Clinical Protocol APX005M-002 Amendment 4.0

Title of Protocol: A Study to Evaluate the Safety and Efficacy of the CD40 Agonistic Antibody APX005M Administered in Combination with Nivolumab in Subjects with Non-Small Cell Lung Cancer and Subjects with Metastatic Melanoma

Protocol Number: APX005M-002
Date of Amendment 4.0: 10-October-2019
NCT03123783

Protocol Number: APX005M-002
IND Number: 122725
Date of Original Protocol: January 16, 2017

CLINICAL PROTOCOL APX005M-002

A Study to Evaluate the Safety and Efficacy of the CD40 Agonistic Antibody APX005M Administered in Combination with Nivolumab in Subjects with Non-small Cell Lung Cancer and Subjects with Metastatic Melanoma

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Date of Amendment 4.0: October 10, 2019

This study will be conducted in accordance with Protocol APX005M-002, the International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the applicable country and regional (local) regulatory requirements.

SPONSOR APPROVAL PAGE

10/21/2019

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Chief Medical Officer, Senior Vice President
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Date

DOCUMENT HISTORY

Version	Date	Replaces	Description of Changes
Original Protocol	January 16, 2017	N/A	• New
Amendment 1	March 29, 2017	Original Protocol	• The protocol was amended to: o Enroll subjects at dose level 0.2 mg/kg (DL 2a) before escalating to 0.3 mg/kg (DL 3) if clinically significant infusion reaction/cytokine release syndrome is observed at the 0.1 mg/kg dose (DL 2) o Provide enrollment suspending rules pending safety review for severe toxicity o Clarify that subject with no or unknown activating mutation (EGFR, ALK or ROS) are eligible for this study o Clarify that a subject with a BRAF activating mutation could have also received a BRAF inhibitor and/or MEK inhibitor prior to anti-PD-1/PDL1 therapy o Amend the definition of DLT related to thrombocytopenia o Extend the duration of treatment for subjects with a CR o Add periodic thyroid function testing o Provide guidance regarding pregnancy testing o Define success/failure in statistical testing
Amendment 2	February 28, 2018	Amendment 1	• The protocol was amended to: o Modify the patient population, specifically ▪ Remove the requirement that subjects with non-small cell lung cancer must have received at least one prior platinum-based chemotherapy regimen ▪ Allow prior exposure to anti-CTLA-4 in subjects with metastatic melanoma as long as treatment was discontinued at least 3 months prior to the start of investigational product ▪ Clarify that for subjects with melanoma previous disease progression during treatment with anti-PD-1/PD-L1 therapy must be confirmed and provide definition of confirmation ▪ Allow subjects with an absolute neutrophil count of $\geq 1.0 \times 10^9$/L (previously ≥ 1.5) ▪ Allow subjects with hemoglobin value of ≥ 8 g/dL (previously ≥ 9) ▪ Allow protocol-defined second malignancy within 3 years (previously 5 years) ▪ Remove the exclusion of more than 30 Gy of thoracic radiation within the 26 weeks prior to first dose of investigational product

			▪ Clarify exclusion criteria for subjects with brain metastases ○ Update the iRECIST guidelines for treatment beyond progression ○ Update the Serious Adverse Events reporting contact information ○ Adjust the Stage 1 and Stage 2 sample size to reflect new response rate assumptions for the Cohort 1 (NSCLC) ○ Clarify that all subjects will be monitored by a caregiver or healthcare professional for 24 hours after the first 2 infusions and then as clinically indicated thereafter; subjects in Phase 2 will be monitored as clinically indicated. ○ Extend the timeframe (from >24 hours to >48 hours) for the recommendation to assess for infections in subjects with symptoms consistent with Cytokine Release Syndrome/Infusion Reaction
Amendment 3	July 26, 2018	Amendment 2	• The protocol was amended to: ○ Introduce Cohort 3 enrolling subjects with metastatic or locally advanced NSCLC with tumor progression on an immediately preceding PD-1/PD-L1 containing regimen. Based on response to previous PD-1/PD-L1 containing regimen, subjects will be enrolled in one of the following groups: ▪ Group A: Subjects with best response of progressive disease or with stable disease < 16 weeks ▪ Group B: Subjects with tumor response or with stable disease ≥ 16 weeks. ○ Add 6-month progression-free survival rate as a secondary endpoint ○ Update to guidance for management of severe cytokine release/infusion reaction symptoms • Correct inconsistencies in the protocol/synopsis
Amendment 3.1	January 16, 2019	Amendment 3	• The protocol was amended to add methods of contraception (Appendix B, only applicable to Europe) and update study period
Amendment 4	October 4, 2019	Amendment 3	• Provide clarification regarding optional biopsies • Provide clarification regarding confirm • Regroup the Eligibility Criteria for easier reference • Relax the requirement to discuss minor study treatment delays with the Medical Monitor • Provide additional guidance regarding the infusion rate following infusion-related reactions and premedication regimen • Modify the supportive care guidelines related to elevated liver function tests and cytokine release syndrome

			• Add supportive care guidelines for myocarditis toxicity • Add definition of correlative laboratory testing • Specify that the dose modification regarding neutropenia related to Grade 3-4 and not Grades 2 to 4 • Remove summary of changes appendices as red-line tracked changes versions of the amendment will be provided. • Remove summary of changes appendices as redline versions will be provided.

Synopsis

Protocol Title
A Study to Evaluate the Safety and Efficacy of the CD40 Agonistic Antibody APX005M Administered in Combination with Nivolumab in Subjects with Non-small Cell Lung Cancer and Subjects with Metastatic Melanoma
Investigational Products • APX005M (humanized IgG1κ mAb that binds CD40) • Nivolumab (fully human IgG4κ mAb that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2)

Sponsor	Protocol Number	Phase of Development
Apexigen, Inc.	APX005M-002	Phase 1b-2

Objectives
Primary: Phase 1b: • Determine the MTD and the RP2D of APX005M when given in combination with nivolumab Phase 2: • Evaluate the ORR by RECIST 1.1 in each cohort/group
Secondary: • Evaluate safety of the APX005M and nivolumab combination • Evaluate the 6-month progression-free survival (PFS) rate (PFSR) in each cohort/group • Evaluate the DOR and median PFS in each cohort/group by RECIST 1.1
Exploratory: • Determine the immune PDn of the APX005M and nivolumab combination • Determine the PK of APX005M • Assess incidence of APX005M ADA • Identify blood and/or tumor biomarkers that correlate with efficacy and/or resistance • Evaluate the ORR by immune related RECIST (iRECIST) in each cohort/group • Evaluate DOR and median PFS in each cohort/group by iRECIST
Study Period
Date first subject enrolled (US): 5/17/2017 Date first subject enrolled (EU): 3/1/2019

Estimated date last subject enrolled: 5/15/2020

Study Design

This is a phase 1b-2 study. Adult subjects with non-small cell lung cancer and subjects with metastatic melanoma will be enrolled. The study will include 2 parts.

Study Phase	Dose Level	APX005M		Nivolumab		
Phase1b Dose-escalation		**mg/kg**		**mg**		**N**
	DL 1	0.03	q 21 days	360	q 21 days	3
	DL 2	0.1	q 21 days	360	q 21 days	3
	DL2a	*0.2*	q 21 days	360	q 21 days	3 to 6
	DL 3	0.3	q 21 days	360	q 21 days	3 to 6
					Subtotal ~	18
Phase 2 Dose-expansion						
Cohort 1 inNSCLC	Stage 1	RP2D	q 21 days	360	q 21 days	24
	Stage 2	RP2D	q 21 days	360	q 21 days	21
Cohort 2 PD1-MM	Stage 1	RP2D	q 21 days	360	q 21 days	12
	Stage 2	RP2D	q 21 days	360	q 21 days	25
Cohort 3 PD1-NSCLC	Stage 1	RP2D	q 21 days	360	q 21 days	12
Group A	Stage 2	RP2D	q 21 days	360	q 21 days	25
Cohort 3 PD1-NSCLC	Stage 1	RP2D	q 21 days	360	q 21 days	12
Group B	Stage 2	RP2D	q 21 days	360	q 21 days	25
					Total ~	174

Phase 1b dose-escalation:

Subjects with non-small cell lung cancer or subjects with metastatic melanoma who meet all of the eligibility criteria will be enrolled in the dose-escalation portion of the study.

There will be a maximum of 3 escalation DLs and 1 de-escalation DL in this study. It is expected that up to 18 DLT-evaluable subjects will be enrolled in the dose escalation portion of the study over a 6-month period. All subjects that are not DLT-evaluable will be replaced for the purpose of establishing MTD.

The DLT observation period for dose escalation is the 21 days following the first administration of APX005M and nivolumab (first 3-week cycle). Safety and tolerability of the APX005M and nivolumab combination will be monitored by representatives from Apexigen and the Investigators on a regular basis and prior to each dose escalation.

Dose escalation will continue if 0 out of 3 evaluable subjects experience a DLT during the DLT observation period (i.e., <33% DLT-evaluable subjects in that cohort have a DLT). If 1 DLT-evaluable subject in any DL cohort experiences a DLT, that cohort will be expanded to include additional 3 DLT-evaluable subjects (i.e., a total of 6 evaluable subjects). Dose

escalation will continue if 1 out of 6 evaluable subjects experience a DLT during the DLT observation period (i.e., <33% DLT-evaluable subjects in that cohort have a DLT). Decision to open a new DL cohort will be based on the totality of the data available at that time.

The MTD is the maximum dose of APX005M combined with 360 mg of nivolumab for which <33% of DLT-evaluable subjects experience a DLT.

If the DLT rate in DL 3 exceeds 33%, or 2 or more subjects in DL 2 experience a Grade 2 infusion reaction/cytokine release syndrome, or at the discretion of the sponsor, the intermediate lower dose level 2a will be evaluated (de-escalation). Up to 6 subjects can be enrolled in any of dose levels below the MTD or highest DL tested, should sponsor decide to discontinue dose escalation prior to reaching the MTD.

The RP2D will be based on the overall safety and tolerability of the combination of APX005M and nivolumab.

Phase 2 dose-expansion:
After identification of the RP2D of APX005M in combination with nivolumab 360 mg IV every 21 days, study will continue with 3 cohorts.

- Cohort 1: immunotherapy naïve NSCLC (see below)
- Cohort 2: metastatic melanoma progressing during treatment with anti-PD-1/PD-L1 therapy (see below)
- Cohort 3: metastatic or locally advanced NSCLC progressing during treatment with anti-PD-1/PD-L1 (see below)
    - Group A: Subjects with best response of progressive disease or with stable disease < 16 weeks
    - Group B: Subjects with tumor response or with stable disease ≥ 16 weeks

Each cohort of the Phase 2 dose-expansion portion of the study will follow a Simon optimal 2-stage design. Subjects treated at the RP2D in the dose-escalation portion will be included in Stage 1 of the relevant cohort. Additional subjects will be enrolled for a total of 24 subjects in Cohort 1 and 12 subjects each in Cohort 2, Cohort 3 Group A and Cohort 3 Group B.

Subjects will be evaluated for tumor response approximately every 8 weeks following the first dose of investigational product. Subjects that are non-evaluable for tumor response will be replaced. An ORR (CR+PR) of at least 22% in Cohort 1 and 5% in each of Cohort 2, Cohort 3 Group A and Cohort 3 Group B is required in Stage 1 for the study to proceed to Stage 2. Enrollment may continue into Stage 2 while the planned number of subjects for Stage 1 are followed for efficacy.

In Stage 2, an additional 21 subjects will be enrolled in Cohort 1 and an additional 25 subjects will be enrolled in each of Cohort 2, Cohort 3 Group A and Cohort 3 Group B.

A minimum number of 6 subjects per each cohort/group who have a primary or metastatic lesion that can be biopsied without interfering with subsequent tumor assessments and who

consent to collection of tumor biopsies for tumor biomarkers should be enrolled during Phase 1b and Phase 2.

At any time during the study, enrollment will be suspended pending safety review if any of the following events occur since last safety data review:

- ≥1 Grade 5 suspected adverse reaction (SAR) (for definition see Section 6.1.2)
- ≥2 Grade 4 infusion reaction/ cytokine release syndrome
- ≥2 Grade ≥ 3 immune related AEs in more than 1 subject

Enrollment will resume following assessment by the Apexigen Medical Monitor, contract research organization Medical Monitor and Lead Investigator.

Study Population

Number of Subjects (planned):	Number of Sites:
• Phase 1b: approximately 18 subjects • Phase 2: up to 156 subjects	• Multisite (approx. 15-20)

Sample Size Determination:
The sample size for the Phase 1b dose-escalation cannot be precisely estimated but depends upon the observed toxicities. Cohorts of 3 to 6 subjects will be treated at each DL during dose escalation portion of the study. It is anticipated that approximately 18 subjects will be treated in this portion of the study depending on the actual rate of DLTs.

Sample size for Phase 2 is calculated using the Simon optimal 2-stage design:

- Cohort 1 (inNSCLC): Assuming a false positive rate (α) of 0.1 (one-sided), a false negative rate (β) of 0.1, a response probability of poor drug (P0) of 22% and a response probability of good drug (P1) of 40%, first stage sample size (n1) is 24 and the maximum sample size (n) is 45 response evaluable subjects.
- Cohort 2 (PD1-MM): Assuming α of 0.1 (one-sided), β of 0.1, P0 5% and P1 of 20%, n1 is 12 and n is 37 response evaluable subjects.
- Cohort 3 (PD1-NSCLC) Group A and Group B: Assuming α of 0.1 (one-sided), β of 0.1, P0 5% and P1 of 20%, n1 is 12 and n is 37 response evaluable subjects.

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Cohort Specific Inclusion Criteria

Phase 1b: Subjects that meet eligibility criteria for Phase 2 Cohorts 1 or 2 and all of the general eligibility criteria.

Phase 2 Cohort 1: Histologically or cytologically confirmed, immunotherapy naïve, metastatic or locally advanced non-small cell lung cancer not amenable to curative treatment. Subjects may be treatment naïve or could have received one prior platinum-based chemotherapy for non-small cell lung cancer for any indication (adjuvant, part of combined modality therapy or for metastatic disease) within the past 3 years. Subjects with no or

unknown activating mutation (e.g., EGFR, ALK, ROS) are eligible for this study. Subjects with a documented activating mutation (e.g., EGFR, ALK, ROS) amenable to tyrosine kinase inhibitor therapy, must also have received the appropriate therapy and progressed.

Phase 2 Cohort 2: Subjects with histologically or cytologically confirmed unresectable or metastatic melanoma that had confirmed progressive disease during treatment with anti-PD-1/PD-L1 therapy. Subjects with BRAF wild type or unknown status must have received only anti-PD-1/PD-L1 therapy. Subjects with BRAF activating mutation could have also received a BRAF inhibitor and/or MEK inhibitor regimen prior to anti-PD-1/PD-L1 therapy.

Confirmed PD (Section 5.2.1) during treatment with anti-PD-1/PD-L1 therapy should be documented by 2 consecutive tumor assessments at least 4 weeks apart (the second scan may be used as the baseline scan for this study if it was performed within the 21 days prior Cycle 1 Day 1). Subjects should start study treatment no later than 8 weeks following the last dose of anti-PD-1/PD-L1 therapy (with no intervening therapy).

Subjects with ocular melanoma are excluded.

