation Decisions

Number of Patients with DLT at a Given Dose Level	**Dose Escalation Decision Rule**
0/3	Escalation will occur into the next highest dose cohort
1/3	Enroll 3 additional patients at current dose level
≥2/3	Stop enrollment. Enroll 3 more patients at the lower dose level, if only 3 were previously entered, or at an intermediate dose level.
1/6	Open next cohort
≥2/6	Stop enrollment. Enter 3 more patients at the lower dose level at an intermediate dose level.

Dose escalation will continue until either the MTD or maximum planned dose of APX005M is reached, with a minimum of 3 patients enrolled in each cohort.

The MTD is defined as the highest dose associated with DLTs in less than or equal to 33% of patients receiving APX005M in combination with cabiralizumab or with cabiralizumab and nivolumab, 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 RP2D could be lower than the MTD. If the MTD is not reached, and the highest evaluated APX005M dose in combination with cabiralizumab and nivolumab is well tolerated, the data will be reviewed to assess whether further dose escalations of APX005M are warranted.

In order **to calculate the MTD and RP2D**, every patient included in this calculation must have received at least 2 doses of study drugs and have been monitored for at least 2 full cycles (28 days). If a patient does not receive 2 doses of study drugs and does not complete safety assessments (e.g., safety lab and/or AE reporting) in the first 28 days 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 28 days. All such discussions and decisions will be documented as part of the dose escalation decision-making process.

3.1.2.1.1 Dose Limiting Toxicity

A DLT is defined as any of the following AE (graded using National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0), which occurs during the first 28-days of cabiralizumab/APX005M or nivolumab/cabiralizumab/APX005M administration that is not clearly due to a cause other than the study medication (e.g., disease under study, car accident).

1. Grade 4 neutropenia or grade 4 thrombocytopenia lasting ≥ 7 days
2. Neutropenic fever of any duration
3. Grade ≥ 3 thrombocytopenia if associated with:
    a. Clinically significant bleeding or requirement for platelet transfusion, or
    b. A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit
4. Any grade ≥3 non-hematologic toxicity (not laboratory) **with the exception of**:
    - Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor)
    - Grade 3 joint pain
    - Grade 3 fatigue lasting less than 1 week
    - Serum elevations of CK > 15X ULN and ≤ 20X ULN that last for < 7 days
    - Grade 3 or Grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 72 hours and either resolve spontaneously or respond to conventional medical intervention
    - Grade 3 nausea, vomiting, or diarrhea lasting less than 72 hours, and either resolves spontaneously or responds to conventional medical intervention including adequate anti-emetics or other supportive care
    - Grade 3 or grade 4 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
    - Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion)
    - Grade 3 endocrinopathy that is well controlled by hormone replacement
    - Grade 3 infusion reaction that returns to Grade 1 in < 6 hours
5. Any Grade ≥ 3 non-hematologic laboratory value if:
    a. Immune suppression other than corticosteroids is required to treat the subject, or
    b. The abnormality itself soley leads to hospitalization, or
    c. The abnormality persists for >1 week. For AST/ALT > 12x ULN, DLT is defined as not improving after >7 days or the value increases by more than 5X ULN over 72 hours;

e.g. if an AST of 300 rises to 500 in 72 hours, where AST 36 is ULN, a rise of 200 is greater than 5X ULN (180) and would be considered a DLT

6. Any Grade ≥ 3 AST/ALT elevation combined with total bilirubin >2x ULN (for patients with Gilbert's syndrome, use bilirubin ≥ 2X baseline) or INR > 1.5 not on warfarin
7. Failure to recover from a treatment-related AE to baseline or ≤ Grade 1 within 12 weeks of last dose of investigational product (except Grade 2 alopecia and Grade 2 fatigue)
8. Any death not clearly due to the underlying malignancy or extraneous causes (e.g. car accident)
9. Recurrence of Grade 4 rash, or other Grade 3 immune-related AE (irAE), or Grade 4 infusion-related AE. Recurrent grade 3 infusion reactions should be discussed with the study PI.
10. Any toxicity requiring dose reduction of APX005M or permanent discontinuation of any of the study drugs.

irAE is defined as a clinically significant AE that is associated with study drug exposure, with the exception of AEs related to cytokine release, attributable to APX005M, and is consistent with an immune-mediated mechanism.

Certain toxicities, even if already resolved, will make it unacceptable to advance to subsequent cohorts as planned, including but not limited to:

- Grade 4 myocarditis; Grade 3 myocarditis will need to be discussed with the study PI
- Grade 3 neurotoxicity with the exception of peripheral neuropathy
- Grade 4 pneumonitis
- Bone marrow aplasia

3.1.2.2 Phase 1 Dose Escalation Extended Treatment Period

Patients from the Phase 1 dose escalation combination cohorts are allowed to continue to receive APX005M in combination with nivolumab and/or cabiralizumab at the same dose levels until disease progression, unacceptable toxicity, or other reason for treatment discontinuation.

If a complete response (CR) is achieved, patients will be allowed to continue on therapy until disease progression, unacceptable toxicity, or other reason for treatment discontinuation.

3.1.2.3 Phase 1b Expansion Cohorts

To further characterize safety and efficacy of APX005M in combination with nivolumab and cabiralizumab, Phase 1b will enroll patients of 3 advanced cancer types: melanoma, NSCLC, and RCC. Enrollment in Phase 1b will begin when an RP2D for APX005M 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.

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 (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. The maximum time allowed time on study treatment will be up to 2 years unless the study is terminated sooner by the Sponsor.

3.1.6 Stopping Rules

3.1.6.1 Stopping Rules for All Cohorts

Management of drug-related toxicities and laboratory abnormalities will follow the guidelines outlined in Section 4.8 and Section 4.9.

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

3.1.6.2 Treatment Beyond Progression

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 PI.

3.2 Study Population

3.2.1 Planned Number of Patients

In the Phase 1 dose escalation portion of the trial, we will enroll at least 3 patients per cohort. There are a total of 6 cohorts. In the Phase 1b portion, a Simon two stage design will be used. At least 13 patients per each disease cohort (advanced melanoma, NSCLC, and RCC) will be enrolled in the first phase and in the second phase, an additional 21 patients per disease cohort, for a maximum of 34 patients per disease cohort, are expected to be enrolled, for a total of 102 subjects.

3.2.2 Inclusion Criteria for All Cohorts

1. Biopsy proven metastatic melanoma, NSCLC or RCC whose disease has progressed on anti-PD(L)-1 therapy without any intervening therapy. Progression will be determined by the investigator based on clinical and/or radiographic features. Additional requirements as below:

   Melanoma:
   - Unresectable stage III or stage IV melanoma, irrespective of *BRAF* status, with histologic or cytologic confirmation

   RCC:
   - Histologic or cytologically documented, locally advanced unresectable or metastatic RCC irrespective of histologic subtype

   NSCLC:
   - Histologic or cytologically documented, locally advanced or metastatic (i.e. Stage IIIB not eligible for definitive chemoradiotherapy, stage IV, or recurrent) NSCLC.

- Patients known to harbor an ALK rearrangement or EGFR mutation known to be sensitive to FDA-approved tyrosine kinase inhibitors (TKI), are only eligible after experiencing disease progression (during or after treatment) or intolerance to an FDA approved ALK TKI or EGFR TKI, respectively.
- Patients with TKI-treated EGFR mutant NSLC harboring the secondary EGFR T790M tumor must have received prior osimertinib.
- Patients with crizotinib-treated ALK rearranged NSCLC must have received a next generation ALK inhibitor.

2. At least 1 site of disease must be accessible to provide repeat biopsies for tumor tissue. This site may be a target lesion as long as it will not be made unmeasurable by the biopsy procedure. Subjects may forgo the pretreatment biopsy if 1) an entire archival FFPE tumor block is available that was taken after the last systemic therapy was administered or 2) if the Investigator deems that the subject does not have tumor in a site that is amenable to biopsy.

3. Age ≥18, able to understand and sign the informed consent form

4. ECOG performance status < 2

5. Any number of previous treatments. Other prior systemic therapies must have been administered at least 4 weeks before administration of the study drugs; the exception to this is molecular targeted therapies which must have been administered at least 2 weeks prior to the start of the study drugs or after 5 half-lives have occurred, whichever is shorter.

6. Life expectancy of at least 6 months

7. A history of previously treated brain metastases is allowed, provided that they are stable for at least 4 weeks.

8. Willingness to undergo mandatory tumor biopsy prior to initiation of therapy and before the fifth cycle.

9. Willingness to provide an archival specimen block, if available, for research.

10. Patients must have normal organ and marrow function as defined below:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of	≤1.5 X upper limit of normal (ULN) **OR** ≥50 mL/min for subject with creatinine levels > 1.5 X institutional ULN

creatinine or CrCl)	
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

11. Female subject of childbearing potential should have a negative urine or serum pregnancy within 24 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

12. Female subjects of childbearing potential should be willing to use a highly effective contraception (hormonal or IUD) or be surgically sterile, or abstain from heterosexual activity for a period of at least 5 months after the last dose of study drug. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

13. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through at least 7 months after the last dose of study drug.

14. 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.

15. Prior focal radiotherapy must be completed before first dose of study drug administration, although palliative radiation may be allowed on treatment (see permitted concomitant therapies below). Radiation to pulmonary or intestinal sites must be completed at least 4 weeks prior to study Day 1. There is no time restriction prior to study Day 1 for patients who have received radiation to bone, soft tissue sites or other sites. No radiopharmaceuticals (strontium, samarium) within 8 weeks before first dose of study drug administration.

16. Major surgery must be completed at least 4 weeks 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. Surgical wounds must be healed.

3.2.3 Exclusion Criteria for All Cohorts

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

1. Untreated brain metastases.

2. A patient who has had prior immune therapy or chemotherapy within 4 weeks prior to study Day 1, or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent will be excluded. Patients who have had prior molecular targeted therapy using small molecule inhibitors must have received their last dose no less than 2 weeks prior to or no less than five half-lives from study Day 1.
    a. Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
    b. Note: Toxicity that has not recovered to ≤ Grade 1 is allowed if it meets the inclusion requirements for laboratory parameters.

3. Has had prior treatment with any other CSF1R inhibitor or CD40 agonist.

4. Use of corticosteroids to control immune related adverse events at enrollment will not be allowed, and patients who previously required corticosteroids for symptom control must be off steroids for at least 2 weeks. Low-dose steroid use (≤10 mg of prednisone or equivalent) as corticosteroid replacement therapy for primary or secondary adrenal insufficiency is allowed.

5. Has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to prior treatments with the exception of clinically insignificant adverse events such as alopecia, clinically insignificant laboratory abnormalities, clinically insignificant rash and Grade 2 neuropathy.

6. History of grade 3-4 neurologic or cardiac toxicity or life-threatening liver toxicity poorly responsive to steroids with prior anti-PD-1/anti-PDL1 monotherapy.

7. Presence of leptomeningeal disease.

8. Has active autoimmune disease unrelated to immune checkpoint inhibitors that has required systemic treatment in the past year (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

9. Pregnancy or breast feeding. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with nivolumab, cabiralizumab or APX005M, breastfeeding must be discontinued if the mother is enrolled on this trial.

