Protocol Number: APX005M-010
IND Number: 122725
EudraCT Number: 2018-003864-30
Date of Original Protocol: November 2, 2018

CLINICAL PROTOCOL APX005M-010

A Phase II Multicenter, Open label Study to Evaluate the Safety and Efficacy of the CD40 Agonistic Antibody APX005M With or Without Stereotactic Body Radiation Therapy in Adults with Unresectable or Metastatic Melanoma

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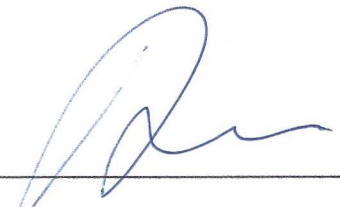
Date of Amendment 2: December 28, 2020

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

SPONSOR APPROVAL PAGE



11/8/21

Thomas Jahn, M.D., Ph.D.
Vice President Clinical Development,
Apexigen, Inc.

Date

SIGNATURE PAGE OF THE INVESTIGATOR

Title: A Phase II Multicenter, Open label Study to Evaluate the Safety and Efficacy of the CD40 Agonistic Antibody APX005M With or Without Stereotactic Body Radiation Therapy in Adults with Unresectable or Metastatic Melanoma
Protocol Number: APX005M-010
Amendment: 2
Date: December 28, 2020
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Sponsor: Apexigen, Inc.

I have read and agreed to the protocol of the above-mentioned clinical study. I am aware of my responsibilities as an Investigator and will conduct this study in compliance with 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

DOCUMENT HISTORY

Version	Date	Replaces	Description of Changes
Original Protocol	November 2, 2018	N/A	New Document
Version 1.1	January 16, 2019	Original Protocol	The protocol was amended to add methods of contraception (Appendix C)
Amendment 1.0	March 8, 2019	Version 1.1	The protocol title was amended to reflect study design. The protocol was amended to edit Inclusion Criteria #2. The protocol was amended to add Exclusion Criteria of previous participation in another clinical trial of an investigational drug (or a medical device) within 30 days of study enrollment. The protocol was amended to update and resolve inconsistencies in sample collection schedule for correlative studies described in Section 4.4.
Amendment 2.0	December 28, 2020	Amendment 1.0	The protocol was amended to introduce Cohort 3 combining APX005M with stereotactic body radiation therapy in subjects with unresectable or metastatic melanoma that failed available therapies and to adjust the sample size in Cohorts 1 and 2.

SYNOPSIS

Protocol Number:	APX005M-010
Protocol Title:	A Phase II Multicenter, Open label Study to Evaluate the Safety and Efficacy of the CD40 Agonistic Antibody APX005M With or Without Stereotactic Body Radiation in Adults with Unresectable or Metastatic Melanoma
Phase of Development:	Phase 2
Investigational Therapy(ies):	APX005M Stereotactic Body Radiation (SBRT)
Study Design:	This is a multicenter, open label, Phase 2 study, with 3 parallel cohorts. The aim of the study is to evaluate the efficacy of: a) APX005M administered at 2 different schedules to adult subjects with unresectable or metastatic melanoma who have not received prior immunotherapy. Enrolled subjects will be alternately assigned to one of the following 2 cohorts as long as both cohorts are open: **Cohort 1:** APX005M administered IV at 0.3 mg/kg every 3 weeks (21-day cycle) **Cohort 2:** APX005M administered IV at 0.3 mg/kg every 2 weeks (14-day cycle) The intent of the alternating cohort assignment is to maintain approximately the same number of treated subjects in each of these 2 cohorts at any given time. Therefore, enrolled subjects assigned to Cohorts 1 or 2 that do not receive APX005M or are not evaluable for tumor response will be replaced in that cohort before assigning new subjects to the other cohort. b) APX005M in combination with stereotactic body radiation therapy (SBRT) in adults with unresectable or metastatic melanoma who have failed approved immunotherapy regimens: **Cohort 3:** APX005M administered IV at 0.3 mg/kg in combination with radiation therapy every 2 weeks (14-day cycle) up to 16 weeks followed by APX005M administered IV at 0.3 mg/kg every 2 weeks (14-day cycle).
Study Objectives:	**Primary Objective** • Evaluate the overall response rate (ORR) by RECIST 1.1 in each cohort **Secondary Objectives** • Evaluate the safety of APX005M alone or in combination with radiation therapy in each cohort • Evaluate ORR by modified RECIST 1.1 for immune-based therapeutics (iRECIST) in each cohort • Evaluate median duration of response (DOR) in each cohort

	Exploratory Objectives • Evaluate PFS (by RECIST 1.1 and iRECIST) in each cohort • Evaluate the association between potential tumor and blood biomarkers and antitumor activity and/or resistance • Determine the presence and titer of anti-APX005M antibodies (ADA)
Study Population	**Inclusion Criteria** 1. Histologically or cytologically confirmed unresectable or metastatic melanoma 2. Subjects with BRAF activating mutation must have received a BRAF inhibitor and/or MEK inhibitor regimen prior to study entry 3. Signed written informed consent approved by the relevant local ethics committee(s) 4. Male or female ≥18 years old at time of consent 5. Measurable disease by RECIST 1.1 a. For Cohort 3 only, subjects must have at least 3 measurable target lesions 6. ECOG performance status of 0 or 1 7. Resolution of all disease or 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 8. Adequate organ function within 14 days prior to first dose of investigational therapy(ies): a. WBC ≥2 x 10^9/L in absence of growth factor support b. ANC ≥1.0 x 10^9/L in absence of growth factor support c. Platelet count ≥100 x 10^9/L d. Hemoglobin ≥9 g/dL e. Serum creatinine ≤1.5 mg/dL f. Calculated (using the formula of local laboratory) or measured creatinine clearance ≥60 mL/min g. AST and ALT ≤2.5 x ULN h. Total bilirubin ≤1.5 x ULN, or direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 x ULN i. 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