Phase 2 Cohort 3: Subjects with histologically or cytologically confirmed, metastatic or locally advanced NSCLC not amenable to curative treatment. Subjects must have disease progression on an immediately preceding PD-1/PD-L1 containing regimen. Subjects could have received no more than one platinum containing regimen, or if subjects have a documented activating mutation (e.g. EGFR, ALK, ROS) amenable to tyrosine kinase inhibitor therapy, must also have received the appropriate therapy and progressed before the PD-1/PD-L1 containing regimen. Based on response to previous PD-1/PD-L1 containing regimen, subjects will be enrolled in one of the following groups:

- Group A: Subjects with best response of progressive disease or with stable disease < 16 weeks
- Group B: Subjects with tumor response or with stable disease ≥16 weeks.

If possible, confirmed PD (Section 5.2.1 during treatment with anti-PD-1/PD-L1 therapy should be documented by 2 consecutive tumor assessments at least 4 weeks apart (the second scan may be used as the baseline scan for this study if it was performed within the 21 days prior Cycle 1 Day 1). Subjects should start study treatment no later than 8 weeks following the last dose of anti-PD-1/PD-L1 containing regimen.

<u>General Inclusion Criteria:</u>

- Subjects willing and able to provide written informed consent for this study
- Male or female ≥18 years old at time of consent
- Measurable disease by RECIST 1.1
- ECOG performance status of 0 or 1
- Resolution of prior treatment-related toxicities to Grade 1, with the exception of alopecia, Grade 2 neuropathy and laboratory abnormalities (parameters below apply). If subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention
- Adequate organ function within 14 days of first dose of investigational product:
- WBC ≥1.5 x 10^9/L in absence of growth factor support

- ANC ≥1.0 x 10^9/L in absence of growth factor support
- Platelet count ≥100 x 10^9/L
- Hemoglobin ≥8 g/dL
- Serum creatinine ≤1.5 mg/dL AND creatinine clearance ≥60 mL/min (calculated [using the formula of local laboratory] or measured)
- AST and ALT ≤2.5 x ULN
- Total bilirubin ≤1.5 x ULN, or direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 x ULN
- INR or PT ≤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
- 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
- Women of childbearing potential must have a negative serum pregnancy test within the 7 days prior to first dose of investigational product and a negative urine pregnancy test within the 3 days prior to first dose of investigational product, or a negative serum pregnancy test within the 3 days prior to first dose of investigational product
- Women of childbearing potential must agree to follow instructions for method(s) of contraception for the duration of study treatment and 5 months after the last dose of investigational product. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment and 7 months after the last dose of investigational product
- Available archived or fresh tumor tissue sample for PD-L1 and other biomarker analysis
- For subjects that consent to collection of tumor biopsies at study entry and before the first scheduled tumor assessment, primary or metastatic tumor that can be safely biopsied. A minimum of 24 subjects (6 subjects with each cohort/group) must consent to fresh core biopsies.

<u>General Exclusion Criteria</u>:

1. Previous exposure to any immunomodulatory agents (e.g., anti- CD40, CTLA-4, PD-1/ PD-L1, IDO inhibitors) with the following exceptions:
    a. For Cohort 2 (unresectable or metastatic melanoma):
        i. All subjects must have confirmed disease progression while on treatment with anti-PD-1/PD-L1 therapy
        ii. Subjects could have received anti-CTLA-4 therapy provided they did not have disease progression while on therapy and they discontinue treatment with anti-CTLA-4 therapy at least 3 months prior to first dose of investigational product
    b. For Cohort 3 (metastatic or locally advanced NSCLC):

2. All subjects must have disease progression while on treatment with anti-PD-1/PD-L1 therapy. Second malignancy (solid or hematologic) within the past 3 years except:
    a. Adequately treated basal cell or squamous cell skin cancer, or
    b. Carcinoma in situ of the cervix, or
    c. Prostate cancer Gleason score < 6 with undetectable prostate specific antigen (PSA) over 12 months, or

d. Ductal breast carcinoma in situ with full surgical resection (i.e., negative margins), or
e. Treated medullary or papillary thyroid cancer

3. Active, known, clinically serious infections (≥ Grade 2 according to NCI-CTCAE v4.03) within the 14 days prior to first dose of investigational product
4. Use of systemic corticosteroids or other systemic immunosuppressive drugs within the 28 days prior to first dose of investigational product (except inhaled corticosteroids); the use of physiologic doses of corticosteroids may be approved after consultation with the Apexigen Medical Monitor (or designee)
5. Major surgery within 4 weeks of first dose of investigational product
6. Concurrent treatment with any anti-cancer agent, except for hormonal therapy and palliative radiation as clinically indicated unless approved by the Medical Monitor
7. History of allogeneic bone marrow transplantation
8. Uncontrolled diabetes or hypertension
9. Active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
10. History of (non-infectious) pneumonitis that required corticosteroids or current pneumonitis
11. History of interstitial lung disease
12. History of life-threatening toxicity related to prior anti-PD-1/PD-L1 treatment for subjects with metastatic melanoma except those that are unlikely to re-occur with standard countermeasures (e.g. hormone replacement after adrenal crisis)
13. History of sensitivity or allergy to mAbs or IgG
14. Congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, or myocardial infarction within 6 months prior to the first dose of investigational product
15. History of any thromboembolic event within 3 months prior to first dose of investigational product or an active coagulopathy
16. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with untreated brain metastases ≤ 3mm that are asymptomatic, do not have significant edema, cause shift, require steroids or anti-seizure medications are eligible after discussion with the Medical Monitor. Lesions of any size in posterior fossa are excluded. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using corticosteroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability
17. Known human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection
18. Has received a live-virus vaccination within 30 days of the first dose of investigational product. Seasonal flu vaccines that do not contain live virus are permitted
19. Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study
20. Any clinically significant psychiatric, social, or medical condition that, in the opinion of the Investigator, could increase subject's risk, interfere with protocol adherence, or affect a

subject's ability to give informed consent.

Statistical Methods and Analyses

Primary Endpoint

- Establish MTD (Phase 1b)
- ORR (rate of CR and PR) by RECIST 1.1 in each cohort/group (Phase 2)

Secondary Endpoints

- Incidence and severity of AEs and specific laboratory abnormalities graded according to NCI-CTCAE, v4.03
- 6-month PFSR by cohort/group (Phase 2)
- DOR (by RECIST 1.1) by cohort/group
- PFS (by RECIST 1.1) by cohort/group

Exploratory Endpoints

- PK parameters of APX005M, including C_{max}, t_{max}, AUC_{0-t}, and AUC0-∞
- Presence and titer of anti-APX005M antibodies
- Association between potential PDn markers and PK of APX005M; association between potential predictive biomarkers and anti-tumor activity
- ORR by iRECIST in each cohort/group (Phase 2)
- DOR (by iRECIST) by cohort/group
- PFS (by iRECIST) by cohort/group

Safety Analyses

- Safety will be assessed through summaries of DLT, AEs, changes in laboratory test results, ECG, vital signs, and APX005M exposure. All AE data collected will be listed by study site, cohort, subject number, and cycle day.

Efficacy Analyses

- Tumor assessments by Investigator will follow RECIST 1.1 and iRECIST. ORR (and 90% confidence interval), DOR and PFS (Kaplan-Meier estimate) will be estimated for each cohort/group and for each tumor assessment criteria.

Pharmacokinetic Analyses

- PK parameters of APX005M will be determined using model-independent methods.

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1. Introduction and Study Rationale

1.1 Background

Among the promising approaches to activating therapeutic anti-tumor immunity is the modulation of host immune system. Immune modulation includes inhibitory or stimulatory pathways in the immune system that are crucial for activating the immune response, maintaining self-tolerance, and modulating the duration and amplitude of physiological immune responses. Modulation of immune checkpoints by antibodies against immune inhibitory molecules has shown clinical benefits for patients with various solid tumors such as melanoma, lung cancer, bladder cancer, renal cell carcinoma [1-3]. Currently, both antagonistic monoclonal antibodies (mAb) against immune inhibitory molecules such as cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed death receptor-1 (PD-1)/ programmed death-ligand 1 (PD-L1) and agonistic antibodies against immune costimulatory molecules such as CD40 and OX40 are under active development for different cancer indications and is believed that combination of such immunomodulatory agents could lead to a cure for cancer [4].

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 [5]. CD40 is expressed by dendritic cells (DC), B cells, monocytes, and some non-lymphoid cells [6]. 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 [7, 8]. 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 [9]. Activation of CD40 on tumor cells results in tumor cell apoptosis and inhibition of tumor growth [10]. 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 [11-14].

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.

1.2 APX005M

1.2.1 Pharmacology

APX005M is an IgG1 humanized mAb with the S267E mutation at the Fc region. APX005M binds with high affinity to human CD40 ($K_d = 1.2 \times 10^{-10}$ M) and monkey CD40 ($K_d = 3.5 \times 10^{-10}$ 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 [15].

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.

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 [16]. 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.

1.2.2 Pharmacokinetics

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 (C_{max}) and area under the curve at the last measurable time point (AUC_{0-t}). No accumulation of APX005M was observed with every 21 days dosing.

1.2.3 Clinical Experience

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.

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 and the overall safety of APX005M please refer to latest version of the APX005M Investigator's Brochure [16].

1.2.4 Summary of the Known and Potential Risks and Benefits

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 recently completed 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.

Please refer to the most recent version of the APX005M Investigator Brochure for the most current summary of APX005M to date.

1.3 Nivolumab

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA [17]. PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression 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 [18]. 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.

Nivolumab (BMS-936558, MDX1106) is a fully human monoclonal antibody (IgG4 kappa) that targets PD-1. In vitro, nivolumab binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 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 the mixed lymphocyte reaction (MLR). Using a CMV re stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of

PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02) [19].

Nivolumab is investigated both as monotherapy and in combination with chemotherapy, targeted therapies and other immunotherapies. For study details please refer to the nivolumab Investigator's Brochure [20].

1.3.1 Summary of the Known and Potential Risks and Benefits

Extensive details on the safety profile of nivolumab are available in the Investigator Brochure, and will not be repeated herein. Overall, the safety profile of nivolumab monotherapy 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. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related adverse events has been defined, for which management algorithms have been developed; these are provided in the Investigator's Brochure. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab Investigator's Brochure.

Nivolumab (Opdivo) monotherapy is approved in multiple countries, including the US and members of the EU, for unresectable or metastatic melanoma, previous treated metastatic non-small cell lung cancer and previously treated advanced renal cell carcinoma. It is also approved for the treatment of classical Hodgkin lymphoma in the US. IN addition, nivolumab has been approved for use in combination with ipilimumab for unresectable melanoma in multiple countries, including the US.

1.4 Rationale for APX005M in Combination with Nivolumab

Antibody therapies blocking PD-1, PD-L1 and CTLA-4 function enhance anti-tumor immunity, leading to durable clinical responses for a subset of patients with melanoma, lung cancer and other tumor types [21]. However, the majority of patients with melanoma or lung cancer continue to have a short response or no response to checkpoint blockade therapies [22].

CD40 is a member of the TNFR superfamily, which is expressed on the surface of APCs, plays a critical role in the control and regulation of both innate and adaptive immunity against tumors [23]. Although phase I studies with monotherapy agonistic CD40 antibodies have demonstrated objective tumor responses in solid tumors [24], the greatest potential for CD40 activation lies in the combination with other therapeutic agents. The combination of CD40 agonists with chemotherapy (e.g., cell death resulting in the release of tumor antigens) may lead to synergistic therapeutic effects, as indicated by recent phase I clinical trials [25, 26].

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 [27] 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 [28-30].

This clinical protocol will explore the safety and efficacy of APX005M in combination with nivolumab in:

- Subjects with histologically or cytologically confirmed, immunotherapy naïve, metastatic or locally advanced non-small cell lung cancer (NSCLC) not amenable to curative treatment. Subjects may be treatment naïve or could have received one prior platinum-based chemotherapy for non-small cell lung cancer for any indication (adjuvant, part of combined modality therapy or for metastatic disease) within the past 3 years, or if subjects have a documented activating mutation (e.g. EGFR, ALK, ROS) amenable to tyrosine kinase inhibitor therapy, must also have received the appropriate therapy and progressed (inNSCLC)
- Subjects with histologically or cytologically confirmed unresectable or metastatic melanoma (MM) that had confirmed progressive disease during treatment with anti-PD-1/PD-L1 therapy. Subjects with BRAF wild type or unknown status must have received only anti-PD-1/PD-L1 therapy. Subjects with BRAF activating mutation could have also received a BRAF inhibitor and/or MEK inhibitor regimen prior to anti-PD-1/PD-L1 therapy. Subjects with ocular melanoma are excluded (PD1-MM).
- Subjects with histologically or cytologically confirmed, metastatic or locally advanced NSCLC not amenable to curative treatment. Subjects must have disease progression (PD) on an immediately preceding PD-1/PD-L1 containing regimen. Subjects could have received no more than one platinum containing regimen, or if subjects have a documented activating mutation (e.g. EGFR, ALK, ROS) amenable to tyrosine kinase inhibitor therapy, must also have received the appropriate therapy and progressed before the PD-1/PD-L1 containing regimen (PD1-NSCLC).

2. Investigational Plan

2.1 Study Objectives

2.1.1 Primary Objective

Phase 1b:

- Determine the MTD and the RP2D of APX005M when given in combination with nivolumab

Phase 2:

- Evaluate the overall response rate (ORR) by RECIST 1.1 in each cohort/group

2.1.2 Secondary Objectives

- Evaluate safety of the APX005M and nivolumab combination
- Evaluate the 6-month progression-free survival (PFS) rate (PFSR) in each cohort/group
- Evaluate duration of response (DOR) and median PFS in each cohort/group by RECIST 1.1

2.1.3 Exploratory Objectives

- Determine the immune PDn of the APX005M and nivolumab combination
- Determine the PK of APX005M
- Assess incidence of APX005M ADA
- Identify blood and/or tumor biomarkers that correlate with efficacy and/or resistance
- Evaluate the ORR by immune related RECIST (iRECIST) in each cohort/group
- Evaluate DOR and median PFS in each cohort/group by iRECIST

2.2 Study Design and Duration

This is a Phase 1b-2 study. The study will include 2 parts (Table 1).

- Phase 1b dose-escalation of APX005M:
  - Up to 4 dose levels of APX005M administered IV every 21 days
  - In combination with nivolumab 360 mg IV every 21 days
  - Subjects with inNSCLC or PD1-MM
- Phase 2 dose-expansion (Simon optimal 2-stage design):
  - The RP2D dose of APX005M administered IV every 21 days in combination with nivolumab 360 mg IV
  - 3 cohorts
    - Cohort 1: Subjects with inNSCLC
    - Cohort 2: Subjects with PD1-MM
    - Cohort 3: Subjects with PD1-NSCLC
      - Group A: Subjects with PD1-NSCLC with best response of progressive disease or with stable disease < 16 weeks while on

previous PD-1/PD-L1 containing regimen
- Group B: Subjects with PD1-NSCLC with tumor response or with stable disease ≥ 16 weeks while on previous PD-1/PD-L1 containing regimen

Table 1: Planned Number of Subjects in Study APX005M-002

Study Phase	Dose Level	APX005M		Nivolumab		
Phase1b Dose-escalation		**mg/kg**		**mg**		**N**
	DL 1	0.03	q 21 days	360	q 21 days	3
	DL 2	0.1	q 21 days	360	q 21 days	3
	DL2a	*0.2*	q 21 days	360	q 21 days	3 to 6
	DL 3	0.3	q 21 days	360	q 21 days	3 to 6
					Subtotal ~	18

Study Phase	Stage	APX005M		Nivolumab		
Phase 2 Dose-expansion		**mg/kg**		**mg**		**N**
Cohort 1 inNSCLC	Stage 1	RP2D	q 21 days	360	q 21 days	24
	Stage 2	RP2D	q 21 days	360	q 21 days	21
Cohort 2 PD1-MM	Stage 1	RP2D	q 21 days	360	q 21 days	12
	Stage 2	RP2D	q 21 days	360	q 21 days	25
Cohort 3 PD1-NSCLC Group A	Stage 1	RP2D	q 21 days	360	q 21 days	12
	Stage 2	RP2D	q 21 days	360	q 21 days	25
Cohort 3 PD1-NSCLC Group B	Stage 1	RP2D	q 21 days	360	q 21 days	12
	Stage 2	RP2D	q 21 days	360	q 21 days	25
					Total ~	174

Phase 1b dose-escalation:

Subjects with inNSCLC or PD1-MM who meet all of the general eligibility criteria will be enrolled in the dose-escalation portion of the study.