10. Patients may not be receiving any other investigational agents and may not have participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

11. Patients with either a concurrent medical condition (including medical illness, such as active infection requiring treatment with intravenous antibiotics or the presence of laboratory

abnormalities) or history of a prior condition that places the patient at unacceptable risk if he/she were treated with the study drug or a medical condition that confounds the ability to interpret data from the study.

12. Concurrent, active malignancies in addition to those being studied (other than cutaneous squamous cell carcinoma or basal cell carcinoma)

13. Active (non-infectious) pneumonitis.

14. Has a known Human Immunodeficiency Virus (HIV), Hepatitis B (HBV), or Hepatitis C (HCV) acute or chronic infection.

15. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

16. History of myocardial infarction or unstable angina within 3 months prior to Cycle 1, Day 1

17. Prisoners, or subjects who are under compulsory detention

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

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

20. Concomitant use of statins 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

21. Open wounds and active skin infections

22. Uveal melanoma in the Phase Ib dose expansion trial

3.2.4 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 [79, 80].

3.3 Concomitant Medications

All medications taken within 28 days before the administration of the first dose of any study drug and all concomitant therapy administered during the study until 100 (±7) days after last dose of any study drug (or until initiation of subsequent anti-cancer therapy) will be collected. All subsequent anti-cancer therapy will be collected in the Long-Term Follow-up Period.

Information on all prior treatments indicated for advanced cancer, including chemotherapy, biochemotherapy, immunotherapy, radiation, surgery, biologic, and experimental therapy will be collected.

No concomitant medication information will be collected following patient discontinuation from the study except for concomitant medication use associated with study drug-related AEs or AEs that lead to discontinuation from the study.

3.3.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug-related AE or specified in the eligibility section):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids
- Vaccines except as noted in Section 3.3.2
- Statins for treatment of hypercholesterolemia. Statins will be allowed only if the patient is on a stable dose for over 3 months prior to the study and has a stable status without any CK elevations
- Other therapies including biologic, immunotherapy, extensive non-palliative radiation therapy, standard treatments, or investigational agents or devices

3.3.2 Permitted Therapy

Patients are permitted to use of topical, ocular, intra-articular, intranasal, and inhaled corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses >10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) and also for the treatment of tumor-related AE is permitted.

Concomitant palliative and supportive care for disease-related symptoms (including bisphosphonates and RANK-L inhibitors) is allowed. Transfusions are permitted as needed.

The inactivated seasonal influenza vaccine can be given to patients while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (i.e., pneumovax, varicella, etc.) must be discussed with the Investigators and Industry Collaborators. In general, live vaccines are prohibited within 30 days prior to start of study drugs and within the first 12 cycles on study.

Palliative radiation or metastasectomy is allowed; these lesions will are not subsequently be included for tumor measurements.

Concomitant use of statins will be allowed only if the patient is on a stable dose for over 3 months prior to the study and is in stable status without any CK elevations.

3.4 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, APX005M, 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 APX005M, cabiralizumab and nivolumab.

Please refer to the Pharmacy Manual and/or Investigator's brochures for more specific information on each drug product.

Table 4 Study treatments

Product Description / Class and Dosage Form	Potency/Route of Administration	Blinded or Open Label	Packaging / Appearance	Storage Conditions (Per Label)
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/mL)	Open label	Vial	Refer to the label on container and/or pharmacy manual
Nivolumab (BMS-936558-01) Solution for Injection	40 mg (10 mg/mL)	Open label	Vial	Refer to the label on container and/or pharmacy manual
Cabiralizumab (BMS-986227) Solution for Injection	140 mg (20 mg/mL)	Open label	Vial	Refer to the label on container and/or pharmacy manual
APX005M Solution for Injection	200 mg (10 mg/mL)	Open label	Vial	Refer to the label on container and/or pharmacy manual

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).

Please refer to the current version of the Investigator Brochures and/or pharmacy manual for complete preparation, storage, and handling information.

4.2.1 Cabiralizumab

The investigational supply of cabiralizumab will be provided to the study centers by Bristol-Myers Squibb 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 7 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 7 mL of a 20 mg/mL solution of cabiralizumab (approximately 140 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 Cabiralizumab Investigator's Brochure 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 Bristol-Myers Squibb.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween 80), pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals.

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL.

During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Vials of nivolumab injection must be stored at 2 degrees C to 8 degrees C (36°F to 46°F) and protected from light and freezing. The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

Refer to the Nivolumab Investigator's Brochure for for more specific information on the drug product.

4.2.3 APX005M

The investigational supply of APX005M will be provided to the study centers by Apexigen.

APX005M is supplied in 20 mL Type 1 clear glass vials for IV administration. Each vial contains 10 mg APX005M/mL in a sterile, clear to slightly opalescent, colorless to slightly yellow, preservative-free solution (pH 5.5) containing 25 mM sodium acetate, 248 mM trehalose, and 0.02% polysorbate 20 in water for injection (WFI). The 20 mL vials are intended for single use.

APX005M is intended for IV infusion. For use, APX005M is diluted in normal saline and infused via IV infusion or syringe pump.

Refer to the APX005M Investigator's Brochure for more specific information on the drug product.

4.3 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.

See Section 4.4.1 and Figure 6 for dosing schema. Patients who qualify for Phase 1 dose esclation of the study will be enrolled as follows:

- Cohort 1 will be enrolled first and these patients will be followed one 14-day cycle.
- Once the DLT follow-up period of 28 days is cleared for Cohort 1, simultaneous enrollment to Cohort 2 and Cohort 3 will occur. Patients in these cohorts will be treated for a total of one 14-day cycle.
- Simultaneous enrollment into Cohort 4 and Cohort 5 will proceed once the 14-day DLT

period for dose escalation is cleared in the preceeding Cohorts 2 and 3.

- Once the DLT period of 28 days for dose escalation is cleared Cohorts 4 and 5, enrollment to the final Cohort 6 will occur.
- The MTD will be calculated for patients who have received at least 2 cycles (at least 28 days) of study drug.
- Dose escalation into sequential dose levels of APX005M in combination with cabiralizumab and nivolumab may proceed until DLTs are observed either in the cabiralizumab/APX005M doublet therapy cohorts 1, 3, and 5 or in the nivolumab/cabiralizumab/APX005M triplet therapy cohorts after discussion and agreement between the PIs and Industry Collaborators.

In Phase 1b, a maximum of 34 patients will be enrolled per disease-specific cohort (advanced melanoma, NSCLC, or RCC). Enrollment will be open for all cohorts in parallel and will continue until the enrollment target is reached. Once a disease cohort is filled, further enrollment will be restricted to the cohort(s) that have not been filled. A total of approximately 102 patients will be enrolled in the Phase 1b arm of the study.

4.4 Study Drug Dosing and Dose Modification

4.4.1 Dosing

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 4.8 and Section 4.9. Patients must remain near the vicinity of a hospital with rapid access to an intensive care unit setting during the initial 48 hour period after treatment for the first two treatment cycles.

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

Please refer to the study schema for dosing as follows:

- Phase 1 Dose Escalation (Dosing on Day 1 of each 14-day cycle):
    - Cohort 1: Cabiralizumab 4 mg/kg + APX005M 0.03 mg/kg
    - Cohort 2: Nivolumab 240 mg + Cabiralizumab 4 mg/kg + APX005M 0.03 mg/kg
    - Cohort 3: Cabiralizumab 4 mg/kg + APX005M 0.1 mg/kg

- Cohort 4: Nivolumab 240 mg + Cabiralizumab 4 mg/kg + APX005M 0.1 mg/kg
- Cohort 5: Cabiralizumab 4 mg/kg + APX005M 0.3 mg/kg
- Cohort 6: Nivolumab 240 mg + Cabiralizumab 4 mg/kg + APX005M 0.3 mg/kg

- Phase 1b (Dosing on Day 1 of each 14-day cycle):
  - ALL patients: Nivolumab 240 mg + Cabiralizumab 4 mg/kg + APX005M at the RP2D

4.4.1.1 Nivolumab Dosing

The following patients on the trial will receive nivolumab as follows:

- Phase 1:
  - Cohorts 1, 3, and 5: will NOT receive nivolumab
  - Cohorts 2, 4, and 6: nivolumab 240 mg IV
- Phase 1b:
  - All patients will receive nivolumab 240 mg IV as the first drug in sequence

Nivolumab will be dosed as a 30-minute IV infusion on Day 1 of each 14-day treatment cycle as above.

Routine premedication administered 30 minutes prior to nivolumab should include:

- H1 antagonist (e.g. Benadryl 25 mg PO)
- Oral or IV H2 antagonist (e.g., ranitidine 150−300 mg, cimetidine 300−800 mg, nizatidine 150−300 mg, and famotidine 20−40 mg)
- Oral nonsteroidal anti-inflammatory drug (may comprise ibuprofen 400 mg or equivalent)
- Acetaminophen 650 mg

If a grade 1-2 infusion reaction is observed during the proposed infusion rate of nivolumab 240 mg over 30 minutes, the infusion rate will be extended to 60 minutes. Nivolumab should be held for a grade 3 infusion reaction and retreatment should be discussed with study PI. Nivolumab should be discontinued for a grade 4 infusion reaction.

There will be no dose escalations or reductions of nivolumab allowed. Refer to the Pharmacy Manual for nivolumab preparation instructions.

4.4.1.2 Cabiralizumab Dosing

All patients in all cohorts of the trial will receive cabiralizumab.

Cabiralizumab will be administered as a fixed dose of 4 mg/kg given over 30 minutes by IV infusion. In phase 1 dose escalation cohorts 1, 3, and 5, cabiralizumab will be given first

followed by APX005M. In this case, premedications outlined in Section 4.4.1.1 should be given 30 minutes prior to cabiralizumab on Day 1 of each 14-day treatment cycle.

In phase 1 dose escalation Cohorts 2, 4, and 6, and in all patients on the phase 1b portion of the trial, cabiralizumab will be administered 30 minutes after the end of the nivolumab infusion, on Day 1 of each 14-day treatment cycle.

If any Grade 3 or higher infusion reaction is observed during the proposed infusion rate of cabiralizumab 4 mg/kg over 30 minutes, cabiralizumab should be discontinued permanently. For further management of infusion reactions, please see Section 4.8 and Section 4.9.

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.

4.4.1.3 APX005M Dosing

All patients in all cohorts of the trial will receive APX005M as follows:

- Phase 1:
  - Cohorts 1 and 2: APX005M 0.03 mg/kg
  - Cohorts 3 and 4: APX005M 0.1 mg/kg
  - Cohorts 5 and 6: APX005M 0.3 mg/kg

- Phase 1b:
  - At the determined RP2D

APX005M is administered on Day 1 of each 14-day treatment cycle approximately 30 minutes following cabiralizumab using a 60 minute IV infusion. A window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 55 minutes to 70 minutes).