	j. 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 9. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within the 7 days prior to first dose of investigational therapy(ies) and a negative urine pregnancy test within the 3 days prior to first dose of investigational therapy(ies), or a negative serum pregnancy test within the 3 days prior to first dose of investigational therapy(ies) 10. 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 therapy(ies). 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 therapy(ies). 11. Available archived or fresh tumor tissue sample for biomarker analysis. Note: For Cohort 3, only available archived tissue is required. 12. 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. Up to 18 subjects (6 subjects within each cohort) should consent to fresh core biopsies. **Exclusion Criteria** 1. Prior Therapy: a. Cohorts 1 and 2 only: Previous exposure to any immunomodulatory agent (such as CTLA-4, PD-1/ PD-L1, IDO inhibitors, interferon, CD40 agonists etc.). b. Cohort 3 only: Prior therapy with a CD40 agonist. Any number of prior lines of therapy are eligible. A minimum washout period of 21 days from last line of therapy until investigational therapy(ies) administration should be observed 2. Second malignancy (solid or hematologic) within the past 3 years except locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast 3. Active, known, clinically serious infections (≥ Grade 2 according to NCI-CTCAE v4.03) within the 14 days prior to first dose of investigational therapy(ies) 4. Use of systemic corticosteroids or other systemic immunosuppressive drugs within 28 days prior to first dose of

	investigational therapy(ies) (except inhaled corticosteroids) a. 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 prior to first dose of investigational therapy(ies) 6. Concurrent treatment with any anticancer agent (except for hormonal therapy) and palliative radiation, unless approved by the Apexigen Medical Monitor (or designee) 7. History of allogeneic bone marrow transplantation 8. Active, known or suspected autoimmune disease 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 1 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 sensitivity or allergy to mAbs or IgG 13. 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 therapy(ies) 14. History of any thromboembolic event within 3 months prior to first dose of investigational therapy(ies) or active coagulopathy 15. 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, and do not 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

	16. Known human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection 17. Has received a live (attenuated) vaccine within 30 days prior to the first dose of investigational therapy(ies). Seasonal flu vaccines that do not contain live virus and COVID-19 vaccines are permitted (See Section 3.2.3.4) 18. Has participated in another clinical trial of an investigational drug (or a medical device) within 30 days of study enrollment 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:	**Safety Analyses** Safety will be assessed by cohort through summaries of AEs, 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 by exact distribution), DOR and PFS (Kaplan-Meier estimate) will be estimated for each cohort and for each tumor assessment method. Additional details will be provided in the Statistical Analysis Plan. **Exploratory Analyses** Potential tumor and blood biomarkers identified in the exploratory biomarker research may be correlated with safety and efficacy outcomes.

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1. INTRODUCTION AND RATIONALE

1.1 Background

Among the promising approaches to activating therapeutic antitumor 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 [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, upregulation of costimulatory molecules 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, all of which could lead to therapeutic effects in tumors with high mutational burden such as melanoma. Thus, the desired therapeutic CD40 agonist antibody should have these functionalities.

A few CD40 agonistic antibodies have been evaluated in human clinical trials. Many of the clinical studies in cancer subjects with solid tumors have been conducted with the fully human IgG2 CD40 antibody CP-870,893. In a Phase 1 clinical trial, CP-870,893 was well tolerated; the MTD was found to be 0.2 mg/kg. The main toxicity of CP-870,893 was cytokine release syndrome (CRS) of mild to moderate severity. Single agent antitumor activity was observed in several melanoma subjects treated with CP-870,893 [15, 16].

In several preclinical models the combination of RT with drugs that activate APCs results in synergistic anti-tumor effects [17, 18]. Activating tumor APCs via CD40 will enhance tumor antigen presentation and help prime or boost antitumor T cells in lymph nodes or in tumor-embedded tertiary lymphoid structures. In addition, properly activated APCs provide potent costimulatory signals to CD8+ tumor-infiltrating lymphocytes in the tumor microenvironment and release appropriate chemokines, which guide effector T cells to home in the tumor microenvironment. In a triple-negative breast cancer model the combination of a CD40 agonist antibody and RT resulted in improved innate and adaptive immune response. Importantly, CD40 treatment increased tumor response to radiotherapy and protected against metastatic spread in a metastatic model [19].

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 (Kd = 1.2 × 10−10 M) and monkey CD40 (Kd = 3.5 × 10−10 M), but does not cross-react with mouse or rat CD40. APX005M blocks the binding of CD40 to CD40L. The APX005M binding epitope has been mapped to 2 specific regions on CD40. These are 92TSEACESCVLHRSCSP107 and 125PCPVGFFSNVSSAFEKCHPW144. The region 92TSEACESCVLHRSCSP107 is known as a CD40L binding domain. It has been shown that CD40L-blocking antibodies tend to have more potent CD40 agonistic activities than CD40L-non-blocking antibodies [20].

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 [21]. 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 was 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) [18]. 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 every 3-week IV administration of APX005M at dose levels of 0.03 mg/kg or less were for the most part below the limit of quantitation (BLOQ). Administration of APX005M at dose levels between 0.1 and 1 mg/kg lead to rapid increase in serum concentrations, reaching a maximum just after the end of the infusion. Concentrations 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

APX005M has been administered to cancer patients with heavily pretreated solid tumors at doses ranging from 0.0001 mg/kg to 1 mg/kg body weight every 3 weeks, 0.1 mg/kg and 0.3 mg/kg every 2 weeks and 0.1 mg/kg and 0.3 mg/kg every 1 week. In all 3 administration schedules, the dose of 0.3 mg/kg body weight was well tolerated, with toxicities ≤ Grade 2, and is the recommended Phase 2 dose. In the every 3-week administration schedule, APX005M

demonstrated a dose-dependent activation of APCs, T-cell activation, and increases in circulating levels of cytokines.

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.

Asymptomatic transient transaminase elevations, with or without transient bilirubin increase, have been observed in subjects receiving APX005M and these elevations seem to correlated with the presence of liver metastases. 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 pharmacodynamic (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 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 1 mg/kg body weight suggest a best-in-class profile for APX005M and the possibility of a safe and efficacious treatment for patients with melanoma.