There will be a maximum of 3 escalation dose levels (DL) and 1 de-escalation dose level in this study. The doses of APX005M and minimum number of subjects to be enrolled in each dose level are presented in Table 2. It is expected that up to 18 DLT-evaluable subjects (see definition in Section 7.2) will be enrolled in the dose-escalation portion of the study over a 6-month period. All subjects that are not DLT-evaluable will be replaced for the purpose of establishing MTD.

Table 2: APX005M Dose Levels

Escalation Dose Level	**DL1**	**DL2**		**DL3**
De-escalation Dose Level			***DL2a***	
APX005M mg/kg body weight	0.03	0.1	*0.2*	0.3
Minimum number of DLT evaluable subjects	3	3	*3*	3

Abbreviations: DL = dose level; DLT = dose-limiting toxicity.

The DLT observation period for dose escalation is the 21 days following the first administration of APX005M and nivolumab (first 3-week cycle). Safety and tolerability of the APX005M and nivolumab combination will be monitored by representatives from Apexigen and the Investigators on a regular basis and prior to each dose escalation.

Dose escalation will continue if 0 out of 3 evaluable subjects experience a DLT during the DLT observation period (i.e., <33% DLT-evaluable subjects in that cohort have a DLT). If 1 DLT-evaluable subject in any DL cohort experiences a DLT, that cohort will be expanded to include additional 3 DLT-evaluable subjects (i.e. a total of 6 evaluable subjects). Dose escalation will continue if 1 out of 6 evaluable subjects experience a DLT during the DLT observation period (i.e., <33% DLT-evaluable subjects in that cohort have a DLT). Decision to open a new DL cohort will be based on the totality of the data available at that time.

The MTD is the maximum dose of APX005M combined with 360 mg of nivolumab for which <33% of DLT-evaluable subjects experience a DLT.

If the DLT rate in DL 3 exceeds 33%, or 2 or more subjects in DL 2 experience a Grade 2 infusion reaction/cytokine release syndrome, or at the discretion of the sponsor, the intermediate lower DL 2a will be evaluated (de-escalation). Up to 6 subjects can be enrolled in any of dose levels below the MTD or highest DL tested, should sponsor decide to discontinue dose escalation prior to reaching the MTD.

The RP2D will be based on the overall safety and tolerability of the combination of APX005M and nivolumab.

Phase 2 dose-expansion:
After identification of the RP2D of APX005M in combination with nivolumab 360 mg IV every 21 days, study will continue with 3 cohorts.

- Cohort 1: inNSCLC
- Cohort 2: PD1-MM
- Cohort 3: PD1-NSCLC
    - Group A
    - Group B

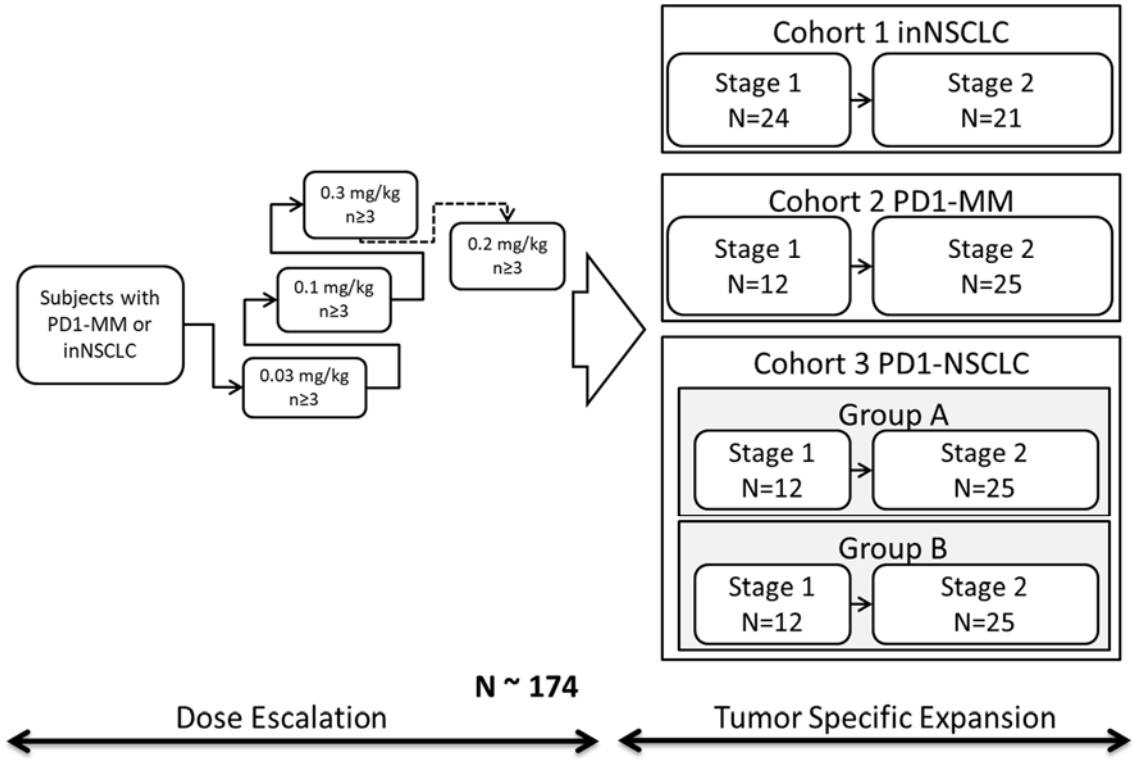
Each cohort and group of the Phase 2 dose-expansion portion of the study will follow a Simon optimal 2-stage design. Subjects treated at the RP2D in the dose-escalation portion will be included in Stage 1 of the relevant cohort. Additional subjects will be enrolled for a total of 24

subjects in Cohort 1 and 12 subjects in each of Cohort 2, Cohort 3 Group A and Cohort 3 Group B.

Subjects will be evaluated for tumor response approximately every 8 weeks following the first dose of investigational product. Subjects that are non-evaluable for tumor response (see definition in Section 7.2) will be replaced. An ORR [complete response (CR) + partial response (PR)] of at least 22% (6 confirmed out if 24 response evaluable subjects) in the inNSCLC cohort and 5% (1 confirmed out if 12 response evaluable subjects) in the PD1-MM cohort or PD1-NSCLC (Group A or B) is required in Stage 1 for that cohort to proceed to Stage 2. Enrollment may continue into Stage 2 while the planned number of subjects for Stage 1 are followed for efficacy.

In Stage 2, an additional 21 subjects will be enrolled in Cohort 1 (inNSCLC) and an additional 25 subjects will be enrolled in each of Cohort 2 (PD1-MM) and Cohort 3 (PD1-NSCLC) Group A and B. The study schema is presented in Figure 1.

Figure 1: APX005M-002 Study Design



A minimum of 6 subjects per cohort/group who have a primary or metastatic lesion that can be biopsied without interfering with subsequent tumor assessments and who consent to collection of paired tumor biopsies for tumor biomarkers should be enrolled during Phase 1b and Phase 2.

At any time during the study, enrollment will be suspended pending safety review if any of the following events occur since last safety review:

- ≥1 Grade 5 suspected adverse reaction (SAR) (for definition see Section 6.1.2)
- ≥2 Grade 4 infusion reaction/ cytokine release syndrome

- ≥2 Grade ≥ 3 immune related AEs in more than 1 subject

Enrollment will resume following assessment by the Apexigen Medical Monitor, contract research organization Medical Monitor and lead Investigator.

For subjects that require confirmation of PD while on treatment with anti-PD-1/PD-L1 therapy, any of the following criteria must be met:

- ≥ 5mm further increase in sum of measures of target lesion
- ≥ 5mm further increase in sum of measures of new lesion
- further increase in the size of non-target lesion(s)
- new non-target lesions
- appearance of new lesion(s) when none have previously been recorded
- increase in the number of new lesions
- all of the following
    - maintain > 20% increase in target lesion burden at confirmed PD scan relative to nadir (as per RECIST1.1)
    - target lesion burden at confirmatory PD scan greater than 90% of target lesion burden at uncomfirmed PD (initial PD) scan (to account for intra-subject reader variability)
    - no disappearance of all new lesions.

2.2.1 Study Population

2.2.1.1 Inclusion Criteria

Cohort Specific Inclusion Criteria

Phase 1b: Subjects that meet eligibility criteria for Phase 2 Cohorts 1 or 2 and all of the general eligibility criteria.

Phase 2 Cohort 1: Histologically or cytologically confirmed, immunotherapy naïve, metastatic or locally advanced non-small cell lung cancer not amenable to curative treatment. Subjects may be treatment naïve or could have received one prior platinum-based chemotherapy for non-small cell lung cancer for any indication (adjuvant, part of combined modality therapy or for metastatic disease) within the past 3 years. Subjects with no or unknown activating mutation (e.g., EGFR, ALK, ROS) are eligible for this study. Subjects with a documented activating mutation (e.g., EGFR, ALK, ROS) amenable to tyrosine kinase inhibitor therapy, must also have received the appropriate therapy and progressed.

Phase 2 Cohort 2: Subjects with histologically or cytologically confirmed unresectable or metastatic melanoma that had confirmed progressive disease during treatment with anti-PD-1/PD-L1 therapy. Subjects with BRAF wild type or unknown status must have received only anti-PD-1/PD-L1 therapy. Subjects with BRAF activating mutation could have also received a BRAF inhibitor and/or MEK inhibitor regimen prior to anti-PD-1/PD-L1 therapy.

Confirmed PD (Section 5.2.1) during treatment with anti-PD-1/PD-L1 therapy should be documented by 2 consecutive tumor assessments at least 4 weeks apart (the second scan may be used as the baseline scan for this study if it was performed within the 21 days prior Cycle 1 Day

1). Subjects should start study treatment no later than 8 weeks following the last dose of anti-PD-1/PD-L1 therapy (with no intervening therapy).

Subjects with ocular melanoma are excluded.

Phase 2 Cohort 3: Subjects with histologically or cytologically confirmed, metastatic or locally advanced NSCLC not amenable to curative treatment. Subjects must have disease progression on an immediately preceding PD-1/PD-L1 containing regimen. Subjects could have received no more than one platinum containing regimen, or if subjects have a documented activating mutation (e.g. EGFR, ALK, ROS) amenable to tyrosine kinase inhibitor therapy, must also have received the appropriate therapy and progressed before the PD-1/PD-L1 containing regimen. Based on response to previous PD-1/PD-L1 containing regimen, subjects will be enrolled in one of the following groups:

- Group A: Subjects with best response of progressive disease or with stable disease < 16 weeks
- Group B: Subjects with tumor response or with stable disease ≥16 weeks.

If possible, confirmed PD (Section 5.2.1 during treatment with anti-PD-1/PD-L1 therapy should be documented by 2 consecutive tumor assessments at least 4 weeks apart (the second scan may be used as the baseline scan for this study if it was performed within the 21 days prior Cycle 1 Day 1). Subjects should start study treatment no later than 8 weeks following the last dose of anti-PD-1/PD-L1 containing regimen.

General Inclusion Criteria

1. Subjects willing and able to provide written informed consent for this study
2. Male or female ≥18 years old at time of consent
3. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
5. Resolution of prior treatment-related toxicities to Grade 1, with the exception of alopecia, Grade 2 neuropathy and laboratory abnormalities (parameters below apply). If subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention
6. Adequate organ function within 14 days of first dose of investigational product:
    a. White blood cell count (WBC) ≥1.5 x 10^9/L in absence of growth factor support
    b. Absolute neutrophil count (ANC) ≥1.0 x 10^9/L in absence of growth factor support
    c. Platelet count ≥100 x 10^9/L
    d. Hemoglobin ≥8 g/dL
    e. Serum creatinine ≤1.5 mg/dL AND creatinine clearance ≥60 mL/min (calculated [using the formula of local laboratory] or measured)
    f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN)
    g. Total bilirubin ≤1.5 x ULN, or direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 x ULN
    h. International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or Partial Thromboplastin Time (PTT) is within therapeutic range of intended use of

anticoagulants

i. 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

7. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within the 7 days prior to first dose of investigational product and a negative urine pregnancy test within the 3 days prior to first dose of investigational product, or a negative serum pregnancy test within the 3 days prior to first dose of investigational product
8. WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment and 5 months after the last dose of investigational product. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment and 7 months after the last dose of investigational product
9. Available archived or fresh tumor tissue sample for PD-L1 and other biomarker analysis
10. For subjects that consent to collection of tumor biopsies at study entry and before the first scheduled tumor assessment, primary or metastatic tumor that can be safely biopsied. A minimum of 24 subjects (6 subjects with each cohort/group) must consent to fresh core biopsies.

2.2.1.2 General Exclusion Criteria

1. Previous exposure to any immunomodulatory agents (e.g., anti- CD40, CTLA-4, PD-1/PD-L1, IDO inhibitors) with the following exceptions:
    a. For Cohort 2 (unresectable or metastatic melanoma):
        i. All subjects must have confirmed disease progression while on treatment with anti-PD-1/PD-L1 therapy
        ii. Subjects could have received anti-CTLA-4 therapy provided they did not have disease progression while on therapy and they discontinue treatment with anti-CTLA-4 therapy at least 3 months prior to first dose of investigational product
    b. For Cohort 3 (metastatic or locally advanced NSCLC):
        i. All subjects must have disease progression while on treatment with anti-PD-1/PD-L1 therapy
2. Second malignancy (solid or hematologic) within the past 3 years except:
    a. Adequately treated basal cell or squamous cell skin cancer, or
    b. Carcinoma in situ of the cervix, or
    c. Prostate cancer Gleason score < 6 with undetectable prostate specific antigen (PSA) over 12 months, or
    d. Ductal breast carcinoma in situ with full surgical resection (i.e., negative margins), or
    e. Treated medullary or papillary thyroid cancer
3. Active, known, clinically serious infections (≥ Grade 2 according to NCI-CTCAE v4.03) within the 14 days prior to first dose of investigational product
4. Use of systemic corticosteroids or other systemic immunosuppressive drugs within the 28 days prior to first dose of investigational product (except inhaled corticosteroids); the use of physiologic doses of corticosteroids may be approved after consultation with the

Apexigen Medical Monitor (or designee)
5. Major surgery within 4 weeks of first dose of investigational product
6. Concurrent treatment with any anti-cancer agent, except for hormonal therapy and palliative radiation as clinically indicated unless approved by the Medical Monitor
7. History of allogeneic bone marrow transplantation
8. Uncontrolled diabetes or hypertension
9. Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
10. History of (non-infectious) pneumonitis that required corticosteroids or current pneumonitis
11. History of interstitial lung disease
12. History of life-threatening toxicity related to prior anti-PD-1/PD-L1 treatment for subjects with metastatic melanoma except those that are unlikely to re-occur with standard countermeasures (e.g. hormone replacement after adrenal crisis)
13. History of sensitivity or allergy to mAbs or IgG
14. Congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, or myocardial infarction within 6 months prior to the first dose of investigational product
15. History of any thromboembolic event within 3 months prior to first dose of investigational product or an active coagulopathy
16. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with untreated brain metastases ≤ 3mm that are asymptomatic, do not have significant edema, cause shift, require steroids or anti-seizure medications are eligible after discussion with the Medical Monitor. Lesions of any size in posterior fossa are excluded. Subjects with previously treated brain metastases may participate provided they are stable after treatment (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using corticosteroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability
17. Known human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection
18. Has received a live-virus vaccination within 30 days of the first dose of investigational product. Seasonal flu vaccines that do not contain live virus are permitted
19. Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study
20. Any clinically significant psychiatric, social, or medical condition that, in the opinion of the Investigator, could increase subject's risk, interfere with protocol adherence, or affect a subject's ability to give informed consent.