Premedication should have already been administered 30 minutes prior to first dose of study drug, as described in Section 4.4.1.1. When the time between premedication and scheduled APX005M administration exceeds 4 hours, patients may receive an additional course of premedication prior to APX005M administration.

The APX005M infusion can be interrupted in the case of a grade 1-2 infusion reaction (see Section 4.8 and Section 4.9). Once symptoms resolve, infusion should be restarted at 50% of the initial infusion rate (e.g., from 50 mL/hr to 25 mL/hr). For a grade 3 infusion reaction, APX005M should be held and the investigator should dose reduce with the next cycle. Grade 4 infusion

reactions require discontinuation of APX005M.

The Pharmacy Manual contains specific instructions for the preparation of the APX005M infusion and administration of infusion solution.

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 Dose Modifications, Delays or Discontinuation

Doses of study drugs may be interrupted, delayed, or discontinued depending on how the patient tolerates the treatment. Dose reductions for nivolumab and cabiralizumab are not permitted. Dose reduction for APX005M is permitted as per Section 4.8 and Section 4.9.

If there is an infusion reaction or other unforeseen delay that makes dosing of APX005M impractical on the same day as nivolumab and cabiralizumab, the patient may be infused with APX005M the following day at the discretion of the Investigator.

Administration of nivolumab, cabiralizumab and/or APX005M combination therapy should be skipped for the following reasons:

- The treating physician determines that the patient would benefit from a break in treatment due to non-life threatening grade 1-2 toxicities such as fatigue, arthralgias or edema.
- Any drug-related laboratory abnormalities would not require a dose delay unless clinically indicated or specified in the protocol or abnormal laboratory management guidelines (see Section 4.8 and Section 4.9). Please discuss with the PI as needed.
- For dose delays or modifications for all other AEs please refer to the AE management guidelines in Section 4.8 and Section 4.9.

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

4.7 Criteria to Resume Treatment with APX005M, Cabiralizumab and Nivolumab

Patients may resume treatment with APX005M, cabiralizumab and/or nivolumab when the drug-related AE resolves as noted in Section 4.8 and Section 4.9.

A new treatment cycle should be initiated only if all toxicities are ≤ Grade 1 except:

- Grade 2 neuropathy lasting shorter than 28 days (hold nivolumab only)
- Grade 2 alopecia
- Grade 2 rash or other skin toxicity
- Grade 2 hypophysitis/endocrinopathies
- Grade 2 fatigue
- Grade 2-3 neutropenia/lymphopenia
- CK increase up to 15x ULN

- AST/ALT ≤ 12x ULN for ≤ 7 days with bilirubin <2x ULN

If a subject fails to meet these retreatment criteria then the treatment cycle should be skipped.

The PI can be contacted at any time if further clarification is needed.

4.8 Management of Adverse Events and Supportive Care Guidelines

Immuno-oncology agents are associated with AEs that can differ in severity and duration compared to AEs caused by other therapeutic classes. APX005M, 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. Subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of AEs **with potential immunologic etiology** are outlined below. These treatment guidelines are intended to be applied when the Investigator determines the events to be related to the APX005M + cabiralizumab ± nivolumab combination and should not substitute for investigational product dose delays and/or modifications. Additional guidance for management of AEs with potential immunologic etiology is provided in the APX005M, cabiralizumab and nivolumab Investigator's Brochures.

If after evaluation the event is determined by the Investigator not to be related to investigational products, the Investigator does not need to follow the treatment guidance outlined in this section.

For each disorder, attempts should be made to rule out other causes such as metastatic disease, or bacterial/viral infection, which might require additional supportive care.

Steroid tapering may be necessary for prolonged exposures to corticosteroids, or if symptoms worsen when the corticosteroid dose is decreased.

Diarrhea/Colitis

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

- **Grade 1-2:** for subjects developing Grade 1–2 diarrhea loperamide (2 mg every 2 hours) is strongly recommended at the first onset of symptoms. For subjects with persistent diarrhea despite the use of loperamide (>7 days or recurrent) or Grade 2 colitis, the use of oral corticosteroids (0.5–1 mg/kg/day methylprednisolone or oral equivalent) is recommended. Other antidiarrheal agents (e.g. octreotide) may be used if necessary. When symptoms improve to Grade 1, steroids may be tapered as deemed appropriate by the investigator. If steroids are administered for over weeks, consider prophylactic antibiotics for opportunistic infections. If symptoms worsen or persist >5 days despite steroids treatment, treat as grade 3-4.
- **Grade 3-4:** treat with corticosteroids (1–2 mg/kg/day methylprednisolone or IV equivalent) followed by oral corticosteroids until symptoms improve to Grade 1 or less. Add prophylactic antibiotics for opportunistic infections and consider lower endoscopy.

If persist or recurs continuously after improvement, consider infliximab 5mg/kg (unless sepsis or perforation is detected).

Creatinine Elevation

- **Grade 2-3:** treat with corticosteroids (0.5–1 mg/kg/day methylprednisolone or oral equivalent) until symptoms improve to Grade 1 or less. Consider renal biopsy with nephrology consult. If persist > 14 days treat as grade 4.
- **Grade 4:** treat with corticosteroids (1–2 mg/kg/day methylprednisolone or IV equivalent) followed by oral corticosteroids until symptoms improve to Grade 1 or less. Consider renal biopsy and consult nephrologist. Add prophylactic antibiotics for opportunistic infections. If worsen consider clinical referrals as needed.

Pneumonitis

- **Grade 2:** Treat with IV or oral corticosteroids until symptoms improve to Grade 1 or less. Consider prophylactic antibiotics for opportunistic infection. Consider bronchoscopy, lung biopsy and hospitalization. If does not improve after 2 weeks treat as grade 3-4.
- **Grade 3-4:** Consider pulmonary or infectious disease consults. Hospitalize and treat immediately with IV corticosteroids (2–4 mg/kg/day methylprednisolone or IV equivalent). Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy and lung biopsy. If does not improve after 48h or worsens, add additional anti-inflammatory measures (e.g. cyclosporine, IVIG, mycophenolate mofetil)

Liver Function Tests

- **Grade 3 transaminitis:** Monitor liver function tests more frequently until returned to Grade 2 or less. Start oral or IV corticosteroids if transaminitis > 5 to ≤ 12x ULN persists for > 7 days. Continue steroids until returns to Grade 1 or less. If the first transaminase value is 12X ULN or greater, start steroids immediately.

- **Grade 4 ALT and/or AST elevations, or grade 4 bilirubin increase:** Treat with IV corticosteroids for 24-48 hours followed by oral corticosteroids until improvement to Grade 1 or less. If worsening in 3-5 days, administer additional immunosuppressive measures (e.g. mycophenolate mofetil), as needed. Consider adding prophylactic antibiotics for opportunistic infections. Consult gastroenterologist.

- **Grade ≥*2* transaminitis (>3x ULN) and total bilirubin >2x ULN:** Treat with IV corticosteroids (1–2 mg/kg/day methylprednisolone or IV equivalent) followed by oral corticosteroids. Consider adding prophylactic antibiotics for opportunistic infections. Consult gastroenterologist. Continue steroids until symptoms improve to Grade 1 or less. If worsening in 3-5 days, add mycophenolate mofetil 1g BID. If no improvement consider additional immunosuppressive measures per local guidelines.

Endocrinopathy

- **Asymptomatic TSH elevation:** monitor fT4 if TSH is <0.5 x LLN, > 2 x ULN or consistently out of range in two subsequent measurements.

Symptomatic endocrinopathy: evaluate endocrine function. For abnormal laboratory results initiate hormone repletion.

- **Suspicion of adrenal crisis:** rule out sepsis, administer IV fluids, treat as for symptomatic endocrinopathy. Otherwise, administer stress dose of IV steroids with mineralocorticoid activity.

Skin Adverse Events.

- **Grade 1-2:** symptomatic treatment (e.g. antihistamines, topical steroids). If unresponsive, consider steroid burst. If worsens treat as grade 3-4.
- **Grade 3-4:** Consider skin biopsy. Treat with steroids as deemed appropriate by the treating physician (1–2 mg/kg/day methylprednisolone or IV equivalent).

Infusion Reaction/Cytokine Release Syndrome

Precautions should be observed during the administration of APX005M, nivolumab and cabiralizumab. Emergency agents including oxygen, oral and endotracheal airways, intubation equipment epinephrine, antihistamines, and corticosteroids should be available and used if required at the Investigator's discretion.

Subjects should be instructed that symptoms associated with cytokine release syndrome/infusion reaction can occur within 48 hours following the administration of the investigational products, and if such symptoms develop while they are at home, they should contact the Investigator and/or seek emergency medical care if appropriate.

- **Grade 1:** decrease infusion rate as per protocol
- **Grade 2:** Stop infusion and treat symptoms following guidelines in Table 4. If symptoms resolve within two hours, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr).
- **Grade 3-4:** stop infusion and treat symptoms following guidance in Table 4. If subjects resume study treatment after previously having a grade 3 infusion-related reaction and/or cytokine release syndrome, a 48-hour inpatient observation period is mandatory after the infusion to perform frequent vital sign checks. If grade $\geq$ 3 infusion-related reaction/cytokine release syndrome does not recur upon rechallenge, further cycles may be administered in the outpatient setting.

Table 4: Guidelines for Management of Cytokine Release/Infusion Reaction Symptoms

Suspected Cytokine Release/Infusion-related Toxicity	Recommended Treatment
• Mild toxicity requiring symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise)	• Vigilant supportive care • Maintain adequate hydration • Antipyretics, non-steroidal anti-inflammatory drugs, antihistamines, anti-emetics, analgesics as needed • In case of mild symptoms persisting for > 24 hours assess for infections; empiric treatment

	of concurrent bacterial infections
• Symptoms or clinical findings requiring and responding to moderate intervention, such as: o O_2 requirement < 40% o Hypotension responsive to fluids ± low dose of one vasopressor (e.g., < 50 mg/min phenylephrine) o CTCAE v5.0 Grade 2 organ toxicity	• All of the above • Monitor cardiac and other organ functions closely • Corticosteroids if not resolving with measures above
• Symptoms or clinical findings requiring aggressive intervention, such as: o O_2 requirement ≥ 40% o Hypotension requiring high dose or multiple vasopressors o Ventilator support required • CTCAE v5.0 Grade ≥3 organ toxicity	• All of the above • Monitor cardiac and other organ functions closely • Corticosteroids if not resolving with measures above • Tocilizumab if not responsive to steroids and other measures

Neurological Toxicity

- **Grade 2:** symptomatic treatment per local guidelines. Consider steroids (0.5–1 mg/kg/day methylprednisolone or PO equivalent). If worsen treat as grade 3-4.
- **Grade 3-4 or grade 2 for >28 days:** obtain neurological consult and treat symptoms per local guidelines. Administer corticosteroids (1–2 mg/kg/day methylprednisolone or IV equivalent). Add prophylactic antibiotics for opportunistic infections. Continue steroids until symptoms improve to Grade 2 or less. If symptoms worsen or for atypical presentation consider IVIG, high doses steroids (e.g. 1g methylprednisolone) or other immunosuppressive measures per local guidelines.