2. INVESTIGATIONAL PLAN

2.1 Study Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

- Evaluate the safety of APX005M alone or in combination with radiation therapy in each cohort
- Evaluate ORR by modified RECIST 1.1 for immune-based therapeutics (iRECIST) in each cohort
- Evaluate median duration of response (DOR) in each cohort

2.1.3 Exploratory Objectives

- Evaluate PFS (by RECIST 1.1 and iRECIST) in each cohort
- Evaluate the association between potential tumor and blood biomarkers and antitumor activity and/or resistance
- Determine the presence and titer of anti-APX005M antibodies (ADA)

2.2 Study Design and Duration

This is a multicenter, open label, Phase 2 study, with 3 parallel cohorts. The aim of the study is to evaluate the efficacy of:

a) APX005M administered at 2 different schedules to adult subjects with unresectable or metastatic melanoma who have not received prior immunotherapy. Enrolled subjects will be alternately assigned to one of the following 2 cohorts as long as both cohorts are open:
Cohort 1: APX005M administered IV at 0.3 mg/kg every 3 weeks (21-day cycle)

Cohort 2: APX005M administered IV at 0.3 mg/kg every 2 weeks (14-day cycle)

The intent of the alternating cohort assignment is to maintain approximately the same number of treated subjects in each of these 2 cohorts at any given time. Therefore, enrolled subjects assigned to Cohorts 1 or 2 who do not receive APX005M or are not evaluable for tumor response (see below) will be replaced in that cohort before assigning new subjects to the other cohort.

b) APX005M in combination with stereotactic body radiation therapy (SBRT) in adults with unresectable or metastatic melanoma who have failed approved immunotherapy regimens:

Cohort 3: APX005M administered IV at 0.3 mg/kg in combination with radiation therapy every 2 weeks (14-day cycle) up to 16 weeks followed by APX005M administered IV at 0.3 mg/kg every 2 weeks (14-day cycle).

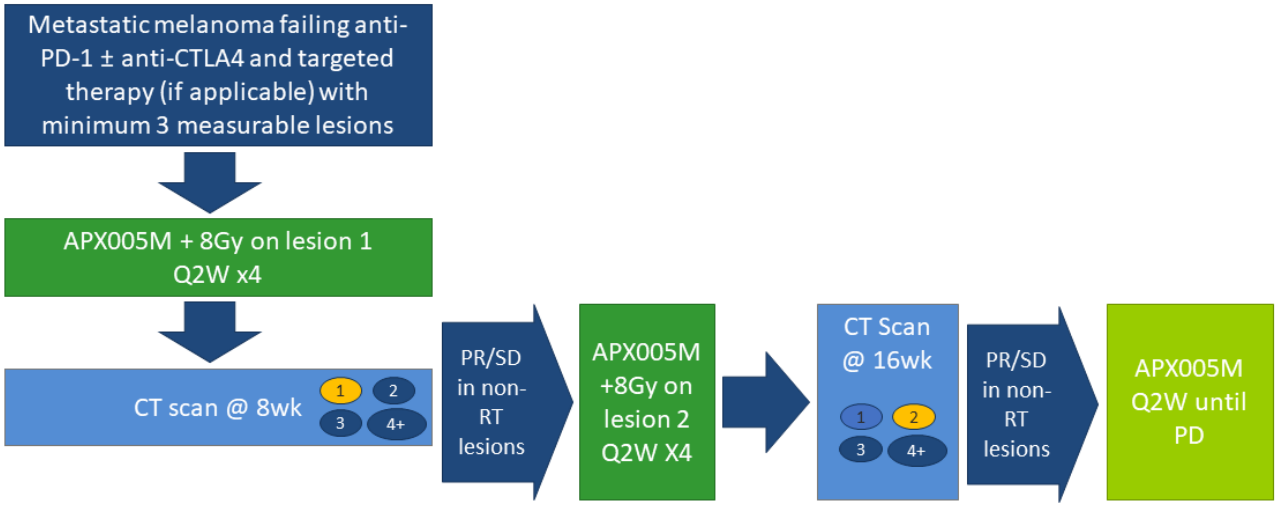
Subjects enrolled in Cohort 3 are required to have a minimum of 3 non-central nervous system (CNS) measurable target lesions as defined in RECIST 1.1 (see Section 3.2.2). Subjects will receive APX005M combined with SBRT followed by single agent APX005M:

- Four cycles consisting of radiation (one fraction of 800 cGy per cycle delivered to the same target lesion) followed by systemic administration of APX005M every 2 weeks for a total period of 8 weeks.
- Tumor assessment
- Four additional cycles consisting of radiation (one fraction of 800 cGy per cycle delivered to one target lesion different from the one previously irradiated) followed by systemic administration of APX005M every 2 weeks for a total period of 8 weeks.
- Tumor assessment

- Single agent APX005M until any of the criteria in Section 3.2.6.1 are met.

If the first or second radiation therapy targets disappear during radiation treatment, radiation induced toxicity occurs, or radiation dose constrains are met, the remaining radiation fraction scheduled for that particular radiation therapy target can be omitted (Sections 3.2.2 and 3.2.5).

Figure 1: Cohort 3 Study Design



Subjects in all 3 cohorts with unconfirmed PD (iUPD, iRECIST) (Section 4.3.2) will be permitted to continue treatment as long as

- they meet the criteria in Section 3.2.6.2and
- they do not have confirmed PD as defined by iRECIST on a repeated tumor assessment 4-8 weeks later.

Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

For every subject the participation in the study consists of 3 periods: Screening Period, Treatment Period and Follow-up Period.

All subjects signing the informed consent form will enter the Screening Period. Procedures and timing of all study related procedures are outlined in Section 4. Treatment period will start with the administration of 1st dose of APX005M ± SBRT and will continue for up to 12 months or until criteria in Section 3.2.6.1 are met.

For the first 2 treatment cycles, subjects will be observed for at least 4 hours following the infusion of APX005M and will return for safety evaluations on Day 2 (24 hours post infusion) and Day 8 (168 hours post infusion). In subsequent cycles, the 4-hour post-infusion observation period and any intracycle safety visits should be scheduled as clinically indicated.

Tumor responses will be evaluated approximately every 8 weeks following the first dose of APX005M. Subjects that discontinue treatment before the first scheduled on-study tumor assessment (8 weeks following the first dose of APX005M) should have the tumor response evaluated at the end of treatment visit. Subjects that are non-evaluable for tumor response will be replaced.

Subjects consenting to collection of tumor biopsies for tumor biomarkers must have a primary or metastatic lesion that can be biopsied without interfering with subsequent tumor assessments.