2.2.2 APX005M Dose

APX005M has been administered in the APX005M-001 study to subjects with solid tumors as a single-agent at 7 dose levels starting at 0.1 μg/kg up to 1.0 mg/kg body weight every 21 days. At

0.6 and 1 mg/kg dose level 1 out of 6 subjects experienced a DLT. The RP2D for APX005M as a single agent every 21 days is 0.3 mg/kg body weight.

The proposed starting dose level for APX005M in this study is 0.03 mg/kg which is approximately 33 times lower than the highest dose of APX005M administered to human subjects. Three subjects were enrolled at this dose level in the APX005M-001 study and received a total of 8 infusions of APX005M. One additional subject enrolled at a lower dose level was allowed per protocol to have the dose of APX005M escalated and received 3 infusions of 0.03 mg/kg of APX005M. The only AE considered as possibly related to APX005M for all subjects receiving 0.03 mg/kg of APX005M was one event of vomiting (Grade 1) shortly after the administration of APX005M. This dose level was also the lowest to show a PDn effect across multiple markers of APC activation measured 24 hours after the start of infusion, although APX005M was detectable in the peripheral blood only during and at the end of infusion.

The highest dose level of APX005M to be tested in combination with nivolumab will be 0.3 mg/kg body weight (Table 1). At all dose levels proposed, APX005M has been well tolerated; all adverse reactions have been moderate (≤ Grade 2), transient and easily managed in outpatient setting. All available data suggests that 0.03 mg/kg every 21 days is a safe and pharmacodynamically active dose of APX005M.

2.2.3 Nivolumab Dose

The approved dose of nivolumab is 240 mg infused over 60 minutes every 2 weeks for NSCLC, unresectable or metastatic melanoma and advanced renal cell carcinoma (RCC). In this study, a flat dose of 360 mg nivolumab administered as an IV infusion over 30 minutes and a dosing schedule of every 3 weeks has been selected. Nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg (Bristol-Myers Squibb, internal data). Population pharmacokinetic analyses have shown that the pharmacokinetics of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg; no differences in pharmacokinetics across ethnicities and tumor types were observed. Using the population pharmacokinetic model developed, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including 360 mg administered every 3 weeks. The simulated steady state average concentration following administration of nivolumab 360 mg every 3 weeks are expected to be similar to those following administration of nivolumab 240 mg every 2 weeks and 3 mg/kg every 2 weeks to subjects weighing 80 kg, the approximate median weight of subjects with NSCLC, unresectable or metastatic melanoma and RCC used in the population pharmacokinetic analyses. The steady state peak concentrations following nivolumab 360 mg every 3 weeks are predicted to be less than those following the administration of nivolumab 10 mg/kg every 2 weeks providing sufficient safety margins. Finally, nivolumab is being studied as nivolumab 360 mg combined with platinum-doublet chemotherapy administered every 3 weeks for the treatment of NSCLC in a Phase 3 study.

Previous clinical studies of nivolumab monotherapy have used a 60 minute infusion duration wherein, nivolumab has been safely administered up to 10 mg/kg over long treatment periods. Infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical program. In CA209010, a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10

mg/kg). All the events were Grade 1-2 and were manageable. An infusion duration of 30 minutes for nivolumab 360 mg is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60 minute duration. The safety of nivolumab 3 mg/kg administered as a 30 minutes infusion was assessed in subjects (n=322) with previously treated advanced NSCLC. Overall, there were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions (of any cause or treatment-related) in subjects administered nivolumab over a 30 minutes infusion compared with that reported for subjects with the 60 minutes infusion. Thus, it was shown that nivolumab can be safely infused over 30 minutes.

3. Treatment of Subjects

3.1 Subject Enrollment and Treatment Administration

All subjects who sign a consent form will be assigned a unique Subject Identification Number. This number will be used to identify the subject throughout the study and must be used on all study documentation. Subjects will be considered enrolled after receiving any investigational product; consented subjects who do not receive investigational product will be considered screen failures.

The Apexigen Medical Monitor (or designee) will review the subject's information before enrollment. Only subjects who are approved by the Apexigen Medical Monitor (or designee) will be allowed to enroll in the study. During normal business days, a minimum of 24 hours will be required for the Apexigen Medical Monitor (or designee) to approve a subject for enrollment. Additional time may be required when approval is sought during a weekend or holiday.

Subject enrollment into a DL cohort of the Phase 1b dose-escalation or in the Phase 2 dose-expansion will follow the rules outlined in Section 2.2.

On treatment days, nivolumab will be administered first, followed by APX005M.

During Phase 1b dose-escalation, in any of the multi-subject cohorts, the first two subjects must receive the first dose of investigational product at least 72 hours apart.

During the Phase 1b dose-escalation portion of the study all subjects will be monitored in the research clinic for 4 hours after the first 2 infusions of APX005M and as clinically indicated thereafter and during the Phase 2 dose-expansion portion of the study.

All subjects will be discharged from clinic after a clinical evaluation. Subjects should have stable vital signs including: lack of orthostatic hypotension (systolic blood pressure >100 mmHg, or no lower than 10 mm from baseline) without IV hydration (no hydration for at least 2 hours prior to discharge), lack of hypoxia (oxygen saturation >90% without oxygen), temperature <38˚C, heart rate <110 beats/min.

After discharge, all subjects in Phase 1b should be monitored by a caregiver or by a healthcare professional for 24 hours after the first 2 infusions of APX005M and as clinically indicated thereafter. Subjects in the Phase 2 dose-expansion portion of the study should be monitored as clinically indicated.

3.2 Study Treatment

3.2.1 Investigational Products

An investigational product, also known as investigational medicinal product, is defined as follows:

> A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a different way 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 and nivolumab.

The Pharmacy Manual contains detailed information about packaging, labeling, storage, dispensing, preparation and administration of the infusion solutions of APX005M and nivolumab.

3.2.2 Non-Investigational Product

Any other medications used in the study as support or rescue medication for preventative, diagnostic, or therapeutic reasons, components of the standard of care for a given diagnosis, are considered non-investigational products.

3.3 Timing of Investigational Products Administration

Investigational products may be administered up to 3 days before or after the scheduled Day 1 in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays); if retreatment criteria are met subjects should restart treatment within 12 weeks of last dose of investigational product unless otherwise discussed with Apexigen (or designee). Every effort should be made to maintain a 21-day dosing schedule. The reason for delay will be documented in the patient's study record.

3.3.1 Nivolumab

Nivolumab is administered on Day 1 of each 3-week treatment cycle as a dose of 360 mg using a 30-minute IV infusion. 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 1 mg/mL. Nivolumab injections should be administered through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter and are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 25 minutes to 40 minutes). The nivolumab infusion can be interrupted in the case of infusion reaction (see Section 3.4.1.2). Once symptoms resolve, infusion should be restarted at 50% of the initial infusion rate (e.g., from 100 mL/hr to 50 mL/hr).

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

3.3.2 APX005M

APX005M is administered on Day 1 of each 3-week treatment cycle approximately 30 minutes following nivolumab using a 60 minute IV infusion. Sites should make every effort to target infusion timing to be as close to 60 minutes as possible. A window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 55 minutes to 70 minutes).

The APX005M infusion can be interrupted in the case of infusion reaction (see Section 3.4.1.2). Once symptoms resolve, infusion should be restarted at 50% of the initial infusion rate (e.g., from 50 mL/hr to 25 mL/hr). A lower infusion rate may be considered for patients who experience repeated infusion reactions, after discussion with Apexigen Medical Monitor (or designee).

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

3.4 Concomitant Treatments

3.4.1.1 Premedication Prior to Administration of Investigational Product

All subjects should be premedicated approximately 30 minutes before the administration of first investigational product with a regimen containing:

- Oral H1 antagonist (e.g., loratadine 10 mg)
- Optional 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 or IV nonsteroidal anti-inflammatory drug (may comprise ibuprofen 400 mg or equivalent)
- Oral or IV acetaminophen 500-650 mg.

When the time between premedication and scheduled APX005M administration exceeds 4 hours,

or if a subject experiences a Grade 2 infusion reaction to nivolumab, subjects may receive an additional course of premedication prior to APX005M administration.

3.4.1.2 Rescue Medications & Supportive Care Guidelines

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 and nivolumab combination and should not substitute for investigational product dose delays and/or modifications (Section 3.7). Additional guidance for management of AEs with potential immunologic etiology is provided in the APX005M and nivolumab Investigator's Brochures.

If after evaluation the event is determined by the Investigator not to be related, 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, or Grade 2 colitis, the use of oral corticosteroids is recommended. Other antidiarrheal agents (e.g. octreotide) may be used if necessary.
    - **Grade 3-4:** treat with IV corticosteroids followed by oral corticosteroids until symptoms improve to Grade 1 or less. Add prophylactic antibiotics for opportunistic infections and consider lower endoscopy.

- **Creatinine Elevation Due to Inflammatory Causes**
    - **Grade 2-3:** treat with IV or oral corticosteroids until symptoms improve to Grade 1 or less. Consider renal biopsy with nephrology consult.
    - **Grade 4:** treat with IV corticosteroids followed by oral corticosteroids until symptoms improve to Grade 1 or less. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy and consult nephrologist.

- **Pneumonitis**

- **Grade 2:** request pulmonary and infectious disease consults. Treat with IV or oral corticosteroids until symptoms improve to Grade 1 or less. Consider bronchoscopy, lung biopsy and hospitalization.
- **Grade 3-4:** request pulmonary and infectious disease consults. Hospitalize and treat immediately with IV corticosteroids. Administer additional anti-inflammatory measures, as needed. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy and lung biopsy.

- **Liver Function Tests**
  - **Grade 2:** monitor liver function tests more frequently until returned to Grade 1 or less. If no improvement in 5-7 days, treat with IV or oral corticosteroids until symptoms improve to Grade 1 or less.
  - **Grade 3 and 4:** treat with IV corticosteroids for 24-48 hours followed by oral corticosteroids until symptoms improve to Grade 1 or less. If no improvement in 3-5 days administer additional immunosuppressive measures (e.g. mycophenolate mofetil), as needed. Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist.

- **Endocrinopathy**
  - **Asymptomatic TSH abnormality:** monitor fT4 if TSH is <0.5 x LLN, > 2 x ULN or consistently out of range in two subsequent measurements. Consider endocrinology consult.
  - **Symptomatic endocrinopathy:** evaluate endocrine function and consider a pituitary scan. For abnormal laboratory results/pituitary scan initiate IV corticosteroids followed by oral or IV corticosteroids until symptoms improve to Grade 1 or less. Initiate appropriate hormone therapy. For normal laboratory results/pituitary scan repeat labs in 1-3 weeks and pituitary scan in 1 month.
  - **Suspicion of adrenal crisis:** rule out sepsis, administer IV fluids. Consult endocrinologist and if adrenal crisis is ruled out, 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). For persistent (>1-2 weeks) or recurrent symptoms consider skin biopsy and treatment delay.
  - **Grade 3-4:** consider skin biopsy and consult dermatologist. Treat with IV corticosteroids followed by oral corticosteroids until symptoms improve to Grade 1 or less.

- **Infusion Reaction/Cytokine Release Syndrome**
  Precautions should be observed during the administration of APX005M and nivolumab. 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 APX005M or nivolumab, and if such symptoms develop while they are at home, they should contact the Investigator and/or seek emergency medical care if appropriate.

- **Grade 2:** stop infusion and treat symptoms following guidance in Table 3. 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 3.

Table 3: Guidance for Management of Cytokine Release/Infusion Reaction Symptoms

<table>
<tr><th colspan="2">Suspected Cytokine Release/Infusion-related Toxicity</th><th>Recommended Treatment</th></tr>
<tr><td colspan="2">• Mild toxicity requiring symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise)</td><td>• Vigilant supportive care
• Maintain adequate hydration
• Antipyretics, non-steroidal anti-inflammatory drugs, antihistaminics, anti-emetics, analgesics as needed
• In case of mild symptoms persisting for > 48 hours assess for infections; empiric treatment of concurrent bacterial infections</td></tr>
<tr><td rowspan="2">• 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 Grade 2 organ toxicity</td><td>• No extensive co-morbidities</td><td>• All of the above
• Monitor cardiac and other organ functions closely</td></tr>
<tr><td>• Extensive co-morbidities
• Age ≥ 70 years</td><td rowspan="2">• All of the above
• Administer tocilizumab (per ACTEMRA prescribing information)
• Administer corticosteroids if symptoms worsen or do not improve in <4 hours.</td></tr>
<tr><td colspan="2">• 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
o CTCAE Grade ≥3 organ toxicity</td></tr>
</table>

- **Neurological Toxicity**
  - **Grade 2:** symptomatic treatment per local guidelines.
  - **Grade 3-4:** obtain neurological consult and treat symptoms per local guidelines. Administer IV corticosteroids followed by oral corticosteroids until symptoms improve to Grade 2 or less. If symptoms worsen or for atypical presentation consider and additional immunosuppressive measures per local guidelines.

- **Myocarditis Toxicity**
  - **Grade 2:** Hospitalize with cardiac monitoring. Obtain cardiology consult for evaluation and monitoring. Administer IV corticosteroids followed by oral corticosteroids until symptoms improve.

- **Grade 3-4:** Hospitalize to intensive cardiac monitoring. Obtain cardiology consult for evaluation and monitoring. Immediately, administer IV corticosteroid bolus. For Grade 4, transfer to institution with cardiac expertise and consider Antithymocyte Globulin (ATG) as second agent.

3.4.1.3 Permitted Concomitant Medications

All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the electronic case report form (eCRF) including all prescription, over-the-counter, herbal supplements and IV medications and fluids. If changes occur during the Treatment Phase, documentation of drug dosage, frequency, route, and date may also be included on the eCRF.

All concomitant medications received from the time of first dose of investigational product and up to 30 days after the last dose of trial treatment should be recorded.

3.4.1.4 Prohibited and/or Restricted Therapies

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Investigational agents other than APX005M and nivolumab
- Radiation therapy (radiation therapy to a symptomatic solitary lesion or to the brain may be considered on a case by case basis after consultation with Apexigen Medical Monitor (or designee). The subject must have clear measurable disease outside the radiated field.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu - Mist®) are live attenuated vaccines and are not allowed.
- Systemic corticosteroids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Apexigen Medical Monitor (or designee). Inhaled corticosteroids are allowed for management of asthma.
- Medications described in the Exclusion Criteria.