Periorbital Edema:

- **Grade 1:** Monitor edema
- **Grade 2-4:** Consider IV or oral corticosteroids until symptoms improve to Grade 1 or less. Consider adding eye drops, or analgesics as needed. Seek ophthalmologic consult if needed.

Uveitis:

- **Grade 1:** Watch for worsening of symptoms including visual disturbances, light sensitivity, decrease vision, monitor weekly.
- **Grade 2-4:** Treat with IV or oral corticosteroids until symptoms improve to Grade 1 or less. Consider additional immunosuppressive agents if not responsive (such as infliximab). Consider adding prophylactic antibiotics for opportunistic infections and seek ophthalmologic consult.

CK Increase:

- **CK > 10x ULN:** Consider measuring CK isoenzymes as clinically indicated. If CK isoenzymes are abnormal consider measuring troponin levels and other assessments (including uromyoglobin) as clinically indicated. If CK isoenzymes are normal monitor CK level as clinically indicated.
- **CK > 15x ULN:** If clinically indicated, measure CK isoenzymes and test more frequently until returned to Grade 2. If CK isoenzyme panel is normal continue monitoring the subject. If CK isoenzyme panel is abnormal then consider measuring troponins.

4.9 Criteria for Holding, Discontinuing, or Modifying Study Drug

Management of suspected adverse drug reactions may require temporary treatment hold (until re-treatment criteria are met), reducing the dose of APX005M, or discontinuation of some or all investigational products as per Table 5. If a subject experiences several toxicities, the recommended dose modification should be based on the highest grade toxicity.

Up to two dose reductions are permitted for APX005M. There are no dose reductions for cabiralizumab or nivolumab.

Table 5: **Criteria for Holding, Discontinuing, or Modifying Study Drug**

	Toxicity	Grade	APX005M	Cabiralizumab	Nivolumab
Gastrointestinal AEs	Diarrhea/colitis	2-3	1st occurrence: Hold 2nd occurrence: dose reduction¥	Hold If not improving in 28 days with oral steroids: Discontinue	Hold If not improving in 28 days with oral steroids: Discontinue
		4	Discontinue	Discontinue	Discontinue
	Vomiting	2-4	Hold	Hold	Hold
Endocrine AEs	Hypophysitis/ Endocrinopathies	2-4	Hold only if clinically unstable	Hold only if clinically unstable	Hold only if clinically unstable

	Toxicity	Grade	APX005M	Cabiralizumab	Nivolumab
	Hyperthyroidism	2-4	Hold only if clinically unstable	Hold only if clinically unstable	Hold only if clinically unstable
Hepatic AEs	Increased AST/ALT	3 (> 5 to ≤ 12x ULN) and bilirubin <2x ULN	Continue	Continue	Continue
		3 (> 12x ULN) for >14 days and not decreasing on steroids and bilirubin <2x ULN	Hold	Hold	Hold
		2-3 and total bilirubin >2x ULN or 3x baseline for patients with Gilbert's syndrome and no cholestasis or INR >1.5 not on warfarin	Discontinue	Discontinue	Discontinue
		4	Discontinue	Discontinue	Discontinue
	Increased bilirubin	2	Hold	Hold	Hold
		3	Hold If >48 hours with no cholestasis or > 5 days with cholestasis: Discontinue	Hold If >48 hours with no cholestasis or > 5 days with cholestasis: Discontinue	Hold If >48 hours with no cholestasis or > 5 days with cholestasis: Discontinue
		4	Discontinue	Discontinue	Discontinue

	Toxicity	Grade	APX005M	Cabiralizumab	Nivolumab
Skin AEs	Rash or other skin toxicity	3	Hold If not improving in 28 days: Discontinue	Hold If not improving in 28 days: Discontinue	Hold If not improving in 28 days: Discontinue
		4	Hold If not improving in 28 days: Discontinue	Hold If not improving in 28 days: Discontinue	Discontinue
Neurological AEs	Neurological Toxicity	2	Continue	Continue	Hold
		3	Hold	Hold	1st occurrence: Hold 2nd occurrence: Discontinue
		4	Hold	Hold	Discontinue
Infusion Reaction/ Cytokine Release Syndrome	Nivolumab infusion reaction	1-2	Administer additional premedication. Increase infusion time to 90 min	Administer additional premedication. Increase infusion time to 60 min	Administer additional premedication and increase the infusion time to 60 min
		3	Hold	Hold	Hold. Re-challenge with nivolumab must be discussed with study PI
		4	Discontinue	Discontinue	Discontinue
	Cabiralizumab infusion reaction	1-2	Administer additional premedication. Increase infusion time to 90 min	Administer additional premedication. Increase infusion time to 60 min	Already given
		3	Hold	Discontinue	Already given
		4	Discontinue	Discontinue	Discontinue

	APX005M infusion reaction/	1-2	Administer additional premedication. Increase infusion time to 90 min*	Already given	Already given
		3	Hold and dose reduce¥ for next cycle	Already given	Already given
	cytokine release syndrome	4	Discontinue	Discontinue	Discontinue
Pulmonary AEs	Pneumonitis	2-3	1st occurrence: Hold 2nd occurrence or if not improving in 14 days: Discontinue	1st occurrence: Hold 2nd occurrence or if not improving in 14 days: Discontinue	1st occurrence: Hold 2nd occurrence or if not improving in 14 days: Discontinue
		4	Discontinue	Discontinue	Discontinue
Renal AEs	Creatinine Elevation	2-3	Hold If not improving in 21 days: Discontinue	Hold If not improving in 21 days: Discontinue	Hold If not improving in 21 days: Discontinue
		4	Discontinue	Discontinue	Discontinue
Systemic AEs	Fatigue	3	Hold. Consider dose reduction for next cycle	Hold	Hold

	Toxicity	Grade	APX005M	Cabiralizumab	Nivolumab
Hematologic AEs	Neutropenia	4	Hold	Hold	Hold
	Febrile Neutropenia	3-4	Hold	Hold	Hold
	Thrombocytopenia	2-3	Hold	Continue	Continue
		3 with significant bleeding or transfusion or 4	Hold. Dose reduction¥	Hold	Hold
Ocular AEs	Periorbital edema	2-3	Continue	Hold at discretion of treating investigator	Continue
		4	Continue	Discontinue	Continue
	Uveitis	2	Hold If not improving in 28 days: Discontinue	Hold If not improving in 28 days: Discontinue	Hold If not improving in 28 days: Discontinue
		3-4	Discontinue	Discontinue	Discontinue
Laboratory AEs	CK increase without clinical or laboratory evidence of myocarditis or myositis	4 (> 15 to ≤ 20x ULN)	Continue	Hold until returns to ≤ 15x ULN	Continue
		4 (>20x ULN)	Resume once < 10x ULN	Discontinue	Resume once < 10x ULN
Toxicity All Other Drug-Related		3 or Severe	Hold	Hold	Hold
		4	Discontinue	Discontinue	Discontinue

4.10 Dose Reduction

Dose reduction for nivolumab and cabiralizumab are not permitted. Dose reduction for APX005M is permitted as below and as per Section 4.8 and Section 4.9.

¥APX005M Dose Reductions

Dose Level (mg/kg)	DL1 (0.03)	DL2 (0.1)	DL3 (0.3)
First Dose Reduction	0.01	0.06	0.2
Second Dose Reduction	Not applicable	0.03	0.1

4.11 Treatment Discontinuation Criteria

Subjects ***must*** discontinue receiving investigational products for any of the following reasons:

- Withdrawal of informed consent (patient's decision to withdraw for any reason)
- Toxicity requiring discontinuation of all investigational products as outlined in the dose modification guidelines
- 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
- Failure to recover from a disease or treatment-related AE to baseline or ≤ Grade 1 within 12 weeks of last dose of investigational product (except Grade 2 alopecia and Grade 2 fatigue), unless the subject is benefiting from therapy and after discussion with and approval by the PI
- Failure to recover within 4 weeks of last dose of investigational product if AE is related to infusion reaction/cytokine release
- Inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks of last dose of investigational product
- 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
- Requirement for alternative therapy
- Non-compliance with study procedures, including use of prohibited medications
- Subject is lost to follow-up
- Death

For comprehensive discontinuation rules, refer to the Table 5 in Section 4.4. The PI can be contacted at any time if further clarification is needed.

Other treatment discontinuation not specifically listed in Table 5 (Section 4.4) may include:

- 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 for up to 12 weeks between doses. Prior to re-initiating treatment in a patient with a dosing delay lasting

> 6 weeks from the previous dose, the PI 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 PI. Prior to re-initiating treatment in a patient with a dosing delay lasting > 6 weeks, the PI must be consulted. Tumor assessments should continue per protocol every 8 weeks for the first 4 months and every 12 weeks (±7 days) thereafter, 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 APX005M, cabiralizumab and/or nivolumab dosing.

All patients who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 5. 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 nivolumab, cabiralizumab, and APX005M 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.

4.12 Infusion Delays and Missed Doses with Nivolumab, Cabiralizumab and APX005M

In case an infusion cannot be administered at a scheduled visit, it must be administered as soon as possible. If the delay is more than two days, the infusion at the originally scheduled visit will be considered a missed dose and the procedures at the next visit should be performed. There must be at least 12 days between study drug administration.

4.13 Treatment Beyond Progression

Accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease [60].

Patients treated with nivolumab, cabiralizumab and APX005M combination therapy will be permitted to continue 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
- No decline in current ECOG performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)
- Absence of signs, symptoms, and worsening laboratory values that would indicate rapid disease progression

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 investigational products.

If the Investigator feels that any patient receiving nivolumab, cabiralizumab and APX005M 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 nivolumab, cabiralizumab and APX005M 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. APX005M, cabiralizumab and nivolumab treatment should be discontinued permanently upon documentation of further progression.

4.14 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 PI 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.

4.15 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 PI to review throughout the clinical trial period.

If conditions for destruction cannot be met, the responsible PI will make arrangements for return of study drug (Section 4.16).

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.

4.16 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 PI.

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 1 Dose Escalation

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 APX005M, cabiralizumab, and/or 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 A).