Subjects who discontinue APX005M will enter the Follow-up Period unless treatment discontinuation is due to withdrawal of consent for all study procedures, initiation of any anticancer therapy, subject lost to follow-up, death, or study termination by Apexigen.

2.2.1 Study Population

2.2.1.1 Inclusion Criteria

1) Histologically or cytologically confirmed unresectable or metastatic melanoma
2) Subjects with BRAF activating mutation must have received a BRAF inhibitor and/or MEK inhibitor regimen prior to study entry
3) Signed written informed consent approved by the relevant local ethics committee(s)
4) Male or female ≥18 years old at time of consent
5) Measurable disease by RECIST 1.1
    a. For Cohort 3 only, subjects must have at least 3 measurable non-CNS target lesions
6) ECOG performance status of 0 or 1
7) Resolution of all disease or 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
8) Adequate organ function within 14 days prior to first dose of investigational therapy(ies):
    a. WBC ≥2 x 10^9/L in absence of growth factor support
    b. ANC ≥1.0 x 10^9/L in absence of growth factor support
    c. Platelet count ≥100 x 10^9/L
    d. Hemoglobin ≥9 g/dL
    e. Serum creatinine ≤1.5 mg/dL
    f. Calculated (using the formula of local laboratory) or measured creatinine clearance ≥60 mL/min

g. AST and ALT ≤2.5 x ULN

h. Total bilirubin ≤1.5 x ULN, or direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 x ULN

i. 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

j. 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

9) Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within the 7 days prior to first dose of investigational therapy(ies) and a negative urine pregnancy test within the 3 days prior to first dose of investigational therapy(ies), or a negative serum pregnancy test within the 3 days prior to first dose of investigational therapy(ies)

10) 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 therapy(ies). 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 therapy(ies)

11) Available archived or fresh tumor tissue sample for biomarker analysis. Note: For Cohort 3, only available archived tissue is required.

12) 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. Up to 18 subjects (6 subjects within each cohort) should consent to fresh core biopsies.

2.2.1.2 Exclusion Criteria

1) Prior Therapy:

   a. Cohorts 1 and 2 only: Previous exposure to any immunomodulatory agent (such as CTLA-4, PD-1/PD-L1, IDO inhibitors, interferon, CD40 agonist etc.).

   b. Cohort 3 only: Prior therapy with a CD40 agonist. Any number of prior lines of therapy are eligible. A minimum washout period of 21 days from last line of therapy until investigational therapy(ies) administration should be observed

2) Second malignancy (solid or hematologic) within the past 3 years except locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast

3) Active, known, clinically serious infections (≥ Grade 2 according to NCI-CTCAE v4.03) within the 14 days prior to first dose of investigational therapy(ies)

4) Use of systemic corticosteroids or other systemic immunosuppressive drugs within 28 days prior to first dose of investigational therapy(ies) (except inhaled corticosteroids)

   a. 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 prior to first dose of investigational therapy(ies)

6) Concurrent treatment with any anticancer agent (except for hormonal therapy) and palliative radiation, unless approved by the Apexigen Medical Monitor (or designee)
7) History of allogeneic bone marrow transplantation
8) Active, known or suspected autoimmune disease
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 1 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 sensitivity or allergy to mAbs or IgG
13) 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 therapy(ies)
14) History of any thromboembolic event within 3 months prior to first dose of investigational therapy(ies) or active coagulopathy
15) 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, and do not 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
16) Known human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection
17) Has received a live (attenuated) vaccine within 30 days prior to the first dose of investigational therapy(ies). Seasonal flu vaccines that do not contain live virus and COVID-19 vaccines are permitted (see Section 3.2.3.4)
18) Has participated in another clinical trial of an investigational drug (or a medical device) within 30 days of study enrollment
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 Rationale for APX005M Dose

The APX005M regimens (dose and frequency) for all cohorts have been evaluated in prior studies and determined to be well-tolerated and pharmacodynamically-active. In an ongoing study, the combination of APX005M with local radiation treatment and chemotherapy did not result in excess or synergistic toxicity.

3. STUDY PERIODS

3.1 Screening Period

3.1.1 Informed Consent

All subjects will provide written informed consent prior to any study-related activities. All subjects who sign a consent form will enter the Screening Period and 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 reconsented, as appropriate, during the course of the study if the informed consent document is revised. Reconsent should be obtained as soon as practicable (e.g., prior to subsequent study drug exposure) or as directed by the local ethics committee(s).

3.1.2 Subject Enrollment

Investigative sites will submit Subject Eligibility Packets (SEPs) for Apexigen Medical Monitor (or designee) review and approval. SEPs will include study-specific eligibility checklist and redacted/anonymized source documents such as the most recent history and physical, imaging reports, and laboratory reports. The Apexigen Medical Monitor (or designee) will review the subject's medical information to confirm eligibility and approve subject's enrollment in the study. During normal business days, a minimum of 2 business days will be required for the Apexigen Medical Monitor (or designee) to review a subject for enrollment. Additional time may be required when approval is sought during a weekend or holiday.

Consented subjects who do not meet eligibility criteria will be considered screen failures.

Enrolled subjects will be alternately assigned to one of the 2 cohorts as long as both cohorts are open. Enrolled subjects assigned to a certain cohort that do not receive APX005M or are not evaluable for tumor response will be replaced in that cohort before assigning new subjects to the other cohort.

3.2 Treatment Period

Enrolled subjects who do not receive APX005M will be considered to have been withdrawn. The Treatment Period will start with the first administration of investigational therapy(ies) and will continue for up to 12 months or until criteria in Section 3.2.6.1 are met.

3.2.1 APX005M Administration

For Cohorts 1 and 2, APX005M is administered on Day 1 of each 3-week or 2-week treatment cycle. In Cohort 3 APX005M will be administered after each fraction of SBRT during the time of combination treatment.

The APX005M infusion time will be 60 minutes. 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 Pharmacy Manual contains specific instructions for the preparation of the APX005M infusion and administration of infusion solution.

The APX005M infusion can be interrupted in the case of infusion reaction (see Section 3.2.3.2). Once symptoms resolve, infusion should be restarted at 50% of the initial infusion rate (e.g., from 100 mL/hr to 50 mL/hr).

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, and heart rate <110 beats/min. After discharge, all subjects 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.