Subjects who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management may be discontinued from study.

Herbal medicine for anticancer treatment (such as botanical formulation 'Xiao Chai Hu Tang') should be stopped 1 week prior to 1st dose of investigational product.

Subjects taking narrow therapeutic index medications (such as warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, and digoxin) should be monitored proactively.

There are no prohibited therapies during the Follow-up Phase.

3.5 Dose Limiting Toxicity

All toxicity will be graded according to the NCI-CTCAE version 4.03. DLT will be defined as any of the following events attributed to APX005M and nivolumab combination (e.g., AEs that are not clearly attributable to extraneous causes), and occurring during the first 21-day following the administration of APX005M and nivolumab (the first 3-week cycle):

- Grade 4 hematologic toxicity lasting ≥ 7 days (except asymptomatic lymphopenia)
- Grade 3 or 4 neutropenia with a single temperature of >38.3° C (101° F) or a sustained temperature of ≥38° C (100.4° F) for more than one hour
- Grade 4 thrombocytopenia (platelet count <25,000 cells/mm^3) or Grade ≥3 thrombocytopenia with signs or symptoms of bleeding or requiring platelet transfusion
- Grade 4 non-hematologic toxicity (not laboratory)
- Grade 3 non-hematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care
- Any Grade ≥ 3 non-hematologic laboratory value if:
- Medical intervention is required to treat the subject, or
- The abnormality leads to hospitalization, or
- The abnormality persists for >1 week
- 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)
- Grade 5 toxicity.

3.6 Retreatment Criteria

Subjects that do not meet any of the criteria for treatment discontinuation (Section 4.1) may start a new cycle of APX005M and nivolumab as scheduled if WBC >1,500/mm^3, ANC >1,000/mm^3, platelets >100,000/mm^3, hemoglobin ≥8 g/dL, and disease or treatment-related AE has resolved to baseline or ≤ Grade 1 (excluding Grade 2 alopecia and Grade 2 fatigue).

Subjects who have experienced a ≤ Grade 2 skin suspected adverse reaction may resume treatment in the presence of Grade 2 skin toxicity.

Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by Apexigen Medical Monitor (or designee).

For subjects requiring corticosteroid treatment, allow for a minimum of 7 days from last dose before beginning a new cycle.

If a subject fails to meet criteria for retreatment then the treatment cycle should be delayed and the subject should be re-evaluated weekly.

3.7 Dose Modifications

Suspected adverse reactions (SAR) (for definition see Section 6.1.2) associated with APX005M and nivolumab exposure may represent an immunologic etiology. These AEs may occur shortly after the administration of investigational products or several months after the last dose of investigational product. Management of suspected adverse drug reactions may require treatment hold, dose reduction of APX005M, or discontinuation of one of both investigational products as per Table 4. If a subject experiences several toxicities, the recommended dose modification should be based on the highest grade toxicity.

See Section 3.4.1.2 for supportive care guidelines, including use of corticosteroids.

Table 4: Dose Modification Guidelines for Suspected Adverse Reactions

Toxicity	Grade	APX005M	Nivolumab
Neutropenia (± febrile)	3-4	Hold	Hold
Thrombocytopenia	3	Hold. Dose reduction if > 7 days	Hold
	4	Hold. Dose reduction	Hold. Discontinue if > 7 days
	3-4 with bleeding	Discontinue	Discontinue
Diarrhea/colitis	2	1st occurrence: hold 2nd occurrence: dose reduction	Hold
	3	1st occurrence: dose reduction 2nd occurrence: discontinue	Discontinue
	4	Discontinue	Discontinue
Uveitis, eye pain or blurred vision that does not improve to Grade 1 before next cycle	2-4	Hold	Discontinue
Increased bilirubin	2	Hold	Hold
	3-4	Discontinue	Discontinue
Increased AST, ALT	2	Hold	Hold
	3	Hold. Dose reduction For subjects with liver metastasis reduce dose only if Grade 3 > 72 hours	Discontinue
	4	Discontinue	Discontinue
Endocrinopathies	2	Hold	Hold
	3-4	1st occurrence: Hold. Institute endocrine replacement therapy 2nd occurrence: discontinue after consultation with Medical Monitor	1st occurrence: Hold. Institute endocrine replacement therapy* 2nd occurrence: discontinue after consultation with Medical Monitor
Nivolumab infusion reaction	2	Administer additional premedication. Increase infusion time to 90 min	1st occurrence: continue 2nd occurrence: discontinue
	3	Hold for 1 cycle. Continue single agent at following cycle	Discontinue
	4	Discontinue	Discontinue

Toxicity	Grade	APX005M	Nivolumab
APX005M infusion reaction/cytokine release syndrome	3	Hold. Dose reduction	Hold
	4	Discontinue	Discontinue
Pneumonitis	2	1st occurrence: hold 2nd occurrence: discontinue	1st occurrence: hold 2nd occurrence or if > 14 days: discontinue
	3-4	Discontinue	Discontinue
Creatinine elevation	2	Hold	Hold. Discontinue if > 7 days
	3	Hold	Hold. Discontinue if > 7 days
	4	Discontinue	Discontinue
Rash or other skin toxicity	2	Hold	Continue. Hold if > 7- 14 days
	3	Hold	Hold
	4	Discontinue	Discontinue
Neurological toxicity	2	Continue	Hold
	3-4	Hold	Discontinue
Hypotension, severe dehydration, shock out of proportion to current illness or suspected adrenal crisis	3	Hold. Dose reduction	Hold
	4	Discontinue	Discontinue
Fatigue	2 >6 weeks 3	Dose reduction	Grade 2: continue Grade 3: hold
Myocarditis	2	Hold	Hold
	3-4	Discontinue	Discontinue
All other drug-related non-hematologic toxicity	3 or Severe	1st occurrence: hold 2nd occurrence: dose reduction	Hold
	4	Discontinue#	Discontinue#

Hold = hold until retreatment criteria are met (Section 3.6)
Dose reduction = reduce dose by one dose level in following cycle (Section 3.7)
Discontinue = permanently discontinue that investigational product
* Adrenal insufficiency requires discontinuation of nivolumab regardless of control with hormone replacement
# Subjects may continue treatment for transient Grade 4 toxicity (such as electrolyte imbalances ≤ 72h, amylase or lipase increase) not associated with clinical sequelae after discussion with the Apexigen Medical Monitor (or designee).

Dose reductions for APX005M are defined in Table 5. Subjects requiring more than 2 dose reductions or a dose reduction below DL1, must discontinue APX005M.

Table 5: Modified DLs for APX005M Following Qualifying Suspected Adverse Reactions

Dose Level (mg/kg)	**DL1** (0.03)	**DL2** (0.1)	**DL2a** (0.2)	**DL3** (0.3)
First Dose Reduction	Discontinue	0.06	0.1	0.2
Second Dose Reduction	Not applicable	0.03	0.06	0.1

3.8 Duration of Treatment

Subjects may continue to receive APX005M and nivolumab until any of the criteria in Section 4.1 are met.

Subjects with confirmed CR may continue combination therapy up to 8 cycles (24 weeks), on a case-by-case basis, after careful evaluation and Investigator discussion with the Apexigen Medical Monitor (or designee) to determine whether the risk-benefit ratio supports administration of further study drug.

4. Study Discontinuation

4.1 Discontinuation of Subjects from Treatment

Subjects MUST discontinue receiving investigational product for any of the following reasons:

- Disease progression by RECIST 1.1, or disease progression following treatment beyond progression (Section 4.1.1)
- Death
- Toxicity requiring discontinuation of both investigational products as outlined in the dose modification guidelines (Section 3.7)
- 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 Apexigen Medical Monitor (or designee)
- 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 and after discussion with and approval by Apexigen Medical Monitor (or designee)
- Subject's decision to withdraw for any reason from study treatment (subject withdraws consent)
- Pregnancy
- Any clinical AE, laboratory abnormality or coincident illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the subject
- Requirement for alternative therapy
- Noncompliance with study procedures, including use of prohibited medications
- Subject is lost to follow-up
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Study termination by Apexigen

The primary reason for treatment discontinuation will be documented in the eCRF.

Apexigen (or designee) must be notified within 24 hours if a subject is withdrawn from treatment.

4.1.1 Treatment Beyond Progression

Accumulating evidence indicates that patients with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease. Subjects will be permitted to continue on treatment beyond initial RECIST 1.1-defined progressive disease as long as they meet the following criteria:

- Investigator-assessed clinical benefit, without rapid disease progression, or with disease progression based primarily on changes in lymph nodes appearance Subject continues to meet retreatment criteria
- Subject tolerates study drug
- Subject has stable ECOG performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., central nervous system metastases).

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the Apexigen Medical Monitor (or designee), and an assessment of the risk/benefit of continuing with study therapy must be documented in the study records.

For subjects who stay on treatment beyond RECIST 1.1-defined progressive disease, all study procedures (Section 5) should be performed continuously, including tumor assessments as described in Section 5.5.

Subjects will be discontinued from the treatment upon further evidence of disease progression, defined as a further increase in tumor burden as evidenced (as applicable) by a ≥5 mm increase in sum of measures of target or new target lesions, further increase in non-target or new non-target lesions, or an increase in the number of new lesions, as described in the iRECIST guidelines by Seymour et al [31].

4.2 Discontinuation of Subjects from Study

Subjects who are withdrawn from both investigational products will enter the follow-up period unless treatment discontinuation is due to any of the following:

- Subject death
- Withdrawal of consent for all study procedures
- Initiation of any anticancer therapy
- Subject is lost to follow-up
- Study termination by Apexigen

For all subjects receiving investigational products, the subsequent anticancer therapy will be documented and response to that therapy, if possible. Once this information is collected, a subject is considered off-study.

4.3 Study Termination

Apexigen has the right to terminate this study or a study site from participating in a study at any time.

Reasons for terminating the study at a specific study site may include, but are not limited to, the following:

- Subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- Investigator does not adhere to the protocol or applicable regulatory requirements in conducting the study

Reasons for terminating the study overall may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other APX005M studies indicates a potential health hazard to subjects
- All subjects enrolled in the study have withdrawn from treatment, completed participation in the study, or are lost to follow-up.

5. Treatment Study Assessments and Procedures

5.1 Time and Events Schedule

Phase 1b Dose-escalation	Screening Phase (within 21 days prior to C1D1)	Treatment Phase								EOT (approx. 21 days after last treatment)	Follow-up
		Cycles 1 & 2					Cycles 3+				
Day / Procedure		1	2	3	8	15	1	8	2nd Biopsy		
Written Informed Consent	X										
Inclusion/Exclusion Criteria	X	X									
Demographics	X										
Medical History	X										
Physical Examination	X	X					X			X	
Height	X										
Weight	X	X								X	
Vital Signs[a]	X	X	X	X	X	X	X	X		X	
12-lead ECG	X										
Urinalysis	X										
ECOG Performance Status	X	X					X			X	
Serum Chemistry[b]	X	X	X	X	X	X	X	X		X	
Thyroid Function Tests[b]	X						X				
Hematology Tests[b]	X	X	X	X	X	X	X	X		X	
Coagulation[b]	X	X			X	X	X	X		X	
PK Blood Tests[c]		X	X	X	X		X				
Immune PDn[d]		X	X	X	X		X	X	X	X	
Cytokines[e]		X	X	X	X		X	X	X	X	
AEs and ConMeds		X	X	X	X	X	X	X		X	X
Dosing Nivolumab		X					X				
Dosing APX005M		X					X				
Tumor Assessment[f]	X						X				X
Archived or Fresh Tumor Submission[g]	X										
Fresh Tumor Biopsy[h]	X								X		
ADA[i]		X					X			X	
Pregnancy Test (if applicable)[j]	X						X[j]				
Date of PD and Subsequent Therapy											X

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; APTT = activated partial thromboplastin time; C1D1 = Cycle 1 Day 1; ConMeds = concomitant medications; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ICF = informed consent form; INR = international normalized ratio; PD = progressive disease/disease progression; PDn = pharmacodynamics; PK = pharmacokinetics; PT = prothrombin time; WOCBP = women of childbearing potential.

[a] Vital signs: Vital signs measured within 30 min prior to nivolumab dose and at the end of the infusion, within 30 min prior to APX005M dose, end of the infusion, and 2 & 4 hours after infusion. All time points are ± 30 min

[b] Serum chemistry, hematology and coagulation tests performed at the local laboratory. Thyroid function tests performed every other cycle starting with Cycle 3

[c] Blood samples for PK analyses collected in Cycles 1 and 2 before APX005M administration and at end of infusion, 4, 24 (Day 2), 48 (Day 3), and 168 hours (Day 8) from start of the infusion in that cycle. In addition, predose and end of infusion blood samples on Cycles 3 and 4 will be collected

[d] Blood samples for immune PDn collected in Cycles 1 and 2 before APX005M administration, and 24 (Day 2), 48 (Day 3), and 168 hours (Day 8) from the start of the infusion in that cycle, in Cycles 3 and 4 before APX005M administration and 168 hours (Day 8), time of second biopsy (if applicable) and at the EOT visit

[e] Blood samples for cytokines collected in Cycles 1 and 2 before APX005M administration, end of infusion, 4, 24 (Day 2), 48 (Day 3), and 168 hours (Day 8) from the start of the infusion in that cycle, in Cycles 3 and 4 before APX005M administration and 168 hours (Day 8), time of second biopsy (if applicable) and at the EOT visit

[f] Tumor assessment: will be performed within 21 days prior to start of investigational products and during Treatment Phase every 8 weeks ± 1 week. For subjects who discontinue treatment without documented PD, every effort should be made to continue monitoring their disease status by tumor imaging using the same schedule used while on treatment

[g] Archived or fresh tumor block or minimum 12 unstained slides with tumor tissue should be obtained. Provision of archived or fresh tumor tissue for analysis is dependent upon the subject's eligibility and signing the designated ICFs

[h] Fresh tumor core biopsies will be collected from consenting subjects prior to start of investigational products and prior to 1st scheduled tumor assessment. Selection of tumor lesions should not affect tumor assessment when feasible

[i] Blood samples for anti-APX005M antibodies will be collected before dosing on Cycles 1, 2, 3, 4, and at the EOT visit

[j] In WOCBP only, serum pregnancy test to be done within 7 days followed by a urine pregnancy test within 3 days of first dose of investigational product, or serum pregnancy test to be done within 3 days prior to first dose of investigational product. Pregnancy testing should be conducted every other cycle

Phase 2 Dose-expansion / Day / Procedure	Screening Phase (within 21 days prior to C1D1)	Treatment Phase			EOT (approx. 21 days after last treatment)	Follow-Up
		1	8	2nd Biopsy		
Written Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Demographics	X					
Medical History	X					
Physical Examination	X	X			X	
Height	X					
Weight	X				X	
Vital Signs[a]	X	X	X		X	
12-lead ECG	X					
Urinalysis	X					
ECOG Performance Status	X	X			X	
Serum Chemistry[b]	X	X	X		X	
Thyroid Function Tests[b]	X	X[b]				
Hematology Tests[b]	X	X	X		X	
Coagulation[b]	X	X	X		X	
Immune PDn[c]		X	X	X	X	
Cytokines[c]		X	X	X	X	
AEs and ConMeds		X	X		X	X
Dosing Nivolumab		X				
Dosing APX005M		X				
Tumor Assessment[d]	X					X
Archived or Fresh Tumor Submission (baseline)[e]	X					
Optional Paired Fresh Tumor Biopsy[f]	X			X		
PK Blood Tests[g]		X				
ADA[h]		X			X	
Pregnancy Test (if applicable)[i]	X	X[i]				
Date of PD and Subsequent Therapy						X

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; APTT = activated partial thromboplastin time; C1D1 = Cycle 1 Day 1; ConMeds = concomitant medications; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ICF = informed consent form; INR = international normalized ratio; PD = progressive disease/disease progression; PDn = pharmacodynamics; PK = pharmacokinetics; PT = prothrombin time; WOCBP = women of childbearing potential.