- Written, signed informed consent must be collected prior to any study-specific procedures
- Collection of a formalin fixed, paraffin-embedded (FFPE) tissue block and/or a fresh tumor biopsy from an accessible site will be mandatory, unless the Investigator deems that the subject does not have tumor in a site amenable to biopsy. Tumor biopsy collection will be performed at least 24 hours prior to dosing (as in Appendix D).
- Complete medical and disease history
- Demographic and baseline characteristics
- Complete physical examination including height and weight
- Vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest)
- Photo of periorbital region
- ECOG performance status evaluation
- Screening labs (as described in Appendix A)
- Clinical safety labs (as described in Appendix A)
- 12-lead ECG (required at screening, and if clinically indicated during the study)
- Radiological imaging: After determining progression on an anti-PD-1/PD-L1 agent, body imaging of disease sites with PET CT, CT scans, and/or MRI is to be performed within 28 days prior to Cycle 1 Day 1. MRI brain is also to be performed within 28 days prior to C1D1. If the Investigator deems that MRI of the brain cannot be performed, CT Head with and without intravenous contrast is acceptable. If the imaging is performed as part of the patient's standard of care is 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 within 7 days of Cycle 1 Day 1
- 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 study drug infusion 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 evaluation
  - Clinical safety labs (as described in Appendix A; results must be reviewed before dosing)
  - Urine pregnancy test (β-hCG) for women of childbearing potential within 24 hours of dosing
  - Blood collection for:
    - Biomarker blood sample collection (analyses described in Appendix D)
    - Serum PK (for APX005M only)
      - pre-infusion (APX005M)
      - end of infusion (APX005M)
      - if possible, 4 hours (±30 minutes) from start of infusion (APX005M)
    - Pre-treatment serum anti-drug antibody (ADA) levels (for APX005M only), Cycle 1 Day 1 and Day 1 of every 3rd cycle (Cycles 3, 6, 9, 12, etc.)
  - AE reporting, if applicable
  - Review of concomitant medications
- Study drug administration
  - Pre- and post-study each drug administration:
    - Vital signs (heart rate, blood pressure, respiratory rate, and temperature in resting position after 5 minutes rest)
    - Additional post-dose vital signs (heart rate, blood pressure, respiratory rate, and temperature in resting position after 5 minutes rest) at 4 hours (± 30 minutes)

post-APX005M infusion

- 4 hour post-dose vital sign criteria for discharge include:
  - Systolic BP no more than 30 mmHg below baseline
  - Oxygen saturation > 90%
  - Heart rate no more than 30 beats per minute above baseline, unless febrile
  - If febrile, subjects can be discharged home as long as their temperature is less than 101 degrees Fahrenheit
- Patients must remain near the vicinity of a hospital with rapid access to an intensive care unit setting during the initial 48 hour period after treatment.

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:

- Physical examination (focused, symptom-based exam)
- 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:
  - Biomarker blood sample collection (analyses described in Appendix D)
  - Serum PK at 24 hours (± 6 hours) from the start of infusion (APX005M)
- AE reporting, if applicable
- Review of concomitant medications

5.2.1.4 Cycle 1, Day 3

Patients will return to the study center on Day 3 for 48-hour (± 6 hours) post-dose assessments. No treatment will be administered during this visit, but the following assessments will be completed:

- Physical examination (focused, symptom-based exam)
- Vital signs (blood pressure, pulse, respiratory rate and temperature in resting position after 5 minutes rest)
- Blood collection for:
  - Biomarker blood sample collection (analyses described in Appendix D)
  - Serum PK at 48 hours (± 6 hours) from the start of infusion (APX005M)

- 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 post-dose assessments. No treatment will be administered during this visit, but the following assessments will be completed:

- Physical Exam (focused, symptom-based exam)
- 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:
  - Biomarker blood sample collection (as described in Appendix D)
  - Serum PK at 168 hours (+ 6 hours) from the start of infusion (APX005M)
- AE reporting, if applicable
- Review of concomitant medications

5.2.1.6 Cycle 2, Day 1

The following procedures will be performed:

- Prior to study drug infusion 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)
  - Urine pregnancy test (β-hCG) for women of childbearing potential within 24 hours of dosing
  - Blood collection for:
    - Biomarker blood sample collection (analyses described in Appendix D)
    - Serum PK (for APX005M only)
      - pre-infusion (APX005M)
      - end of infusion (APX005M)
      - if possible, 4 hours (±30 minutes) from the start of infusion (APX005M)
  - AE reporting, if applicable

  - Review of concomitant medications
- Study drug administration
  - Pre- and post-study each drug administration:
    - Vital signs (heart rate, blood pressure, respiratory rate, and temperature in resting position after 5 minutes rest)
    - Additional post-dose vital signs (heart rate, blood pressure, respiratory rate, and temperature in resting position after 5 minutes rest) at 4 hours (± 30 minutes) post-APX005M infusion
      - 4 hour post-dose vital sign criteria for discharge include:
        - Systolic BP no more than 30 mmHg below baseline
        - Oxygen saturation > 90%
        - Heart rate no more than 30 beats per minute above baseline, unless febrile
        - If febrile, subjects can be discharged home as long as their temperature is less than 101 degrees Fahrenheit
    - Patients must remain near the vicinity of a hospital with rapid access to an intensive care unit setting during the initial 48 hour period after treatment.

5.2.1.7 Cycle 2, 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:

- Physical examination (focused, symptom-based exam)
- 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:
  - Biomarker blood sample collection (analyses described in Appendix D)
  - Serum PK at 24 hours (± 6 hours) from start of infusion (APX005M)
- AE reporting, if applicable
- Review of concomitant medications

5.2.1.8 Cycle 2, Day 3

Patients will return to the study center on Day 3 for 48-hour (± 6 hours) post-dose assessments. No treatment will be administered during this visit, but the following assessments will be completed:

- Physical examination (focused, symptom-based exam)
- Vital signs (blood pressure, pulse, respiratory rate and temperature in resting position after 5 minutes rest)
- Blood collection for:
  - Biomarker blood sample collection (analyses described in Appendix D)
  - Serum PK at 48 hours (+ 6 hours) from the start of infusion (APX005M)
- AE reporting, if applicable
- Review of concomitant medications

5.2.1.9 Cycle 2, Day 8

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

- Physical Exam (focused, symptom-based exam)
- 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:
  - Biomarker blood sample collection (as described in Appendix D)
  - Serum PK at 168 hours (+ 6 hours) from start of infusion (APX005M)
- AE reporting, if applicable
- Review of concomitant medications

5.2.1.10 Subsequent Cycles, Day 1

A ± 2 day window is allowed for Day 1 in subsequent cycles post Cycle 2, Day 1.

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 APX005M until completion of all post-dose assessments for safety monitoring. The following assessments will be performed at each visit unless otherwise noted (Appendix A).

Prior to study drug 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)
- Urine pregnancy test (β-hCG) for women of childbearing potential within 24 hours of dosing
- Blood collection for:
  - Biomarker blood sample collection (analyses described in Appendix D)
  - Serum PK (for APX005M only) on Day 1 of every 3rd cycle (Cycles 3, 6, 9, 12, etc.) during dose escalation
    - pre-infusion (APX005M)
    - end of infusion (APX005M)
  - Pre-treatment serum anti-drug antibody (ADA) levels (for APX005M only) on Day 1 of every 3rd cycle (Cycles 3, 6, 9, 12, etc.) during dose escalation
- Body and brain imaging will be performed every 8 weeks (±7 days) from the first dose for the first 4 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. See Appendix A for further details.
- Biopsy at primary tumor or metastatic site will be collected within 7 days prior to Cycle 5 Day 1 and at least 24 hours prior to dosing
- AE reporting, if applicable
- Review of concomitant medications

- Study drug administration

  Pre- and post-study each drug administration: Vital signs: Patients can be discharged from clinic if: oxygen saturation > 90%, SBP no more than 30 mmHg below baseline, heart rate no more than 30 beats per minute above baseline, unless febrile. If febrile, subjects can be discharged home as long as their temperature is less than 101 degrees Fahrenheit.

5.2.1.11 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 study drug, 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 study drug 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.
- Urine pregnancy test (β-hCG) for women of childbearing potential
- Tumor biopsy when feasible for patients who progressed, (28 [±7] days, post last infusion of study drug visit only) (for analyses described in Appendix D)
- Biomarker blood sample collection
- Serum anti-drug antibody (ADA) levels (for APX005M 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

.2.2 Phase 1b

.2.2.1 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 nivolumab, cabiralizumab, and APX005M (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
- Collection of a formalin fixed, paraffin-embedded (FFPE) tissue block and/or a fresh tumor biopsy from an accessible site will be mandatory, unless the Investigator deems that the subject does not have tumor in a site amenable to biopsy. Tumor biopsy collection will be performed at least 24 hours prior to dosing (as in Appendix D).
- Complete medical and disease history
- Demographic and baseline characteristics
- Complete physical examination including height and weight

- Vital signs (blood pressure, pulse, respiratory rate, and temperature in resting position after 5 minutes rest)
- Photo of periorbital region
- ECOG performance status evaluation
- Screening labs (as described in Appendix B)
- Clinical safety labs (as described in Appendix B)
- 12-lead ECG (required at screening, and if clinically indicated during the study)
- Radiological imaging: After determining progression on an anti-PD-1/PD-L1 agent, body imaging of disease sites with PET CT, CT scans, or MRI is to be performed within 28 days prior to Cycle 1 Day 1. MRI brain is also to be performed within 28 days prior to C1D1. If MRI brain cannot be performed for reasons deemed by the Investigator, CT Head with and without contrast should be performed. If the imaging 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 within 7 days of Cycle 1 Day 1
- SAE reporting, if applicable
- Document prior and concomitant medications

.2.2.2 Cycle 1, Day 1

The following procedures will be performed:

- Prior to study drug 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 evaluation
  - Clinical safety labs (as described in Appendix B); results must be reviewed before dosing)
  - Urine pregnancy test (β-hCG) for women of childbearing potential within 24 hours of dosing
  - Blood collection for:
    - Biomarker blood sample collection (analyses described in Appendix D)
    - Pre-treatment serum anti-drug antibody (ADA) levels (for APX005M only) pre-treatment and post-infusion and on Day 1 of every 3rd cycle thereafter (Cycles 3,

6, 9, 12, etc.)

- Serum PK (for APX005M only) and on Day 1 of every 3rd cycle thereafter (Cycles 3, 6, 9, 12, etc.)
  - pre-infusion (APX005M)
  - end of infusion (APX005M)

– AE reporting, if applicable

– Review of concomitant medications

- Study drug administration
  - Pre- and post-study each drug administration:
    - Vital signs (heart rate, blood pressure, respiratory rate, and temperature in resting position after 5 minutes rest)
    - Additional post-dose vital signs (heart rate, blood pressure, respiratory rate, and temperature in resting position after 5 minutes rest) at 4 hours (± 30 minutes) after the start of the APX005M infusion
      - 4 hour post-dose vital sign criteria for discharge include:
        - Systolic BP no more than 30 mmHg below baseline
        - Oxygen saturation > 90%
        - Heart rate no more than 30 beats per minute above baseline, unless febrile
        - If febrile, subjects can be discharged home as long as their temperature is less than 101 degrees Fahrenheit
    - Patients must remain near the vicinity of a hospital with rapid access to an intensive care unit setting during the initial 48 hour period after treatment.