APX005M and SBRT may be administered up to 3 days after the scheduled Day 1 of Cycle 2 and beyond in 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). Treatment delays related to study therapy are discussed in Section 3.2.4.

Administration of APX005M will continue for up to 12 months or until criteria in Section 3.2.6.1 are met.

3.2.2 Radiation Therapy

All subjects should be evaluated and treated by a local radiation oncologist. All radiation treatment will follow the standard guidelines for a SBRT treatment course. Each radiation therapy target lesion will receive up to a total of 3200 cGy in 4 fractions of 800 cGy, administered on the same day and prior to infusion of APX005M. Fractions will be delivered every 2 weeks with the requirement of a minimum of 4 field 3D conformal planning to meet dose constraints to limit normal tissue toxicity of organs at risk (OAR). The first target lesion and the subsequent target lesion will be identified by the treating investigator based upon considerations of clinical benefit and toxicity risk. The RT target lesions shall not be CNS metastases.

First Radiation Therapy Target: One of 3 or more measurable disease lesions (as defined by RECIST 1.1) will be selected as the first radiation therapy target and will be treated every

2 weeks during the first 8 weeks. The radiation field of the first target shall not overlap with any other target lesions.

Second Radiation Therapy Target: The second target shall be one of the remaining non-irradiated lesions where the radiation field does not overlap with the first radiation target. The radiation field shall not overlap with at least one non-irradiated target lesion.

3.2.2.1 Treatment Technology

Based upon the location and size of tumors, treatment planning will be determined by clinical appropriateness. This protocol requires treatment with photons with minimum nominal energy specification of 6 MV. Intensity modulated radiotherapy (IMRT) is encouraged when dosimetric benefit would reduce risk to OARs and may be implemented with static gantry or volumetric modulated arc therapy (VMAT). Tomotherapy delivery is allowed. Though each individual dose may not require high level of precision requiring high level of technology, immobilization and verification the total dose over the 8 weeks will require close monitoring.

3.2.2.2 Immobilization and Simulation

Immobilization: Proper immobilization is important for this protocol. Subject setup reproducibility must be achieved using appropriate clinical devices. A custom immobilization device (such as Alpha Cradle or Vac-Loc) is suggested to minimize set-up variability. SBRT frame and abdominal compression may be appropriate for thoracic and abdominal treatments to minimize motion.

Simulation Imaging: CT Simulation is required, and the images must be acquired using a CT-simulator with a slice thickness ≤3 mm. Care should be taken to use the smallest possible FOV that contains the entire surface of the patient with a 512x512 image matrix. Oral and IV CT contrast is optional depending upon the location of the target lesions. The CT simulation must be performed with the patient in the treatment position.

Typical CT scan limits will vary depending on the site. However, it is recommended that the patient will be imaged at least 10 cm cranial and caudal to the target especially if noncoplanar beams will be used.

3.2.2.3 Definition of Target Volumes and Margins

The volumes are to be defined by planning CT/MRI techniques. The extent of palpable tumors should be determined by physical examination to complement imaging and external markers may be helpful for target delineation on CT scans.

3.2.2.4 Detailed Specification

Gross tumor volume (GTV): This includes the target lesion and any adjacent extent or lymph nodes that are considered part of the target lesion. Assessment of the target lesion CT, PET-CT, MRI, or physical exam.

Clinical target volume (CTV): This includes the GTV and suspected microscopic extension and at-risk excluding bone and muscle. Appropriate expansion shall be determined by the treating radiation oncologist and made appropriate for the target site and risk.

Internal target volume (ITV): For target lesions in regions of motion an ITV may be indicated that will take into consideration motion of the target during certain phases of respiration. An appropriate ITV shall be created using 4DCT scans or breath hold scans as indicated for the motion management strategy.

Planning target volume 3200 (PTV): This will provide a margin around the CTV or ITV if appropriate to compensate for the inter- and intra-fraction uncertainty consequent to daily setup uncertainty. By definition, the PTV will consist of a symmetrical 3-7 mm expansion around the CTV or ITV as defined for by radiation oncologist that is specific to institutional standard for the site. In the event that a PTV extends outside of the skin surface, the clinician should manually trim the PTV contours to be 3 mm inside the outer skin (unless there is direct skin involvement).

3.2.2.4.1 Definition of Critical Structures

Because treatment sites may vary throughout the body, the treating radiation oncologist shall define the critical structures for the case. This should be defined by the dose constraints (see Tables 1A and 1B) and the proximity of the treated lesion.

Table 1A: Radiation Dose Constraints - Serial Tissue

Serial Tissue	Vol. (cc)	Vol. Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥ Grade 3)
Optic Pathway	<0.2	19.2	21.2	neuritis
Cochlea	-	-	18	hearing loss
Brainstem (not medulla)	<0.5	20.8	27.2	cranial neuropathy
Spinal Cord and Medulla	<5	30	25.6	myelitis
Cauda Equina	<5	26	28.8	neuritis
Sacral Plexus	<5	26	28.8	neuropathy
Esophagus*	<5	30.4	34	esophagitis
Brachial Plexus	<3	24.8	29.6	neuropathy
Heart/Pericardium	<15	28	33	pericarditis
Great Vessels	<10	32	36	aneurysm
Trachea and Large Bronchus*	<5	32	35	impairment of pulmonary toilet
Bronchus- Smaller Airways	<0.5	28.8	35	stenosis with atelectasis
Rib	<5	32	35	pain or fracture
Skin	<10	32	35	ulceration
Stomach	<5	25	33	ulceration/fistula
Bile Duct	-	-	35	stenosis
Duodenum*	<5	25	33	ulceration
Jejunum/Ileum*	<30	22.4	31.6	enteritis/obstruction

Serial Tissue	Vol. (cc)	Vol. Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥ Grade 3)
Colon*	<20	30.8	35	colitis/fistula
Rectum*	<20	32	35	proctitis/fistula
Ureter	-	-	35	stenosis
Bladder Wall	<15	18.5	35	cystitis/fistula
Penile Bulb	<3	27	-	impotence
Femoral Heads	<10	27	-	necrosis
Renal Hilum/Vascular Trunk	15	21.5	-	malignant hypertension