[a] Vital signs: Vital signs measured within 30 min prior to nivolumab dose and at the end of the infusion, within 30 min prior to APX005M dose and at the end of the infusion. All time points are ± 30min

[b] Serum chemistry, hematology and coagulation tests performed at the local laboratory, within 24-48 hours of day 1 for each cycle. Thyroid function tests performed every other cycle starting with cycle 3. INR only required at

screening and as clinically indicated thereafter. D-dimer test should be performed if available at local lab at baseline and on Day 8 in Cycles 1 and 2 and as clinically indicated thereafter.

[c] Blood samples for immune PDn and cytokines collected in Cycles 1 and 2 before APX005M administration, 168 hours (Day 8) from the start of the infusion in that cycle, Cycle 3 Day 1, time of second biopsy (if applicable) and at the EOT visit. Additional blood samples for cytokines collected in cycles 1 and 2 at the end of infusion and 4 hours after the start of infusion and for TCR/BCR on Cycle 3 preinfusion

[d] Tumor assessment: will be performed within 21 days prior to start of investigational products and during Treatment Phase every 8 weeks ± 1 week. For subjects who discontinue treatment without documented PD, every effort should be made to continue monitoring their disease status by tumor imaging using the same schedule used while on treatment

[e] Archived or fresh tumor block or minimum 12 unstained slides with tumor tissue should be obtained for baseline analysis. Provision of archived or fresh tumor tissue for analysis is dependent upon the subject's eligibility and signing the ICF.

[f] Optional fresh paired tumor core biopsies will be collected from consenting subjects prior to start of investigational products and prior to 1st scheduled tumor assessment. The biopsy should not interfere with the RECIST 1.1 tumor assessment. .

[g] Blood samples for PK analyses collected every 3rd cycle (i.e., Cycles 1, 3, 6, 9, 12, etc) at predose and at end of infusion

[h] Blood samples for anti-APX005M antibodies will be collected before dosing every 3rd cycle (i.e., Cycles 1, 3, 6, 9, 12, etc) and at the EOT visit

[i] In WOCBP only, serum pregnancy test to be done within 7 days followed by a urine pregnancy test within 3 days of first dose of investigational product, or serum pregnancy test to be done within 3 days prior to first dose of investigational product. Pregnancy testing should be conducted every other cycle

5.2 Procedures by Visit

5.2.1 Screening Phase

The following procedures and investigations should be performed during the screening Phase (within 21 days prior to start of investigational product):

- Obtain signed informed consent form (ICF) prior to any study specific procedures; enrollment in the study is defined as the signing the ICF
- Verify study eligibility (inclusion/exclusion criteria)
- Allocate a unique Subject Identification Number
- Document type of tumor histology
- Collect demographic and medical history information, including smoking history
- Collect prior immunotherapy administration and response history (if applicable) including:
    - Date of first and last dose
    - The reason for discontinuation
    - Date of initial PD
    - Date of confirmed radiological PD
    - Confirmation of PD criteria that was met, i.e.:
        - ≥ 5mm further increase in sum of measures of target lesion
        - ≥ 5mm further increase in sum of measures of new lesion
        - further increase in the size of non-target lesion(s)
        - new non-target lesions
        - appearance of new lesion(s) when none have previously been recorded
        - increase in the number of new lesions

        - all of the following
            - maintain > 20% increase in target lesion burden at confirmed PD scan relative to nadir (as per RECIST1.1)
            - target lesion burden at confirmatory PD scan greater than 90% of target lesion burden at uncomfirmed PD (uPD) scan (to account for intra-subject reader variability)
            - no disappearance of all new lesions
    - Date of clinical progression (if applicable)
    - Best overall response to prior PD-1/PD-L1 therapy
- Perform a physical examination (including weight, height, and vital signs) and a 12-lead electrocardiogram
- Determine ECOG performance status (Appendix A)
- Laboratory evaluations:
    - serum chemistry
    - thyroid function tests
    - hematology
    - coagulation
    - urinalysis
- Tumor assessment following RECIST 1.1 Guidelines
- Submit archived or fresh tumor tissue for baseline
- Collect and submit a tumor core biopsy from subjects who consent to optional paired biopsies. Selection of tumor lesions should not interfere with subsequent tumor assessments (RECIST), when feasible
- Perform pregnancy test(s), if applicable

5.2.2 Treatment Phase

The following procedures and investigations should be performed during the Treatment Phase.

Day 1:

- Physical examination (including weight and vital signs)
- Determine ECOG performance status (Appendix A)
- Record AEs and concomitant medication
- Laboratory evaluations (for Cycle 1, laboratory values from Screening Phase may be used if within 72 hours):
    - serum chemistry
    - thyroid function tests (every other cycle starting with cycle 3)
    - hematology
    - coagulation
- Collect blood samples for PK, ADA, cytokines and iPDn at designated timepoints (Section 5.6)
- Administer premedication
- Administer nivolumab
- Administer additional premedication (if applicable)
- Administer APX005M
- Phase 1b dose-escalation collect blood samples for PK, PDn, and cytokines according to

schedule in Section 5.6
- Phase 2 dose-expansion collect blood samples for PDn, and cytokines according to schedule in Section 5.6
- Check criteria for discharge from clinic (see Section 3.1)

Days 2 and 3 of Cycles 1 & 2 Phase 1b:
- Vital signs
- Record AEs and concomitant medication
- Laboratory evaluations:
  - serum chemistry
  - hematology
- In Phase 1b dose-escalation collect blood samples for PK, PDn, and cytokines according to schedule in Section 5.6

Day 8:
- Vital signs
- Record AEs and concomitant medication
- Laboratory evaluations (all test may be performed up to 24 hour in advance):
  - serum chemistry
  - hematology
  - coagulation
- Collect blood samples for PK, PDn, and cytokines according to schedule in Section 5.6

Day 15 of Cycles 1 and 2 Phase 1b:
- Vital signs
- Record AEs and concomitant medication
- Laboratory evaluations (all test might be performed up to 24 hour in advance):
  - serum chemistry
  - hematology
  - coagulation

Tumor assessments:
Tumor assessment will be performed within 21 days prior to start of investigational product and during Treatment Phase every 8 weeks ± 1 week. Tumor response (CR or PR) or PD should be confirmed ≥ 4 weeks later.

Optional Second tumor core biopsy:
From patients who have consented to the optional paired biopsy, fresh tumor core biopsies from the lesion selected at baseline will be collected prior to first scheduled tumor assessment (during Cycle 3, at approximately 7–8 weeks from first dose of investigational product).

5.2.3 End of Treatment Visit

End of treatment visit (EOT) should occur on Day 22 of the last cycle started or as soon as possible thereafter. The following procedures and investigations should be performed:
- Physical exam (including weight and vital signs)
- Determine ECOG performance status (Appendix A)

- Record AEs and concomitant medication
- Laboratory evaluations (all tests can be performed up to 24 hour in advance):
    - serum chemistry
    - hematology
    - coagulation
- collect blood samples for PDn, ADA, and cytokines

5.2.4 Follow-Up

Follow-up period begins after the EOT visit. For subjects who discontinue treatment without documented PD, every effort should be made to continue monitoring their disease status by tumor imaging using the same schedule used while on treatment.
Subjects should be contacted approximately every 1 month for the first 3 months and every 3 months thereafter to:

- Collect information on subsequent therapy and response, if possible
- Record the time of documented PD for subjects who discontinue treatment without documented PD and cannot have regular tumor assessments.
- Collect information on SAEs, AEs with potential immunologic etiology and pregnancies.

5.3 Study Materials

The following study materials will be provided at study start:

- NCI-CTCAE version 4.03
- APX005M and Nivolumab Investigator's Brochures
- Laboratory Manual for collection and handling of archived or fresh tumor tissue, fresh tumor core biopsies, PK, PDn, and cytokines samples
- Pharmacy Manual

5.4 Safety Assessments

5.4.1 Physical Examinations

A physical examination will include examination of the skin, head and neck, chest (heart and lungs), abdomen, limbs, and a brief neurological examination. Rectal and pelvic examinations are optional.

ECOG performance status should be assessed at the time of the physical examination.

At screening, a medical history will be obtained to capture relevant underlying conditions.

5.4.2 Vital Signs

Vital sign measurements include blood pressure, pulse rate, respiration rate, and temperature. Subjects should be monitored during and after nivolumab and APX005M infusions for potential infusion reactions. Vital signs will be measured:

- within 30 minutes prior to nivolumab dose
- at the end of the nivolumab infusion
- within 30 minutes prior to APX005M dose (if APX005M infusion is delayed more than 30 min after the completion of nivolumab infusion)
- end of the APX005M infusion
- 4 hours after the end of APX005M infusion (Cycles 1 and 2 in Phase 1b and as clinically indicated in Phase 2).

All time points are ± 30 minutes. At the Investigator's discretion, vital sign monitoring may be extended beyond the time points specified. Additional measures should be performed as clinically indicated.

5.4.3 Electrocardiogram

A 12-lead electrocardiogram (ECG) including calculation of corrected QT interval will be conducted locally and is required at screening only. Additional ECGs can be performed as clinically indicated.

5.4.4 Laboratory Tests

All laboratory tests (e.g., serum chemistry, hematology, coagulation) will be performed at local laboratories.

5.4.4.1 Serum Chemistry

The laboratory tests included in the full chemistry panel are:

- ALT
- Albumin
- Alkaline phosphatase
- AST
- Bicarbonate
- Blood urea nitrogen
- Calcium
- Chloride
- Creatinine
- Creatinine clearance (calculated or measured)
- Glucose
- Lactate dehydrogenase
- Magnesium
- Phosphorous
- Potassium

- Sodium
- Total bilirubin
- Total protein
- Uric acid

5.4.4.2 Thyroid Function Tests

Thyroid function tests, to be collected every other cycle starting at Cycle 3, should include:

- Thyroid stimulating hormone (TSH)
- Triiodothyronine (T3)
- Free Triiodothyronine (fT3)
- Free thyroxine (FT4)

5.4.4.3 Hematology

The laboratory tests included in the hematology panel are:

- Hemoglobin
- Hematocrit
- White blood cell count with complete manual or automated differential (reported as absolute counts):
  - Total neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
- Red blood cell count
- Platelet count

5.4.4.4 Coagulation

The laboratory tests included in the coagulation panel are:

- Prothrombin time
- Activated partial thromboplastin time
- INR; required only at screening and as clinically indicated thereafter
- D-dimer test; D-dimer test should be performed if available at local lab at baseline and on Day 8 in Cycles 1 and 2 and as clinically indicated thereafter.

5.4.4.5 Urinalysis

Routine urinalysis will be performed at screening and whenever clinically indicated.

5.4.4.6 Pregnancy Test

For WOCBP, a pregnancy test is required for eligibility determination and should be performed at the local laboratory.

This protocol defines a WOCBP as a sexually mature woman who:

a) has not undergone a hysterectomy or bilateral oophorectomy, or
b) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had

menses at any time in the preceding 12 consecutive months)

At a minimum, serum pregnancy test will be done within 7 days followed by a urine pregnancy test within 3 days of first dose of investigational product, or a serum pregnancy test should be done within 3 days prior to first dose of investigational product. Pregnancy testing should be conducted every other cycle. More frequent pregnancy tests may be conducted if required per local regulations.

5.5 Efficacy Assessments

Tumor assessment will be performed within 21 days prior to start of investigational products and during Treatment Phase every 8 ± 1 weeks. Complete or partial responses should be confirmed at a subsequent time point 4-5 weeks later.

Tumor assessments for the purpose of establishing the Phase 2 primary endpoint will follow RECIST 1.1 guidelines.

5.5.1 Modified RECIST 1.1 for Immune-based Therapeutics

Accumulating evidence indicates that patients with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of PD. For the purpose of establishing the Phase 2 secondary endpoint the iRECIST (modified RECIST 1.1 for immune-based therapeutics [31]) will be used to assess tumor response for all treated subjects.

Subjects with RECIST 1.1-defined PD should have a repeated tumor assessment 4-8 weeks later in order to confirm PD and will be permitted to continue treatment as long as they meet the criteria in Section 4.1.1 and they don't have confirmed PD as defined by iRECIST. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

5.6 Correlative Studies

Correlative laboratory samples include whole blood, serum, and plasma samples collected for Pharmacokinetic, anti-drug antibodies, cytokine and immune pharmacodynamic analyses will be obtained in relation to the APX005M infusion. Predose blood samples can be collected up to 72 hours in advance of the scheduled APX005M infusion time. End of infusion samples should be collected within the 5 minutes after the completion of the infusion (before flushing the IV line). The 4 hour post start of infusion should be collected within ± 30minutes. The 24 hour post-start of APX005M infusion should be collected within ± 10 minutes (Phase 1b only); time points on Days 3 and 8 are ± 60 minutes based on start of APX005M infusion. If samples cannot be collected within the protocol-specified window they should be collected as soon as practicable.

5.6.1 APX005M Pharmacokinetic Assessments

Phase 1b: Blood samples will be collected from all subjects at (relative to APX005M infusion):

- Cycles 1 & 2:
  - Day 1: predose, end of infusion and 4 hours after the start of the infusion
  - Day 2: 24 hours after the start of the infusion
  - Day 3: 48 hours after the start of the infusion
  - Day 8: 168 hours after the start of the infusion
- Cycles 3 & 4:
  - Day 1: predose and at end of infusion

Phase 2: Predose and at end of APX005M infusion blood samples will be collected every 3rd cycle (i.e., Cycles 1, 3, 6, 9, 12, etc.).

Details about collection procedure, volumes, and processing and shipping of PK samples are provided in the Laboratory Manual.

5.6.2 Cytokines

When time points are overlapping, blood samples for cytokine analysis should be collected at the same time with PK samples. Blood samples for cytokine analysis will be collected from all subjects at (relative to APX005M infusion):

- Cycles 1 & 2:
  - Day 1: predose, end of infusion and 4 hours after the start of APX005M infusion
  - Day 2: 24 hours after the start of APX005M infusion (Phase 1b dose-escalation only)
  - Day 3: 48 hours after the start of the APX005M infusion (Phase 1b dose-escalation only)
  - Day 8: 168 hours after the start of the APX005M infusion
- Cycles 3 & 4 (Phase 1b dose-escalation only):
  - Day 1: predose
  - Day 8: 168 hours after the start of the APX005M infusion
- Time of 2nd tumor biopsy when applicable
- EOT visit

Details about collection procedure, volumes, and processing and shipping of blood samples are provided in the Laboratory Manual. When time points are overlapping, blood samples for cytokines should be collected at the same time with blood samples for PK and immune PDn. Predose blood samples can be collected up to 72 hours in advance.