.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:

- Physical examination
- Vital signs (blood pressure, pulse, respiratory rate and temperature in resting position after 5 minutes rest)
- Clinical Safety Labs
- AE reporting, if applicable
- Review of concomitant medications

- Blood collection for:
  - Biomarker blood sample collection (analyses described in Appendix D)

.2.2.4 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 study drug infusion 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 B; results must be reviewed before dosing)
  - Urine pregnancy test (β-hCG) for women of childbearing potential within 24 hours of dosing
  - Blood collection for:
    - Biomarker blood sample collection (analyses described in Appendix D)
  - AE reporting, if applicable
  - Review of concomitant medications
- Study drug administration
  - Pre- and post-study each drug administration:
    - Vital signs (heart rate, blood pressure, respiratory rate, and temperature in resting position after 5 minutes rest)
    - Additional post-dose vital signs (heart rate, blood pressure, respiratory rate, and temperature in resting position after 5 minutes rest) at 4 hours (± 30 minutes) after the start of the APX005M infusion
      - 4 hour post-dose vital sign criteria for discharge include:
        - Systolic BP no more than 30 mmHg below baseline
        - Oxygen saturation > 90%
        - Heart rate no more than 30 beats per minute above baseline, unless febrile
        - If febrile, subjects can be discharged home as long as their temperature is less than 101 degrees Fahrenheit
    - Patients must remain near the vicinity of a hospital with rapid access to an intensive care unit setting during the initial 48 hour period after treatment.

.2.2.5 Cycle 2, 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:

- 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 B)
- AE reporting, if applicable
- Review of concomitant medications
- Blood collection for:
    - Biomarker blood sample collection (analyses described in Appendix D)
-

.2.2.6 Phase 1b, Subsequent Cycles, Day 1

At each infusion visit, patients are to remain at the study site after each administration of APX005M 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 study drug infusion 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)
    - Urine pregnancy test (β-hCG) for women of childbearing potential within 24 hours of dosing
    - Blood collection for:
        - Biomarker blood sample collection (analyses described in Appendix D)
        - Pre-treatment serum anti-drug antibody (ADA) levels (for APX005M only) on Day 1 of every 3rd cycle (Cycles 3, 6, 9, 12, etc.)
        - Serum PK (for APX005M only) on Day 1 of every 3rd cycle (Cycles 1, 3, 6, 9, 12, etc.)
            - 15 (±5) minutes pre-infusion (APX005M)
            - 15 (±5) minutes post-infusion (APX005M)

- Body and brain imaging will be performed every 8 weeks (±7 days) from the first dose for the first 4 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. See Appendix B for further details.
- Biopsy at primary tumor or metastatic site will be collected within 7 days prior to Cycle 5 Day 1 and at least 24 hours prior to dosing
- AE reporting, if applicable
- Review of concomitant medications

- Study drug administration

  Pre- and post-study each drug administration: Vital signs: Patients can be discharged from clinic if: oxygen saturation > 90%, SBP no more than 30 mmHg below baseline, heart rate no more than 30 beats per minute above baseline, unless febrile. If febrile, subjects can be discharged home as long as their temperature is less than 101 degrees Fahrenheit.

.2.2.7 End of Treatment Follow-up Period

See Section 5.2.1.11

5.2.3 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. 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), 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 v5.0.

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 guidelines in Section 4.8 and Section 4.9.

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 treated patients who are

evaluable for a response). Tumor response status will be assessed using RECIST v1.1 by investigator review.

Board-certified radiologists will determine radiographic response and/or progression following enrollment in according to RECIST v1.1.

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) for a total of 2 sets of imaging studies, followed by every 12 weeks (± 7 days) thereafter. Imaging will include an initial MRI of the brain with and without contrast as well as body imaging with either PET CT, CT scans, or MRI. If an MRI of the brain is contraindicated, a head CT with and without contrast should be performed. Brain imaging can be performed every 6 months unless clinically indicated in shorter intervals, such as in patients with metastatic melanoma. 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.

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 for Fresh Tumor Tissue Collection

Biopsy at the primary tumor site or metastatic site will be collected prior to Cycle 1 Day 1 and on-treatment (within 7 days prior to Cycle 5, Day 1, and at least 24 hours prior to dosing) for all patients. Patients may also have on-treatment biopsy upon documented tumor response and post-treatment biopsy upon documented tumor progression, as deemed safe and accessible by the Investigator (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 when possible.

5.3.3 Pharmacokinetic Assessments

Blood samples for the PK evaluation of APX005M will be collected from all patients in the Phase 1 dose escalation component, as described in Section 5 and in Appendix A and Appendix D.

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

5.3.4 Biomarker Assessments

A variety of factors that could potentially predict clinical response to the combination of APX005M, 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.

5.3.4.1 Tumor Tissue Specimens

Mandatory tumor tissue specimens in the form of a paraffin embedded block, and/or fresh frozen tissue, will be submitted. These biopsy samples should be excisional, incisional or core needle as fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses. Patients undergoing core needle biopsy will be required to provide a minimum of two cores. Tissue samples are being collected to evaluate the PD effect of study drugs on the tumor microenvironment. These samples may also undergo RNA sequencing to determine the effect of study drugs on gene expression, single cell RNA-seq, CyTOF and quantitative immunofluorescence. These analyses may help predict future response to treatment. A summary of analyses to be performed are described in Appendix D.

Tumor biopsy specimens will be obtained before treatment and on-treatment to examine immune infiltrates and expression of selected tumor markers. 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 immunofluorescence, CyTOF, bulk RNA-seq, and single cell RNA Seq.

Blood samples for exploratory serum biomarker analyses will be drawn at the time points indicated in the Schedule of Assessments (Appendix A, Appendix B, and Appendix C). Blood samples will be processed to collect serum and PBMCs. and stored frozen prior to analysis. In addition to the PK analyses mentioned above, serum samples will be analyzed to determine the

PD effect of study drugs on cytokines, CSF1R ligand, and CD40 ligand concentrations. Whole blood will be collected, spun and stored to profile PBMCs by methods such as CyTOF or single cell RNA-seq. Samples may be also assessed by multiplex 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.

5.3.4.2 Flow Cytometry

Pre-treatment and on-treatment whole blood and PBMC samples will be analyzed by flow cytometry to study the effects of APX005M, cabiralizumab and nivolumab on various peripheral blood immune cell subsets. Timing of sample collection is listed in Appendix C and analyses to be performed are described in Appendix D.

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:

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

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 study drugs or until initiation of subsequent anti-cancer therapy, whichever comes first, 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.]). Potential 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 drug-induced liver injury (DILI), are not always serious by regulatory definition, these events must be handled as SAEs and reported within the SAEs timeline (See Section 6.2.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

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., routine 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, whichever comes first. 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 PI 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 Industry Collaborators. They are to be transmitted via email or fax to the Yale DSMC. If related to study drugs, SAEs will be reported to the HIC within 48 hours.

Yale Safety Reporting:

The PIs and IND holders will monitor the clinical trial for safety. The PI will assess all expedited adverse events and will periodically review all adverse events observed on the trial. Yale Cancer Center standard operating procedures (SOPs) for assessment and reporting of adverse events are followed which are in compliance with 21 CFR 312.32 and 312.22.
The clinical trial data consisting of all required observations, AEs, and laboratory data are entered into a computerized database in a timely manner. The accuracy and completeness of the database, timely submission of SAEs and compliance with the protocol, is assured by periodic auditing conducted by the Yale Cancer Center Office of Protocol Review and Monitoring, which reports to the Yale Data Safety & Monitoring Committee (DSMC). Safety data will be submitted to the DSMC at least once yearly or more often as required by the DSMP. The DSMC will conduct an internal audit of the study every 6-12 months, per institutional requirements. On a regular interval basis, status reports of all laboratory parameters, AEs and SAEs are reviewed by the PI to view composite data across subjects. Regular meetings are held to discuss ongoing patient treatment and adverse events.

Expedited SAE reports submitted by the Investigator to FDA are also copied to the HIC and other relevant institutional safety committees within the timeframes required by Yale. These will also be copied to BMS and Apexigen. The Principal Investigator will distribute manufacturer-provided safety reports and updated Toxicity Lists to the institution's HIC and all relevant personnel involved in the conduct of the study. The Toxicity List, in addition to the Investigator's Brochure, will be used as a reference for reporting any new SAE.
Possible actions taken by the PI or the Yale DSMC if a new unexpected toxicity is identified from the above safety review, or if the periodic review of all adverse events and laboratory data indicates a pattern of incidence or severity of toxicity that raises a safety concern, can be to:
1. Revise consent form
2. Amend the protocol
3. Suspend the protocol

All AEs found to be expected or non-serious, will be included in the Annual Report.

SAE reporting to BMS and Apexigen:

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 (±7) days of discontinuation of dosing or until initiation of subsequent anti-cancer therapy, whichever comes first, must be reported to BMS Worldwide Safety and to Apexigen Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- 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.

A Medwatch SAE form will be used to report SAEs to BMS and Apexigen.

- Worldwide.Safety@bms.com
- drugsafety@apexigen.com
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection
- The Sponsor will reconcile the clinical database AE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com) and to Apexigen Safety (drugsafety@apexigen.com)
  - The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary.
  - The Investigator will request from Apexigen Safety, drugsafety@apexigen.com a CA025-007 specific listing of SAEs and include the Apexigen protocol number on an ever 3-month basis and prior to data base lock or final data summary
  - GPV&E and Apexigen Safety will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E and Apexigen Safety.
  - The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E and Apexigen Safety, the case should be sent immediately to BMS (Worldwide.Safety@bms.com) and Apexigen (drugsafety@apexigen.com).
- In addition to the Sponsor Investigator's responsibility to report events to their local health authority (HA), suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS and by Apexigen to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).
- In accordance with local regulations, BMS and Apexigen will notify sponsor investigators of

all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). An event meeting these criteria is termed a Suspected Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.

- Other important findings which may be reported by BMS or by Apexigen as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
- Upon receiving an ESR from BMS or Apexigen, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS and Apexigen within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS and to Apexigen. Investigator will perform due diligence follow-up using the BMS Pregnancy Form which the investigator must complete.

BMS SAE Email Address: Worldwide.Safety@BMS.com
Apexigen SAE Email Address: drugsafety@apexigen.com

BMS SAE Facsimile Number: +1 609-818-3804
Apexigen SAE Facsimilie Number (required for SAE and pregnancy reporting):
+1 510-295- 6449

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

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 its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS and Apexigen using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). 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.

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

Non-Serious Adverse Event

- Non-serious Adverse Events (AE) are to be provided to BMS and to Apexigen in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g., IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 ($\pm$7) days following the last dose of study treatment or until initiation of subsequent anti-cancer therapy, whichever comes first.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. 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.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such. The following laboratory abnormalities should be documented and reported appropriately:

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

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

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch, BMS Pregnancy Surveillance Form, **or** approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

Adverse Events that are routinely collected according to GCP shall be submitted to BMS every three (3) months by the last working day of the third month.

The Adverse Event information required to be sent to BMS is noted in the 'Bristol-Myers Squibb Early Asset Investigator Sponsored Research (ISR) Import Plan' which describes the method of collection and submission to BMS via the mailbox: MG-RD-GPVE-PHARMACOVIGILANCE@bms.com

When the file is submitted to BMS, it must be noted whether the file contains:

All Non Serious Adverse Events (only adverse events not previously submitted to BMS within the 3 months)

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 after product administration, the investigational product will be permanently discontinued in an appropriate manner.