* avoid circumferential irradiation
** "point" defined as 0.035cc or less
*** or one third of the "native" total organ volume (prior to any resection or volume reducing disease), whichever is greater

Table 1B: Radiation Dose Constraints - Parallel Tissue

Parallel Tissue	Critical Volume (cc)	Critical Volume Dose Max (Gy)	Volumetric Constraint	Endpoint (≥ Grade 3)
Lung (right & left)	1500 cc for males and 950 cc for females***	12	-	basic lung function
Lung (right & left)	-	-	V12.8Gy <37%	pneumonitis
Liver	700***	19.6	-	basic liver function
Renal Cortex (right & left)	200***	1	-	basic renal function

*** or one third of the "native" total organ volume (prior to any resection or volume reducing disease), whichever is greater

3.2.2.4.2 Planning Technique

A 3D conformal or IMRT planning technique must be used. If not using IMRT, field edges and MLC blocking must be conformal to the PTV. The dose distributions must include corrections for tissue density heterogeneities. Regardless of planning technique, the dose prescription criteria specified shall be prioritized.

Table 1C: Radiation Dose Criteria

Name of Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
PTV	Dmin (%)	≥90	≥85
	D100% (%)	≥95	≥85
	Dmax (%)	≤130	≤150

Replanning: Because melanoma can respond robustly to radiation and treatments will be every 2 weeks it is possible that the tumor volume will be considerably smaller for subsequent fractions. It is recommended that response be assessed after two fractions for bigger tumors or

tumors where decrease in size can considerably impact OARs and toxicity risk. If there has been a decrease of tumor volume by more than 2-fold then a new plan should be considered.

3.2.2.4.3 Patient specific Quality Assurance (QA)

For photon IMRT plans, patient specific QA is highly recommended. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Typically, measured dose distributions will be compared to planned dose distribution using a Gamma criterion of 4% dose difference and 3 mm distance to agreement. The pass rate should be at least 90% measured for the entire plan.

3.2.2.4.4 Daily Treatment Localization/IGRT

Daily image-guided radiation therapy (IGRT) localization is required for all patients. Either a daily orthogonal kV pair, or cone-beam computed tomography CBCT is acceptable. Institutional guidelines should be followed for daily treatment localization and IGRT. IGRT credentialing is not required for this protocol.

3.2.2.4.5 Duration of Radiation Therapy

Duration of therapy will be per treatment schedule as above. Duration will be shortened, and treatment can be ended early if the patient develops:

- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant decides to withdraw from the study, OR
- General or specific changes in the patient's condition render the participant unacceptable for further treatment in the judgment of the principal investigator or medical oncologist.

3.2.3 Concomitant Treatments

3.2.3.1 Premedication prior to APX005M

All subjects should be premedicated 30 ± 5 minutes before the administration of APX005M with a regimen containing:

- Oral H1 antagonist (e.g., loratadine 10 mg)
- Optional oral H2 antagonist (e.g., ranitidine 150−300 mg, cimetidine 300−800 mg, nizatidine 150−300 mg, and famotidine 20−40 mg)
- Oral nonsteroidal anti-inflammatory drug (may comprise ibuprofen 400 mg or equivalent)
- Acetaminophen 650 mg.

Equivalent quantities of IV formulations of these drugs should be completed 10 ± 5 minutes before the administration of APX005M.

3.2.3.2 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 adverse events (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 should not substitute for dose delays and/or modifications. Additional guidance for management of AEs suspected to be related to APX005M is provided in the APX005M Investigator's Brochure.

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.

- **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. 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. Consider adding prophylactic antibiotics for opportunistic infections. Consider bronchoscopy and lung biopsy.

- **Liver Function Tests**
  - **Grade 2, and Grade 3 transaminase elevation ≤72 hours:** monitor liver function tests (incl. total bilirubin levels) more frequently until returned to Grade ≤1.
  - **All other Grade 3, and any Grade 4 transaminase elevation:** treat with IV corticosteroids for 24-48 hours followed by oral corticosteroids until symptoms improve to Grade ≤1. If no improvement in 3–5 days administer additional immunosuppressive measures (e.g. mycophenolate mofetil), as needed. Consider adding prophylactic antibiotics for opportunistic infections. Consult gastroenterologist.
- **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: c**onsider 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. Emergency treatment including oxygen, oral and endotracheal airways, intubation equipment epinephrine, antihistamines, and corticosteroids should be available and used as medically required and at the Investigator's discretion.
  - **Grade 2:** stop infusion and treat symptoms following guidance in Table 2. 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 2.

  Subjects should be instructed that symptoms associated with cytokine release syndrome/infusion reaction may occur within 48 hours following the administration of APX005M and if such symptoms develop while they are at home, they should contact the Investigator and/or seek emergency medical care if necessary.

Table 2: 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 >24 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 first
• 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>

- **Any Other Possibly Immune Mediated Toxicity**
  - **Grade 2:** symptomatic treatment per local guidelines
  - **Grade 3–4:** Consult Apexigen Medical Monitor (or designee). Administer IV corticosteroids followed by oral corticosteroids until symptoms improve to Grade 2 or less. Consider adding prophylactic antibiotics for opportunistic infections. If symptoms worsen or for atypical presentation consider and additional immunosuppressive measures per local guidelines.

3.2.3.3 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 received from the time of first dose of APX005M and up to 30 days after the last dose will be recorded on the electronic case report form (eCRF) including all prescription, over-the-counter, herbal supplements and IV medications and fluids.

3.2.3.4 Prohibited and/or Restricted Therapies

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

- Antineoplastic systemic chemotherapy or biological therapy
- Investigational agents other than APX005M
- Radiation therapy not specified in this protocol (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, intranasal influenza vaccines and typhoid (oral) vaccine. Seasonal influenza vaccines for injection and COVID-19 vaccines are allowed as long as they can be administered 6–7 days after last dose of APX005M.
- 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 will be discontinued from study treatment.

Herbal medicine for anticancer treatment (such as botanical formulation 'Xiao Chai Hu Tang') should be stopped 1 week prior to first dose of APX005M. 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 Period.

3.2.4 Retreatment Criteria

Subjects that do not meet any of the criteria for treatment discontinuation may start a new cycle of APX005M ± SBRT as scheduled if WBC ≥2,000/mm^3, ANC≥1,000/mm^3, platelets ≥100,000/mm^3, and suspected adverse reactions have 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.