Concentrations of cytokines including but not limited to interleukin (IL)-1, TNF-α, IL-12p70, IL-6 will be determined in serum.

5.6.3 Immune Pharmacodynamics

When time points are overlapping, blood samples for immune PDn profile should be collected at the same time with PK samples. Blood samples for the immune PDn profile will be collected from all subjects at:

- Cycles 1 & 2:
  - Day 1: predose
  - Day 2: 24 hours after the start of the APX005M infusion (Phase 1b dose-

escalation only)
    - Day 3: 48 hours after the start of the APX005M infusion (Phase 1b dose-escalation only)
    - Day 8: 168 hours after the start of the APX005M infusion
- Cycles 3
    - Day 1: predose
    - Day 8: 168 hours after the start of the APX005M infusion (Phase 1b dose-escalation only):
- Cycle 4 (Phase 1b dose-escalation only):
    - Day 1: predose
    - Day 8: 168 hours after the start of the APX005M infusion
- Time of 2nd tumor biopsy when applicable
- EOT visit

Details about collection procedure, volumes, and processing and shipping of PDn samples are provided in the Laboratory Manual. When time points are overlapping, blood samples for immune PDn should be collected at the same time with blood samples for PK and cytokines. Predose blood samples can be collected up to 72 hours in advance.

Immune PDn testing might include but would not be limited to:

Analysis of APC activation: non-manipulated peripheral blood lymphocytes will be analyzed using flow cytometry to measure cell surface immune markers of peripheral blood B cells and DCs, such as, but not limited to, CD19, CD123, CD11c, CD86, major histocompatibility complex class I and II, CD70, and CD54. Dead cells are excluded using 7-AAD and non-B cells or non-DC are excluded using a panel of mAb, all analyzed on a "dump" channel.

Analysis of T-cell activation: together with complete blood count differentials, flow cytometry of peripheral blood will be used to measure both the percentages and absolute count (cells/mm3) of important T cell subsets defined by immunophenotyping, such as total $CD3^+$ cells, $CD3^+$ $CD8^+$ T cells, $CD3^+$ $CD4^+$ T cells, and $CD3^+$ $CD4^+$ $Foxp3^+$ regulatory T cells. For each subset, differentiation status (e.g. naïve, central memory, and effector memory) or activation status will be assessed using additional markers including CD45RA, CD45RO, CCR7, CD28, CD27, CD57, CD25, CD69, HLA-DR, CTLA4, Eomes, granzyme B, Ki-67, CD154, and PD-1. When possible, trends can be tracked in T cell subsets based on analysis of multiple post-treatment samples. NK cell subsets can also be assessed using CD16 and CD56, with CD69 as an activation marker.

Analysis of T and/or B clonotype changes: the clonotypic composition of the T and/or B cell repertoire will be assessed by T and/or B cell receptor sequencing performed on PBMCs. T and/or B cell clonotype evolution will be assessed at baseline, one certain treatment cycles, and at EOT.

5.6.4 APX005M Anti-drug Antibody

In Phase 1b blood samples for anti-APX005M antibodies will be collected before dosing on Cycles 1, 2, 3, 4, and at the EOT visit.

In phase 2 blood samples for anti-APX005M antibodies will be collected before dosing every 3rd cycle (e.g., Cycles 1, 3, 6, 9, 12, etc.) and at the EOT visit.

5.6.5 Tumor Biomarkers

Archived or fresh tumor tissue will be obtained from all subjects in this study. Submission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; if submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory within 14 days from site slide sectioning date otherwise a new specimen will be requested.

When possible, paired fresh tumor core biopsies will be collected from consenting subjects prior to first dose of investigational product and an optional second biopsy prior to first scheduled tumor assessment (during Cycle 3, at approximately 7–8 weeks from first dose of investigational product of investigational product). A minimum of 24 subjects (6 subjects with each cohort/group) must consent to fresh core biopsies.

Samples might be analyzed by hematoxylin and eosin staining, Masson's trichrome, and by immunohistochemistry for markers such as, but not limited to:

- Immune markers (e.g., PD-L1, CD40, CD45, CD68, CD3, CD8, CD4, Foxp3, CD20, and myeloperoxidase)
- Tumor markers (e.g., EpCAM, Ki-67, and cleaved caspase 3)
- Vascular markers (e.g., CD31)
- Stromal markers (e.g., collagen type I)

If sufficient material is available, cell suspensions of tumor will be studied by flow cytometry to evaluate immune phenotyping. Tumor samples and peripheral blood may also be examined for gene expression (e.g. Quantigene), T and B cell receptor repertoire assessment by deep sequencing, and somatic tumor mutations. Data will be analyzed to examine specific hypotheses about whether drug response is related to alterations in gene regulation. These data will also be used to derive new hypotheses about mechanisms of drug response, resistance, and safety.

6. Adverse Events

The AE definitions and reporting procedures provided in this protocol comply with current 21 Code of Federal Regulations Part 312.32. The Medical Monitor assigned by Apexigen (or designee) must promptly review all information relevant to the safety of the investigational product received from any source. The Investigator or appropriately qualified designee (e.g., a certified nurse practitioner or physician's assistant properly listed on the Form FDA 1572) will carefully monitor each subject throughout the study for possible AEs.

6.1 Definitions

6.1.1 Adverse Event

Adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

6.1.2 Suspected Adverse Reaction

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

6.1.3 Life-threatening AE or Life-threatening SAR

An AE or SAR is considered "life-threatening" if, in the view of either the Investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.

6.1.4 Serious AE or Serious SAR

An AE or SAR is considered "serious" (SAE or SSAR) if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.1.5 Unexpected AE or Unexpected SAR

An AE or SAR is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral

thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator Brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or SARs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

6.1.6 Overdose

For this trial, an overdose will be defined as APX005M >1 mg/kg body weight or nivolumab ≥1000 mg total dose.

It is expected that an overdose of APX005M will be associated with severe cytokine release syndrome. No specific information is available on the treatment of overdose of nivolumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. Retreatment after an overdose must be discussed with Apexigen Medical Monitor (or designee).

6.2 Adverse Event Classification

6.2.1 Relationship to Investigational Products

The Investigator will assign attribution of the possible association of the event with use of the investigational products, and this information will be entered into electronic data capture (EDC) system using the classification system listed below:

Related to Investigational Product

The event is suspected to be related if:

- There is a clinically plausible time sequence between the AE onset and administration of investigational product
- There is a biologically plausible mechanism for the investigational product to cause or contribute to the AE
- The event improves or diminishes upon temporary interruption of the investigational product without the initiation of any specific treatment for the event (dose delay) and/or recurs or worsens when resuming treatment after criteria for retreatment are met
- The AE cannot be reasonably attributed to concurrent or underlying illness, other drugs, or procedures

Apexigen Medical Monitor (or designee) will review all Investigator-reported assessments of relationship and confirm.

Unrelated to Investigational Product

The event is not suspected to be related if:

- The AE is more likely to be explained by the subject's underlying disease, clinical state, concomitant medical, or study or non-study procedure
- The time occurrence of the AE is not reasonably related to administration of investigational product
- The event is not related to the investigational product

6.2.2 Severity

The NCI-CTCAE v 4.03 will be used to describe the event and to assess the severity of AEs. For AEs not adequately addressed in the NCI-CTCAE version 4.03, Table 6 should be used.

Table 6: Toxicity Grading for AEs Not Covered in NCI-CTCAE (Version 4.03)

Severity	Description
GRADE 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
GRADE 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of ADL*
GRADE 3	Severe; medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
GRADE 4	Life-threatening consequences; urgent intervention indicated
GRADE 5	Death related to AE

Abbreviations: ADL = activities of daily living. Semi-colon indicates "or" within the description
* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Abnormal laboratory findings should be reported as AEs only if they are clinically relevant (see Section 6.3.6).

AE will be reported at the highest grade experienced. AEs which completely resolve and then recur will be recorded as a new AE.

6.3 Collection and Reporting

6.3.1 General AE Reporting

All AEs will be collected from the time the subject receives any investigational product through 30 days after receiving the last dose of investigational product, death, or initiation of new anticancer therapy, whichever occurs first. SAEs and AEs with potential immunologic etiology will be recorded up to 100 days and pregnancies up to 120 days after the last dose of investigational product, death, or initiation of new anticancer therapy, whichever occurs first.

Events that occur after the subject signs the informed consent but prior to the first dose of investigational product will be recorded as past medical history; events that start after the first dose of investigational product will be recorded as AEs. In addition, the Investigator should report any AEs that may occur after this time period which are assessed to have a reasonable possibility of being associated with investigational products.

All AEs must be promptly documented on the AE eCRF. The minimum information required for each AE includes event, duration (start and end dates), start time (for events occurring within 48 hours after the start of APX005M infusion) severity, seriousness, causality to investigational product, action taken, and outcome. Whenever possible, reporting specific diagnosis is preferred when reporting AEs in the AE eCRF rather than reporting individual signs and symptoms except for infusion related reactions and cytokine release syndrome.

All AEs that are considered related to investigational products must be followed to resolution, stabilization, until improvement is not expected, 30 days after receiving the last dose of investigational product, death, or initiation of new anticancer therapy, whichever occurs first. SSAR will be followed until resolution, stabilization, or until resolution is not anticipated.

If an office visit is not possible, a follow-up of ongoing AEs should be attempted by telephone and documented in the subject's source file. AEs continuing at 30 days after the last dose of investigational product should have a comment in the source file by the Investigator that the event has stabilized or is not expected to improve.

The Investigator is responsible for evaluating all AEs, obtaining supporting source documents, and determining that documentation of the event is adequate. The Investigator may delegate these duties to subinvestigators and must ensure that these subinvestigators are qualified to perform these duties under the supervision of the Investigator and that they are listed on the FDA Form 1572.

6.3.2 Disease Progression

Disease progression will be documented in an eCRF intended to capture such information. Signs and symptoms related to disease progression should be reported in the appropriate eCRF as an AE or as a SAE if applicable. Verbatim terms such as "disease progression," "progressive disease," etc. should not be reported as AEs or SAEs unless the Investigator considers the progression to be atypical, accelerated, or caused by the investigational products. Similarly, death occurring as a result of disease progression should be reported on the eCRF intended to capture death information and should not be reported as an SAE.

6.3.3 Serious AEs or Serious SARs

Apexigen (or designee) must be notified of the occurrence of any SAE/SSAR within 24 hours of Investigator's knowledge of the event. The SAE/SSAR will be reported by completing and submitting the SAE/SSAR report form by:

Email: DrugSafety002@Apexigen.com

If only limited information is initially available, follow-up reports are required and must be submitted in a timely fashion as additional information becomes available. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses.

The Investigator should also comply with the applicable regulatory requirements related to the reporting of SAEs/SSARs to the regulatory authorities and the Institutional Review Board

(IRB)/Independent Ethics Committee (IEC). The sponsor may request additional source documentation pertaining to the SAE/SSAR from the investigational site. If a subject is permanently withdrawn from the study due to an SAE/SSAR, this information must be included in the initial or follow up SAE/SSAR report in the eCRF.

The sponsor is responsible for notifying the appropriate health authorities of serious and unexpected SAR (SUSAR) through expedited IND safety reports (ISR) in accordance with applicable laws and regulations.

6.3.4 Handling of Expedited Safety Reports

Apexigen (or designee) will notify Investigators of all ISRs. Upon receiving an ISR from Apexigen (or designee), the Investigator must review and retain the ISR with the Investigator's Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, Apexigen (or designee) will submit the ISR 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.

6.3.5 Non-serious AEs

The collection of AE information begins after subject's written consent to participate in the study: AEs that occur after consent, but prior to the first dose should be recorded as Medical History. If an ongoing AE changes in its intensity or in its perceived relationship to investigational product, a new AE entry for the event should be completed. AEs should be followed to resolution, stabilization, a minimum of 30 days after the discontinuation of the investigational product, or reported as SAEs if they become serious.

6.3.6 Laboratory Test Abnormalities

Laboratory test values captured as part of the study should be recorded on the appropriate pages of the eCRF. Laboratory abnormalities that meet any of the following criteria will also be captured on the AE or SAE reporting eCRF page as appropriate:

- Require the subject to have any of the investigational products discontinued, delayed, or interrupted
- Require the subject to receive specific corrective therapy
- Are clinically significant
- Meet the definition of an SAE/SSAR.

6.4 Pregnancy

Subjects will be instructed to notify the Investigator as soon as possible after becoming pregnant or learning of the pregnancy of a partner. If a subject or partner of a subject becomes pregnant during treatment or up to 120 days following the last study drug administration, the Investigator will notify Apexigen (or designee) within 24 hours of learning of the pregnancy.

If the subject becomes pregnant while receiving investigational product, the investigational product will be permanently discontinued. Exceptions to the investigational product discontinuation may be considered for life-threatening conditions only after consultation with the sponsor. The Investigator will discuss the risks and concerns of investigational drug exposure to a developing fetus and counsel the subject and/or pregnant partner (or ensure that such counseling is provided).

Pregnancies will be followed through the outcome of the pregnancy. Newborns should be followed for a minimum of 8 weeks.

The Investigator will complete a Pregnancy Surveillance Form and report the information regarding the pregnancy, outcome, and status of the newborn, as appropriate.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy. Other appropriate pregnancy follow-up procedures should be considered if indicated.

7. Statistics

7.1 Sample Size Determination

This is a Phase 1b-2, study. The sample size for the Phase 1b dose-escalation cannot be precisely estimated but depends upon the observed toxicities. Cohorts of 3 to 6 subjects will be treated at each DL during dose escalation portion of the study. It is anticipated that approximately 18 subjects will be treated in this portion of the study depending on the actual rate of DLTs.

Sample size for Phase 2 is calculated using the Simon optimal 2-stage design [32]:

- Cohort 1 (inNSCLC): Assuming a false positive rate (α) of 0.1 (one-sided), a false negative rate (β) of 0.1, a response probability of poor drug (P0) of 22% and a response probability of good drug (P1) of 40%, first stage sample size (n1) is 24 and the maximum sample size (n) is 45 response evaluable subjects. In the first stage, if there are 5 or less responses in 24 subjects, the enrollment in this cohort will be stopped. Otherwise, if 6 or more responses are observed, 21 additional subjects will be accrued in Stage 2 for total of 45. Enrollment may continue into Stage 2 while the planned number of subjects for Stage 1 are followed for efficacy. By the end of Stage 2, if 13 or less responses are observed in 45 subjects, then no further investigation is warranted. If 14 or more responses are observed, the null hypothesis will be rejected and true RR is 40%.

  The sample size of 45 subjects, provides 97% power to statistically test the null hypothesis of historical 6-month PFS rate (PFSR) of 60% (estimated for pembrolizumab in Keynote-024 [33]) versus the alternative hypothesis of 6-month PFSR rate of 80%. This calculation assumes exponential PFS, 1-sided 5% type I error rate, enrollment of subjects for 8 months with 6 months of follow-up prior to conducting the final analysis.

- Cohort 2 (PD1-MM): Assuming α of 0.1 (one-sided), β of 0.1, P0 5% and P1 of 20%, n1 is 12 and n is 37 response evaluable subjects. In the first stage, if there are no responses in 12 subjects, the enrollment in this cohort will be stopped. Otherwise, if 1 or more responses are observed, 25 additional subjects will be accrued in Stage 2 for total of 37. Enrollment may continue into Stage 2 while the planned number of subjects for Stage 1 are followed for efficacy. By the end of Stage 2, if 3 or less responses are observed in 37 subjects, then no further investigation is warranted. If 4 or more responses are observed, the null hypothesis will be rejected and true RR is 20%.