The Investigator must immediately notify the Industry Collaborators 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 (> 2x baseline in patients with Gilbert's syndrome) 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

7.1 Sample Size Determination

The primary endpoint of safety and MTD of APX005M in combination with cabiralizumab and nivolumab will be determined by a 3+3 dose escalation design as described above. In this first phase, patients will be enrolled regardless of disease (melanoma, NSCLC, and RCC). The maximum tolerated dose (MTD) will be estimated independently of cohort. Upon completion of this determination, we will proceed to three parallel two-stage designs, separately for each of the three disease cohorts using the MTD. Patients exposed to the MTD in the dose escalation phase will be carried over to the appropriate two-stage design.

Simon's two-stage design will be used in the phase 1b portion of the trial which will include 3 separate and parallel disease-specific cohorts (melanoma, NSCLC, and RCC). For each of the three tumor types, an immune therapy regimen which is modestly active in patients whose disease had progressed on PD-1/PD-L1 inhibitors would have a response rate (RR) of 10%. The null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. A regimen worthy of further investigation in any of the three tumor types will have a RR of 25%. In the first stage, 13 patients of each cancer will be accrued. If there are 1 or fewer responses in these 13 patients, that cohort will be stopped. Otherwise, 21 additional patients of the same disease cohort will be accrued for a maximum total of 34 patients per disease cohort. Each of the three null hypotheses will be rejected if 6 or more responses are observed in 34 patients for each cohort. This design yields a type I error rate of 0.1 and a power of 80% when the true response rate is 25% in each of the three cohorts. There will not be a correction for multiplicity across the three separate cohorts.

7.2 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.

7.3 Efficacy Analyses

For each disease type, response to treatment will be summarized for all treated patients 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, which may include patients who die or for which clinical progression has occurred even if a post-treatment scan has not been performed. 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 Safety Analyses

Safety analyses will be performed for all treated patients. 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 v5.0 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.

7.5 Pharmacokinetic Analyses

Individual and mean serum concentration of APX005M 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 APX005M, as appropriate. For APX005M, PK parameters including C_{max}, AUC, C_{min}, CL, and V_{ss} will be estimated.

7.6 Biomarker Analyses

To assess the PD effects of APX005M, cabiralizumab and nivolumab on various exploratory biomarkers (such as soluble factors, peripheral blood immune cell subsets, and other markers as assessed) summary statistics for these markers and their changes (or percent changes) from baseline will be tabulated by visit and dose. In addition, the time course of exploratory biomarker outcomes will be investigated graphically by summary plots or individual patient plots over time. Patterns of change in these biomarker values over time and how the patterns differed among dose levels may be additionally investigated using appropriate modeling, for example, by linear mixed effects models.

Possible associations of biomarker measures with clinical efficacy measures including OS will be investigated based on data availability. Methods such as, but not limited to, logistic regression may be used to further investigate such associations.

If at the time of database lock for the primary and secondary endpoints, biomarker data related to the exploratory objectives are not available, these biomarker results may not be included in the clinical study report (CSR) but reported separately.

Selected serum markers: Analyses are descriptive in nature and intended to examine the distribution of expression and assess potential associations between expression and efficacy measures. If there is an indication of a meaningful association, future work will evaluate expression as a predictive biomarker, including selection of an optimal expression cut-off to classify patients as positive or negative. See Appendix D.

8. Ethical Considerations

8.1 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 Declaration of Helsinki [81]. 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).

8.2 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.

8.3 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 Declaration of Helsinki [81].

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 PIs 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.

9. Study Management

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions will be approved by the sponsor. Investigators should not implement any deviation or change to the protocol without prior review and documented approval of the HIC 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 HIC approval, as soon as possible the deviation or change will be submitted to:

- HIC for review and approval
- BMS and Apexigen

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 HIC for review and approval; (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.

9.1.2 Yale Safety Reporting and Monitoring (DSMP)

The PI and IND holders will monitor the clinical trial for safety. The PI will assess all expedited adverse events and will periodically review all adverse events observed on the trial. Yale Cancer Center standard operating procedures (SOPs) for assessment and reporting of adverse events are followed which are in compliance with 21 CFR 312.32 and 312.22.

The clinical trial data consisting of all required observations, AEs, and laboratory data are entered into a computerized database in a timely manner. The accuracy and completeness of the database, timely submission of SAEs and compliance with the protocol, is assured by periodic auditing conducted by the Yale Cancer Center Office of Protocol Review and Monitoring, which reports to the Yale Data Safety & Monitoring Committee (DSMC). Safety data will be submitted to the DSMC at least once yearly or more often as required by the DSMP. The DSMC will conduct an internal audit of the study every 6-12 months, per institutional requirements. On a regular interval basis, status reports of all laboratory parameters, AEs and SAEs are reviewed by the PI to view composite data across subjects. Regular meetings are held to discuss ongoing patient treatment and adverse events.

Expedited SAE reports submitted by the Investigator to FDA are also copied to the HIC and other relevant institutional safety committees within the timeframes required by Yale. These will also be copied to BMS and Apexigen. The Principal Investigator will distribute manufacturer-provided safety reports and updated Toxicity Lists to the institution's HIC and all relevant

personnel involved in the conduct of the study. The Toxicity List, in addition to the Investigator's Brochure, will be used as a reference for reporting any new SAE.

Possible actions taken by the PI or the Yale DSMC if a new unexpected toxicity is identified from the above safety review, or if the periodic review of all adverse events and laboratory data indicates a pattern of incidence or severity of toxicity that raises a safety concern, can be to:
1. Revise consent form
2. Amend the protocol
3. Suspend the protocol

All AEs found to be expected or non-serious, will be included in the Annual Report. AEs considered to be serious will be communicated to the industry collaborators Bristol-Myers Squibb and Apexigen within 24 hours.

During the study, the DSMC will perform routine monitoring 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.

Yale University will 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 9.1). 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.

9.1.2.1 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.

9.1.3 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.

9.2 Records

9.2.1 Records Retention

The study site will maintain a study file, which should contain, at minimum, the Investigator's Brochures, 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 Sponsor 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 Sponsor 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 the Sponsor. Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor 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.

9.2.2 Study Drug Records

It is the responsibility of the Investigator to ensure that a current disposition record of each study drug 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.

9.2.2.1 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 electronic CRF (eCRF) must be consistent with the source documents or the discrepancies must be explained.

eCRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines.

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 Yale electronic data capture tool.

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

10. References

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11. Appendices

Appendix A: Schedule of Assessments – **Phase 1 Dose Escalation: Cabiralizumab and APX005M (Cohorts 1, 3, and 5) and Nivolumab, Cabiralizumab, and APX005M (Cohorts 2, 4, and 6)**

Procedure[a]	Screening	Cycle 1				Cycle 2				Cycle x[s]	End-of-Treatment Follow-up Period	Long-Term Follow-up Period[u]
	Day –28 to Day 0	Day 1[b]	Day 2	Day 3	Day 8	Day 1[b]	Day 2	Day 3	Day 8	Day 1[b]	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[c]	x	x	x	x	x	x		X	x	x	x	
Height and Weight[d]	x	x				x				x	x	
Vital Signs[e]	x	x	x	x	x	x	x	X	x	x	x	
Photo of Periorbital Region	x											
ECOG Performance Status[f]	x	x				x				x	x	
Screening Labs[g]	x											
Clinical Safety Labs[h]	x	x	x		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]		x	x	x		x	x	X		x		
PD/Biomarker blood Sampling[o, p]		x	x	x	x	x	x	X	x	x	x	
Anti-drug Antibodies[n]		x								x	x	
Study Drug(s)[q,r]		x				x				x		
Adverse Events[s]	x---------- x											
Prior/Concomitant Medications	x---------- x											

Procedure[a]	Screening	Cycle 1				Cycle 2				Cycle x[s]	End-of-Treatment Follow-up Period	Long-Term Follow-up Period[u]
	Day –28 to Day 0	Day 1[b]	Day 2	Day 3	Day 8	Day 1[b]	Day 2	Day 3	Day 8	Day 1[b]	28 (±7) days and 100 (±7) days post-last dose	
Long-Term Follow-up Contact[t]												x

Notes for Phase 1 Dose Escalation Schedule of Assessments

a. Unless specified, prior to infusion procedures are to be completed within 24 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, APX005M, ± nivolumab on Day 1; a ± 2 day window is allowed for Day 1starting with Cycle 3.

c. 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. A symptom-directed physical exam can be performed for days 2, 3, and 8 of Cycles 1 and 2.

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 on Cycle 1 Day 1.

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 each IV infusion for all cycles. For Day 1 of Cycles 1 and 2 only, additionally measure vital signs 4 hours (± 30 min) post-APX005M infusion. Pulse oximetry is performed at rest prior to dosing for day 1 of each cycle and otherwise as clinically indicated. At the Investigator's discretion, vital sign monitoring may be extended beyond the time points specified. Additional measures should be performed as clinically indicated.

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

g. Screening labs include serology for Hepatitis B (HBsAg) and Hepatitis C (HCV antibody).

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 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.
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. 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.

j. PET CT, CT scans or MRI of the Tumor sites and MRI brain 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.) If there is a contraindication to brain MRI, CT head with and without contrast can be performed.

k. Performed every 8 weeks (±7 days) from the first dose for the first 4 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. The exception is MRI of the brain, which can be performed every 6 months in patients with NSCLC and RCC, unless clinically indicated to be done in shorter intervals. 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.

l. All women of childbearing potential will have a serum pregnancy test at screening, and urine pregnancy test on Day 1 of each cycle and at the 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 5 Day 1 [within 7 days prior to Cycle 5 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. Collect an FFPE tissue block or 10 slides of archival tumor sample at Screening.

n. Serum PK for APX005M and ADA samples will be collected as indicated in Appendix C.

o. Samples will be collected for PD and biomarker analyses for correlative studies.

p. Biomarker blood sample collection will be collected on Day 1, 2, 3, and 8 of Cycles 1 and 2, and on Day 1 of every cycle thereafter. See Appendix C and D for further information.

q.Nivolumab and cabiralizumab will both be administered by IV infusion over 30 minutes (± 5 minutes). APX005M will be administered by IV infusion over 60 minutes. Nivolumab will be given

first (in Cohorts 2, 4, and 6), with a 30- to 60-minute rest, followed by cabiralizumab as a 30-minute infusion. APX005M will be administered 30 minutes after cabiralizumab and will be given for a 60 minute infusion period. For Cohorts 1, 3, and 5, cabiralizumab will be given first, followed by APX005M with the same parameters as above.

r. Cabiralizumab and APX005M will be administered every 2 weeks in 14-day cycles for cohorts 1, 3, and 5. Nivolumab, cabiralizumab, and APX005M will be administered every 2 weeks in 14-day cycles for cohorts 2, 4, and 6. The dosing may continue until PD or unacceptable toxicity.

s. 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.

t. Patients should be contacted every 12 (±2) weeks for survival status. Patients should have tumor scans every 8 weeks for the first 4 months on study drugs, followed by every12 (±2) weeks thereafter, 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: Nivolumab + Cabiralizumab + APX005M