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

3.2.5 Dose Modifications

Management of suspected adverse drug reactions may require reduction of the APX005M dose or interruptions of the radiotherapy. If a subject experiences several toxicities, the recommended dose adjustment should be based on the highest grade toxicity. All dose reductions for APX005M, if required, will follow the instructions described in Table 3.

Table 3: Dose Modifications for Toxicity

	Action Taken with APX005M			**Action Taken with SBRT**
	1st Occurrence	**2nd Occurrence**	**3rd Occurrence**	
Hematologic Toxicity				
Neutrophils (ANC) <500/mm^3 Lasting ≥5 days	Reduce to 0.2 mg/kg	Reduce to 0.1 mg/kg	Discontinue	Defer to radiation oncologist*
Neutropenic Fever (Body Temperature ≥38.5ºC (oral) and ANC <1000/mm^3)	Reduce to 0.2 mg/kg	Reduce to 0.1 mg/kg	Discontinue	Defer to radiation oncologist*
Platelets <25,000/mm^3	Reduce to 0.2 mg/kg	Reduce to 0.1 mg/kg	Discontinue	Defer to radiation oncologist*
Platelets <50,000/mm^3 with Significant Bleeding or Requiring Blood Transfusion	Reduce to 0.2 mg/kg	Reduce to 0.1 mg/kg	Discontinue	Defer to radiation oncologist*
Non-hematologic Toxicities				
Nausea/Vomiting ≥ Grade 3 Despite Optimal Medical Treatment	Reduce to 0.2 mg/kg	Reduce to 0.1 mg/kg	Discontinue	Hold treatment until symptoms improve to Grade ≤1
Diarrhea ≥ Grade 3 Despite Optimal Medical Treatment	Reduce to 0.2 mg/kg	Reduce to 0.1 mg/kg	Discontinue	Hold treatment until symptoms improve to Grade ≤1
CRS Grade 3 ≤7 days	Reduce to 0.2 mg/kg	Reduce to 0.1 mg/kg	Discontinue	Defer to radiation oncologist*
CRS Grade 3 >7 days	Discontinue	-	-	Discontinue
CRS Grade 4	Discontinue	-	-	Discontinue
Increased Bilirubin Grade ≥ 3	Discontinue	-	-	Discontinue

	Action Taken with APX005M			Action Taken with SBRT
	1st Occurrence	2nd Occurrence	3rd Occurrence	
Increased AST, ALT Grade 3	Reduce to 0.2 mg/kg#	Reduce to 0.1 mg/kg#	Discontinue	Hold treatment until Grade ≤1
Increased AST, ALT Grade 4	Discontinue	-	-	Discontinue
Pneumonitis Grade 2	Reduce to 0.2 mg/kg	Reduce to 0.1 mg/kg	Discontinue	Hold treatment until Grade ≤1. Discontinue on 2nd occurrence
Pneumonitis Grade ≥3	Discontinue	-	-	Discontinue
Esophagitis Grade 2	Reduce to 0.2 mg/kg	Reduce to 0.1 mg/kg	Discontinue	Hold treatment until Grade ≤1
Esophagitis Grade ≥3	Discontinue	-	-	Discontinue
Gastric or Small Bowel Ulcer Grade ≥2	Reduce to 0.2 mg/kg	Reduce to 0.1 mg/kg	Discontinue	Discontinue
Colitis or Proctitis Grade ≥3	Discontinue	-	-	Discontinue
Other ≥3 Grade Toxicities (except Alopecia)§	Adjusted as medically indicated after discussion with Sponsor			Defer to radiation oncologist*

Abbreviations: CRS = cytokine release syndrome

For all toxicity ≤Grade 2, the current dose should be maintained

* Investigator will defer to the radiation oncologist as to whether an interruption of the radiation therapy is also indicated.

\# For subjects with liver metastasis reduce dose only if Grade 3 >72 hours

§ In the event of the "other" Grade 3 or 4 non-hematologic toxicities that, in the opinion of the Investigator, are unrelated to the investigational therapy, subject may continue on therapy with or without dose reduction only after documented discussion with the Apexigen Medical Monitor (or designee).

3.2.6 Duration of Treatment

Subjects may continue to receive SBRT and APX005M up to 16 weeks and APX005M for up to 12 months or until any of the criteria in Section 3.2.6.1 are met.

Tumor assessment will be performed within 21 days prior to start of investigational therapy and during the Treatment Period (every 8 ± 1 weeks). Tumor assessments will follow RECIST 1.1 guidelines.

Subjects with confirmed CR may continue APX005M up to 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.

3.2.6.1 Discontinuation of Subjects from Treatment

Subjects MUST discontinue receiving APX005M for any of the following reasons:

- Disease progression by RECIST 1.1, or disease progression following treatment beyond progression (Section 3.2.6.2)
- Death
- Toxicity requiring discontinuation of investigational therapy(ies) as outlined in the dose modification guidelines
- Failure to recover from a disease or treatment-related AE to baseline or ≤ Grade 1 within 12 weeks of last dose of APX005M (except Grade 2 alopecia, Grade 2 fatigue or Grade 2 skin toxicity), unless the subject is benefiting from therapy and after discussion with and approval by Apexigen Medical Monitor (or designee)
- Failure to recover from an AE related to infusion reaction/cytokine release within 4 weeks of last dose of APX005M
- Inability to reduce corticosteroid to ≤10 mg of prednisone or equivalent per day within 12 weeks of last dose of APX005M
- Subject's decision to withdraw for any reason from study treatment (if subject withdraws from study treatment the subject should enter the Follow-up Period)
- 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

Apexigen (or designee) must be notified within 24 hours if a subject is withdrawn from treatment. The primary reason for treatment discontinuation will be documented in the eCRF.

3.2.6.2 Treatment beyond Progression

Accumulating evidence indicates that patients with solid tumors treated with immunotherapy or the combination of immunotherapy with RT 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 (iUPD, [iRECIST]) 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 (Section 3.2.4)
- Subject tolerates study treatment
- Subject has stable ECOG performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS 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 should 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 should be performed continuously, including tumor assessments (Section 4).

Subjects will be discontinued from the treatment upon further evidence of disease progression, as described in the iRECIST guidelines by Seymour et al [22].