  The sample size of 37 subjects, provides 92% power to statistically test the null hypothesis of historical 6-month PFSR of 19% (estimated for ipilimumab following nivolumab or pembrolizumab [34]) versus the alternative hypothesis of 6-month PFSR rate of 38%. This calculation assumes exponential PFS, 1-sided 5% type I error rate, enrollment of subjects for 8 months with 6 months of follow-up prior to conducting the final analysis.
- Cohort 3 (PD1-NSCLC) Group A and Group B: Assuming α of 0.1 (one-sided), β of 0.1, P0 5% and P1 of 20%, n1 is 12 and n is 37 response evaluable subjects in each group. In the first stage, if there are no responses in 12 subjects, the enrollment in that group will be stopped. Otherwise, if 1 or more responses are observed, 25 additional subjects will be accrued in Stage 2 for total of 37 per group. Enrollment may continue into Stage 2 while the planned number of subjects for Stage 1 are followed for efficacy. By the end of Stage 2, if 3 or less responses are observed in 37 subjects, then no further investigation is warranted. If 4 or more responses are observed, the null hypothesis will be rejected and true RR is 20%.

  The sample size of 37 subjects/group, provides 94% power to statistically test the null hypothesis of historical 6-month PFSR of 22% (estimated for chemotherapy regimens [35, 36]) versus the alternative hypothesis of 6-month PFSR rate of 43%. This calculation assumes exponential PFS, 1-sided 5% type I error rate, enrollment of subjects for 8 months with 6 months of follow-up prior to conducting the final analysis.

Accrual is expected to be completed within 24 months from study start.

7.2 Populations for Analyses

All subjects receiving both investigational products will be included in the safety population.

Subjects evaluable for DLT are defined as those who meet study eligibility criteria, receive the entire planned dose of APX005M and nivolumab and have follow-up for at least 21 days (i.e., subject does not come off study for reasons other than toxicity).

Subjects evaluable for efficacy (tumor response) are defined as those who meet study eligibility criteria and have at least one on treatment (post baseline) tumor assessment.

Subjects evaluable for PK are defined as those who have adequate APX005M serum concentration-versus-time data to allow proper estimation of PK parameters.

7.3 Endpoint Definitions

7.3.1 Primary Endpoint

- Establish MTD (Phase 1b)
- ORR (rate of CR and PR) by RECIST 1.1 in each cohort/group (Phase 2).

7.3.2 Secondary Endpoints

- Incidence and severity of AEs and specific laboratory abnormalities graded according to NCI-CTCAE, v4.03
- 6-month PFSR by cohort/group (Phase 2), defined as the proportion of subjects that did not have disease progression (by RECIST 1.1) or died due to any cause at 6 months from the first dose of investigational product
- DOR (by RECIST 1.1) by cohort/group, defined as the time from the first evidence of confirmed PR or better to disease progression or death due to any cause
- PFS (by RECIST 1.1) by cohort/group, defined as time from first dose of investigational product to the earlier of PD or death due to any cause.

7.3.3 Exploratory Endpoints

- PK parameters of APX005M, including C_{max}, time to maximum serum concentration (t_{max}), area under the curve at the last measurable time point (AUC_{0-t}), and $AUC_{0-\infty}$
- Presence and titer of anti-APX005M antibodies
- Association between potential PDn markers and PK of APX005M; association between potential predictive biomarkers and anti-tumor activity
- ORR by iRECIST in each cohort/group (Phase 2)
- DOR (by iRECIST) by cohort/group, defined as the time from the first evidence of confirmed PR or better to disease progression or death due to any cause
- PFS (by iRECIST) by cohort/group, defined as time from first dose of investigational product to the earlier of PD or death due to any cause

7.4 Analyses

7.4.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics by cohort/group will be summarized using descriptive statistics.

7.4.2 Safety Analyses

Safety will be assessed through summaries of DLT, AEs, changes in laboratory test results, ECG, vital signs, and APX005M exposure. All AE data collected will be listed by study site, cohort, subject number, and cycle day.

The MTD is maximum dose for which <33% of DLT-evaluable subjects experience a DLT.

The RP2D will be taking into account the MTD of APX005M (if applicable), as well as the nature, severity and causal relationship for all AEs. Prior to establishing the RP2D all subjects enrolled in the phase 1 portion of the study must be followed until PD, study discontinuation due to toxicity or at least 2 cycles.

7.4.3 Efficacy Analyses

Tumor assessments by Investigator will follow RECIST 1.1 and iRECIST. ORR (and 90% confidence interval by exact distribution), DOR and PFS (Kaplan-Meier estimate) will be estimated for each cohort/group and for each tumor assessment method. Additional details will be provided in the Statistical Analysis Plan.

7.4.4 Pharmacokinetic Analyses

Blood samples will be collected from all subjects for determination of serum concentrations of APX005M at time points specified in Section 5.6.1.

PK parameters of APX005M will be determined using model-independent methods. The following parameters will be calculated whenever practical:

Parameter	Description
t_{max}	Time from the start of dosing at which the maximum concentration was observed.
C_{max}	Maximum observed concentration.
C_{max}/D	Dose-normalized C_{max}.
AUC_{0-t}	Area under the concentration versus time curve from the start of dose administration to the last quantifiable point within the dosing interval.
$AUC_{0-\infty}$	Area under the concentration versus time curve for the dosing interval, using the trapezoidal rule.
$AUC_{0-\infty}/D$	Dose-normalized $AUC_{0-\infty}$.

When the concentration-time data permit, the slope of the terminal phase of each individual concentration versus time curve (λ_z) will be determined by log-linear regression for the first and third doses, and the following additional parameters will be estimated.

Parameter	Description
$t_{1/2}$	Terminal half-life.
$AUC_{0-\infty}$	Area under the concentration versus time curve from the start of dose administration to infinity, using the trapezoidal rule (first dose only).
CL	Total body clearance, calculated as $D/AUC_{0-\infty}$ (first dose only).
V_z	Terminal volume of distribution, calculated as CL/λ_z (first dose only).

Steady-state achievement will be assessed by comparing predose and end-of-infusion concentrations on Cycles 2, 3, and 4. Accumulation on Cycle 3 will be assessed by comparing $AUC_{0-\infty}$ and C_{max} of the third and first doses and comparing predose concentrations of Cycles 3 to the predose sample of Cycle 2. Pharmacokinetic linearity will be examined by examining the

relationship between exposure (C_{max}, C_{max}/D, $AUC_{0-\infty}$, and $AUC_{0-\infty}$/D) with dose on the first and third doses.

Individual and mean serum concentration-time profiles will be tabulated separately for each dose by subject and nominal sampling time and summarized using descriptive statistics (mean and standard deviation). Pharmacokinetic parameters will also be summarized using descriptive statistics (mean and standard deviation) by dose and dosing day.

7.4.5 Exploratory Analyses

Potential tumor and blood biomarkers identified in the exploratory biomarker research may be correlated with PK, safety, and efficacy outcomes.

8. Administrative Section

8.1 Ethics

8.1.1 Compliance with the Protocol and Protocol Revisions

This study will be conducted in accordance with this study protocol and with ICH GCP guidelines, the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50), as well as all other applicable country and regional legal and regulatory requirements. The Investigator is responsible for ensuring that this protocol, the site's ICF, and any other information that will be presented to potential subjects are reviewed and approved by the appropriate IRB/IEC prior to the enrollment of any study subjects.

If an amendment substantially alters the study design or increases the potential risk to the subject:

1. The consent form must be revised and submitted to the IRB/IEC for review and approval/favorable opinion
2. The revised consent form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment
3. The new consent form must be used to obtain consent from new subjects prior to enrollment

If the revision is an administrative letter, Investigators must inform their IRB/IEC.

8.1.2 Institutional Review Board/Independent Ethics Committee

The Investigator must obtain written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g., subject leaflets), and any other written information to be provided to subjects. The Investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates. Amendments to the protocol must also be approved by the IRB/IEC prior to the implementation of changes in this study.

The Investigator or sponsor 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.

8.1.3 Informed Consent

Written informed consent is required from each subject prior to any testing under this protocol, including screening tests and evaluations. The ICF, as specified by the clinical site's IRB/IEC, must follow the Protection of Human Subjects regulations listed in the CFR, Title 21, Part 50.

Investigators must ensure that subjects or, in those situations where consent cannot be given by subjects, their legally acceptable representative, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding this clinical study in which they volunteer to participate. The information that is given to the subject or the representative shall be in a language understandable to the subject or representative. Freely given written informed consent prior to clinical study participation must be obtained from every subject or, in those situations where consent cannot be given by subjects, their legally acceptable representative, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written ICF and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form, and any other written information, was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

Preparation of the consent form is the responsibility of the Investigator and must include all elements required by ICH, GCP and applicable regulatory requirements as well as adhere to GCP and ethical principles that have their origin in the Declaration of Helsinki. The consent form must also include a statement that sponsor and Regulatory Authorities have direct access to subject records. Apexigen (or designee) will provide the Investigator with a sample consent form.

Prior to the beginning of the study, the Investigator must have the IRB/IEC's written approval/favorable opinion of the written ICF and any other information to be provided to the subjects. The Investigator must provide the subject or legally acceptable representative with a copy of the consent form and allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the trial.

8.1.4 Monitoring

The Investigator/institution must agree to the inspection of study-related records by the regulatory authority/Apexigen (or designee) representative and must allow direct access to source documents to the regulatory authority/Apexigen (or designee) representative/IRB/IEC. Apexigen (or designee) representative will review onsite study records and directly compare them with source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

The Investigator must notify Apexigen (or designee) promptly of any inspections by regulatory authorities and forward promptly copies of inspection reports to Apexigen (or designee).

8.1.5 Confidentiality

All records identifying the subject will be kept confidential to the full extent of the law.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded on the eCRF. If the subject name appears on any other document (e.g., pathologist report) or study materials (e.g., biopsy tissue slides), then that information must be redacted before a copy of the document is supplied to Apexigen (or designee). Study data stored on a computer will be stored in accordance with local data protection laws and regulations. Subjects will be informed in writing that representatives of the sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws and regulations.

If the results of the study are published, the subject's identity will remain confidential.

The Investigator will maintain a list to enable subjects' records to be identified in accordance with applicable laws and regulations and according to the terms and agreed upon in such subjects' signed consent forms.

8.1.6 Investigational Site Training

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

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 or debarment).

Systems with procedures that assure the quality of every aspect of the study will be implemented.

If necessary, Apexigen (or designee) will provide investigational staff training prior to study initiation. Training topics will include, but are not limited to, GCP, AE reporting, study details and procedure, study documentation, informed consent, and enrollment of WOCBP.

8.2 Data Collection and Handling

8.2.1 Case Report Forms

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include subject diaries, laboratory reports, and other documents. Apexigen (or designee) will supply the eCRF, which will be completed in English.

Data collection will involve the use of the EDC system, to which only authorized personnel will have access.

The Investigator or designee must enter all results collected during the clinical study into eCRFs. Guidelines for completion of eCRFs will be reviewed with study site personnel at the site initiation visits. Investigators are responsible for approval of the entered/corrected data. Detailed instructions may be found in the other study-specific documents.

All entries made on the eCRF must be verifiable against source documents. In addition to periodic monitoring occurring within the system by study monitors, programmatic edit checks and data listings will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks and queries may be electronically issued to the clinical study sites and electronically resolved by those sites.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to assure subject confidentiality in accordance with the legal and regulatory requirements applying to protected health information. Study records (e.g., copies of eCRFs and regulatory documents) will be retained at the study site, along with adequate source documentation. The study file and all source data should be retained for the time period required by applicable regulatory requirements and will not be destroyed until written notification is given by Apexigen (or designee) for destruction.

8.3 Publications

The data collected during this study are confidential and proprietary to Apexigen. Any publications or abstracts arising from this study require approval by Apexigen prior to publication or presentation and must adhere to Apexigen’s publication requirements (as set forth in the approved clinical trial agreement). All draft publications, including abstracts or detailed

summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission. Apexigen shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

9. List of Abbreviations

Abbreviation	Definition
ADA	Anti-drug antibodies
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APC	Antigen-presenting cell
aPTT	Activated partial thromboplastin time
AR	Adverse reaction
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the curve extrapolated to infinity
AUC_{0-t}	Area under the curve at the last measurable time point
BCR	B-cell receptor
BRAF	Human proto-oncogene encoding B-Raf protein
CD40	Cluster of differentiation 40
CD40L	CD40 ligand
C_{max}	Maximum serum concentration
CNS	Central nervous system
CR	Complete response
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
DCs	Dendritic cells
DOR	Duration of response
DL	Dose level
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
IND	Investigational New Drug application
INR	International normalized ratio

Abbreviation	Definition
inNSCLC	Immunotherapy naïve NSCLC
IRB	Institutional Review Board
iRECIST	Immune-related RECIST Modified RECIST 1.1 for Immune-based Therapeutics
ISR	IND safety report
IV	Intravenous
K_d	Dissociation constant
mAb	Monoclonal antibody
mL	Milliliter
MTD	Maximum tolerated dose
MM	Unresectable or metastatic melanoma
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease/disease progression
PD-1	Programmed death receptor-1
PD-L1	Programmed death-ligand 1
PD1-MM	MM with progressive disease during treatment with anti-PD-1/PD-L1
PDn	Pharmacodynamics
PK	Pharmacokinetics
PFS	Progression-free survival
PFSR	Progression-free survival rate
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
RCC	Advanced renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAR	Suspected adverse reaction
SSAR	Serious suspected adverse reaction
TCR	T-cell receptor
TKI	Tyrosine kinase inhibitor
t_{max}	Time to maximum serum concentration
TNFR	Tumor necrosis factor receptor
ULN	Upper limit of normal
WOCBP	Women of childbearing potential

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APPENDIX A: Eastern Cooperative Oncology Group Performance Scale

Grade	Description
0	Normal activity, fully active, able to carry on all pre-disease performance without restriction
1	Symptoms, but fully ambulatory, restricted in physically strenuous but ambulatory and able to carry out work of a light or sedentary nature (e.g., 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
5	Death

APPENDIX B: Methods of Contraception Europe only

Highly Effective Methods of Contraception	Progestogen only hormonal contraception associated with inhibition of ovulation
	Hormonal methods of contraception including oral contraceptive pills (combination of estrogen and progesterone), vaginal ring, injectables, implants, transdermal, and intrauterine hormone-releasing system (IUS)
	Bilateral tubal ligation
	Vasectomized Partner
	Intrauterine devices (IUD)
	Complete abstinence
Additional Methods for Male Subjects	Condom
	NOTE: Partners of male subjects are to use one highly effective method of contraception

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SIGNATURE PAGE OF THE INVESTIGATOR

Title: A Study to Evaluate the Safety and Efficacy of the CD40 Agonistic Antibody APX005M Administered in Combination with Nivolumab in Subjects with Non-small Cell Lung Cancer and Subjects with Metastatic Melanoma
Protocol Number: APX005M-002
Version: Amendment 4.0
Date: October 10, 2019
EudraCT Number: 2018-003866-14
Sponsor: Apexigen, Inc.

I have read and agree to the protocol of the above-mentioned clinical study. I am aware of my responsibilities as an Investigator under the ICH guidelines for GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who are involved in the study.

_____
Signature

_____ _____
Name, title and affiliation of Investigator Date