	Screening	**Cycle 1**		**Cycle 2**		**Cycle x[s]**	**End-of-Treatment Follow-up Period**	**Long-Term Follow-up Period[t]**
	Day –28 to Day 0	Day 1[b]	Day 2	Day 1[b]	Day 2	Day 1[b]	28 (±7) days and 100 (±7) days post-last dose	
Procedure[a]	Week 0	Week 1		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	x	
Height and Weight[d]	x	x		x		x	x	
Vital Signs[e]	x	x	x	x	X	x	x	
Photo of Periorbital Region	x							
ECOG Performance Status[f]	x	x		x		x	x	
Screening Labs[g]	x							
Clinical Safety Labs[h]	x	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	x	
Tumor Biopsy[m]	x					x	x	
PK Sampling[n]		x		x		x		
Anti-drug Antibodies[n]		x				x	x	
PD/Biomarker blood sample collection[o]		x	x	x	x	x	x	
Study Drugs[p,q]		x		x		x		
Adverse Events[r]	x ---------- x							

Procedure[a]	Screening	Cycle 1		Cycle 2		Cycle x[s]	End-of-Treatment Follow-up Period	Long-Term Follow-up Period[t]
	Day –28 to Day 0	Day 1[b]	Day 2	Day 1[b]	Day 2	Day 1[b]	28 (±7) days and 100 (±7) days post-last dose	
	Week 0	Week 1		Week 3		Week ≥ 5		
Prior/Concomitant Medications	x ---------- x							
Long-Term Follow-up Contacts[s]								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 study drug administration day. 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 nivolumab + cabiralizumab + APX005M 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 each IV infusion. Pulse oximetry is performed at rest prior to dosing for day 1 of each cycle and otherwise as clinically indicated. At the Investigator's discretion, vital sign monitoring may be extended beyond the time points specified. Additional measures should be performed as clinically indicated.

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)

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 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.
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. 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. PET CT, CT scans or MRI of the Tumor sites and MRI brain 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.) If there is a contraindication to brain MRI, CT head with and without contrast can be performed.

k. Performed every 8 weeks (±7 days) from the first dose for the first 4 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. The exception is MRI of the brain, which can be performed every 6 months in patients with NSCLC and RCC, unless clinically indicated to be done in shorter intervals. 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, and urine pregnancy tests will be done on Day 1 of every Cycle 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 5, Day 1 [within 7 days prior to Cycle 5 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 analysis and anti-drug antibodies (ADA) as in Appendix C.

o. Biomarker blood sample collection will be collected on Day 1 of each cycle and on C1D2 and C2D2. See Appendix C and D for further information.

p. Nivolumab and cabiralizumab will both be administered by IV infusion over 30 minutes (± 5 minutes. Nivolumab will be given first, with a 30-to 60-minute rest, followed by cabiralizumab as a 30-minute infusion. A 30-minute rest period will then occur, followed by APX005M as a 60-minute infusion.

q. Nivolumab + cabiralizumab + APX005M study drug will be administered every 2 weeks in 14-day cycles and will continue until PD or unacceptable toxicity.

r. 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.

s. 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 tumor and Blood Biomarker Sample Collection

	Study Cycle	Study Day	Time Point	Type of Sample
Phase 1 dose escalation	Screening	Screening (Day –28)	At least 24 hours prior to dosing	Tumor Biopsy (or archival FFPE tumor block available)
	Cycles 1 and 2 only	Day 1	Prior to infusion	PK for APX005M (serum)
				Biomarker blood sample collection
				Anti-drug antibody blood sample (Cycle 1 only)
			End of infusion	PK for APX005M (serum)
			If possible, 4 (±30 min) hours from start of infusion	PK for APX005M (serum)
		Day 2	24 (±6) hours from start of infusion	PK for APX005M (serum)
				Biomarker blood sample collection
		Day 3	48 (±6) hours from start of infusion	PK for APX005M (serum)
				Biomarker blood sample collection
		Day 8	168 (±6) hours from start of infusion	Biomarker blood sample collection
	Prior to Cycle 5 only	Within 7 days prior to C5D1 and at least 24 hours prior to dosing	Prior to infusion	Tumor Biopsy
	Subsequent Cycles on every cycle (Cycles 3, 4, 5, etc.	Day 1	Prior to infusion	Biomarker blood sample collection
	Subsequent Cycles on every 3rd cycle (Cycles 3, 6, 9, 12, etc.)	Day 1	Prior to infusion	PK for APX005M (serum)
				Anti-drug antibody blood sample
			End of infusion	PK for APX005M (serum)
Phase 1b	Screening	Screening (Day –28)	At least 24 hours prior to dosing	Tumor Biopsy (or archival FFPE tumor block available)
	Cycles 1, 2, and each cycle therafter *Every 3rd cycle (Cycles 1, 3, 6, 9 , 12, etc.)	Day 1	Prior to infusion	Biomarker blood sample collection
				PK for APX005M (serum)*
				Anti-drug antibody blood sample*
			End of infusion	PK for APX005M (serum)*

		Day 2 of C1 and C2	Prior to Infusion	Biomarker blood sample collection
		Within 7 days prior to C5D1 and at least 24 hours prior to dosing	Prior to infusion	Biopsy Tissue (prior to Cycle 5 only)

	End-of-Treatment Follow-up Period (28 [±7] days and 100 [±7] days post-last dose)	Treatment discontinuation/PD	Post completion of treatment course	*Optional biopsy for patients who have documented response within 28 (±14) days post-tumor assessment*
				Anti-drug antibody blood sample
				Biomarker blood sample collection

Appendix D: PD Analyses

Exploratory endpoints will include description of antitumor activity of APX005M administered in combination with nivolumab and cabiralizumab as measured in mandatory serial tumor biopsy and blood collection specimens. Biopsies will be taken pre-treatment (at least 24 hours prior to dosing), before Cycle 5 Day 1 (within 7 days and at least 24 hours prior to dosing), and at time of disease progression, if this occurs. PBMCs (for CyTOF and single cell RNA Seq) and plasma (for ELISA cytokine panel) samples will also be collected at the same time points. These samples will be used to study biomarkers to assess for prediction of response or resistance to therapy and to search for pharmacodynamic indicators of anti-tumor activity. Tumor assessment will include the following:

- Routine histologic examination
- Quantitative immunofluorescence (QIF)
- Flow cytometry by CyTOF
- Single cell RNA-seq studies

QIF utilizing formalin-fixed paraffin embedded (FFPE) tumors will be profiled for:

Immune cells identifiers	TIL/TAM markers	TIL/TAM markers
CD3	CD27	CD206
CD4	PD-1	CD200R
CD8	TIM-3	PDL1
CD20	LAG-3	CD155 (PVR)
CD68	CTLA-4	CD40
FOXP3	PD1h/ VISTA	PD-L1/B7-H1
Neut. elastase	TIGIT	B7H3
	IFNγ	B7H4
	Granzyme B	Galectin-9
	TNFa	PDL2/B7DC
	41BB	CD70
	CD40L	CD80/86
	IDO	IL-10
	MHC class I/II	CD200

Marker expression will be analyzed in responders versus non-responders. Assays for the biomarkers listed in the table above have already been developed.

Flow cytometry by CyTOF will be performed on tumor infiltrating immune cells and PBMCs to explore and potentially validate the markers outlined for QIF. We will profile shifts in TAM types from pre-treatment to post-treatment initiation and will also measure production of TNF-α, IFN-γ, IL-6, IL-12, p40, CCL3, CCL4, and CCL5. Cell sorting by FACS will be performed for CD3, CD4, and CD68. We aim to determine the functional properties of the immune infiltrates in promoting or inhibiting tumor growth.

Biomarkers of effect for cabiralizumab include:

- Peripheral blood changes in CD14+/CD16^{hi} non-classical monocytes

Biomarkers of effect for APX005M include:

- Peripheral blood analysis for antigen presenting cell activation using flow cytometry: Cell surface immune markers that will be examined include but are not limited to: CD19,

CD123, CD11c, CD86, MHC class I and II, CD70, CD54.

Please note that patients undergoing core biopsy will be required to provide two cores for these analysis – one snap frozen and one paraffin embedded.

All samples will be banked at Yale in the Kluger laboratory.

Appendix E: Biopsy Requirements

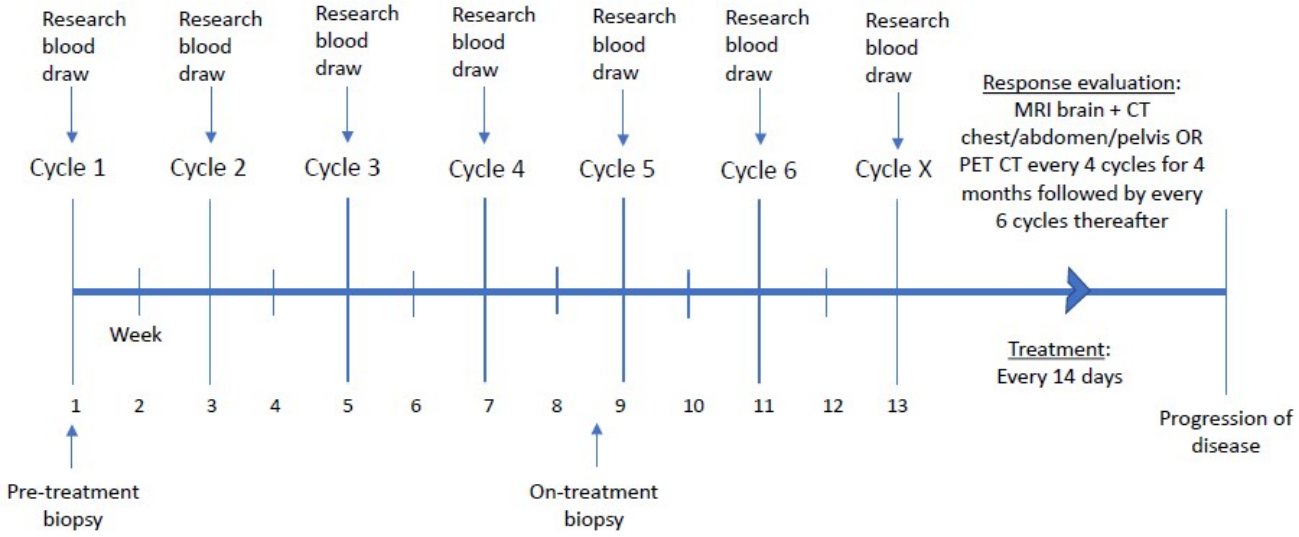
Biopsy at primary tumor or metastatic tumor site are mandatory and will be collected at:

- At time of screening
  - At least 24 hours prior to dosing

- Prior to Cycle 5 Day 1
  - Within 7 days prior to Cycle 5 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 patients who have progression receive another biopsy at the final End-of–Treatment visit. The post-response and post-progression biopsies are optional.

If available, patients will be required to provide an archival FFPE tissue block as well at screening. Patients undergoing core biopsy for the study will be required to provide two cores for these analysis – one snap frozen and one paraffin embedded.



Appendix F: 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.