3.3 Follow-up Period

Subjects who discontinue APX005M will enter the Follow-up Period until criteria in Section 3.3.1 are met. Regular follow-up visits (or phone contact or chart reviews) should be scheduled every 3 months or more frequently if clinically indicated.

All AEs that are considered related to APX005M must be followed to resolution, stabilization, until improvement is not expected, 30 days after receiving the last dose of APX005M, death, or initiation of new anticancer therapy, whichever occurs first. Serious AEs (SAEs), pregnancies and AEs with potential immunologic etiology will be recorded and followed up to 90 days after the last dose of APX005M, death, or initiation of new anticancer therapy, whichever occurs first.

3.3.1 Discontinuation of Subjects from Study

Subjects who are withdrawn from APX005M will enter the Follow-up Period unless study treatment discontinuation is due to any of the following:

- Subject death
- Withdrawal of consent for all study procedures
- Initiation of any anticancer therapy (except for subjects continuing immediately following this study on a PD-1/PD-L1 containing regimen for whom the regimen and the response to that regimen should be documented)
- Subject is lost to follow-up
- Study termination by Apexigen.

Subsequent anticancer regimen should be documented. For subjects, who switch to a PD-1/PD-L1 containing regimen immediately after study treatment the response to that regimen should be documented. Once this information is collected, a subject is considered off-study.

3.3.2 Subject Premature Withdrawal

Any subject has the right to withdraw consent or to discontinue study treatment or study participation at any time for any reason.

In the case that a subject decides to prematurely discontinue study treatment ("refuses treatment"), he/she should be asked if he/she agrees to continue to be followed-up until criteria for discontinuation from study are met (enter Follow-up Period).

3.4 Study Termination

Apexigen has the right to terminate this study or a study site from participating in the 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 completed the Treatment Period
- All subjects enrolled in the study have completed the Follow-up Period.

4. STUDY ASSESSMENTS AND PROCEDURES

Time and events schedule is presented in Appendix A.

4.1 Procedures by Visits

4.1.1 Screening Period

All patients must provide written informed consent before any study specific assessments or procedures are performed.

The screening assessments should be performed within 21 days before beginning of the Treatment Period. The following study evaluations will be performed during the screening period:

- Collect demographics
- Collect medical history (including concomitant medications)
- Perform physical examination including (including weight, height, and vital signs) and a 12-lead electrocardiogram
- ECOG performance status
- Laboratory evaluations:
  1) urinalysis
  2) serum chemistry
  3) hematology
  4) coagulation
- Assess eligibility (inclusion/exclusion criteria)
- Tumor assessment following RECIST 1.1 Guidelines
- Collect archived tumor tissue
- Collect and submit a tumor core biopsy from consenting subjects. Selection of tumor lesions should not interfere with subsequent tumor assessments when feasible
- For Cohort 3: SBRT treatment planning
- Pregnancy test (if applicable)

4.1.2 Treatment Period

The following procedures and investigations should be performed during the Treatment Period:

4.1.2.1 Cycles 1 & 2: Day 1

- Confirm eligibility (only in Cycle 1)
- Perform physical examination (including weight and vital signs at preinfusion, end of infusion, 4 hours after the end of infusion)
- ECOG performance status
- Laboratory evaluations:
  1) Serum chemistry
  2) Hematology
  3) Coagulation
- PK serum sample (preinfusion, end of infusion, 4 hours ± 30 minutes after the end of infusion)
- ADA serum sample (preinfusion)
- Whole blood and plasma (preinfusion)

- Cytokines plasma samples (preinfusion, end of infusion, 4 hours ± 30 minutes after the end of infusion)
- Record AEs and concomitant medications (ConMeds)
- For Cohort 3: administer SBRT
- Administer premedication before APX005M
- Administer APX005M

4.1.2.2 Cycles 1 & 2: Day 2

- Collect vital signs
- Laboratory evaluations:
  1) Serum chemistry
  2) Hematology
  3) Coagulation
- PK serum sample (24 ± 2 hours after the end of infusion)
- Whole blood and plasma (24 ± 2 hours after the end of infusion)
- Cytokines plasma sample (24 ± 2 hours after the end of infusion)
- Record AEs and ConMeds

4.1.2.3 Cycles 1 & 2: Day 8

- Collect vital signs
- Laboratory evaluations:
  1) Serum chemistry
  2) Hematology
  3) Coagulation
- Whole blood and plasma (168 ± 2 hours after the end of infusion)
- Cytokines plasma sample (168 ± 2 hours after the end of infusion)
- Record AEs and ConMeds

4.1.2.4 Cycles 3+ Day 1

- Perform physical examination (including weight and vital signs at preinfusion, end of infusion)
- ECOG performance status
- Laboratory evaluations:

1) Serum chemistry
2) Hematology
3) Coagulation
4) Pregnancy test every other cycle (if applicable)

- PK serum sample in Cycles 3 and 5 (preinfusion, end of infusion)
- ADA serum sample in Cycles 3 and 5 (preinfusion)
- Whole blood and plasma -- Cohort 1: Cycles 3 and 6 (preinfusion); Cohorts 2 and 3: Cycles 4 and 8 (preinfusion)
- Record AEs and ConMeds
- For Cohort 3: administer SBRT for up to 8 cycles
- Administer premedication before APX005M
- Administer APX005M

4.1.2.5 Cycles 3+ Optional Safety Visit

- Collect vital signs
- Laboratory evaluations:
  1) Serum chemistry
  2) Hematology
- Record AEs and ConMeds

4.1.2.6 Tumor Assessment Visit

- Tumor Assessment

4.1.2.7 Second Tumor Biopsy Visit

- Laboratory evaluations:
  1) Serum chemistry
  2) Hematology
- Record AEs and ConMeds
- Whole blood and plasma
- Cytokines plasma sample
- Collect fresh tumor tissue sample

4.1.2.8 End of Treatment Visit

- Perform physical examination (including weight and vital signs)
- ECOG performance status
- Laboratory evaluations:
  1) Serum chemistry
  2) Hematology
  3) Coagulation
  4) Pregnancy test (if applicable)
- ADA serum sample
- Whole blood and plasma
- Cytokines plasma sample
- Record AEs and ConMeds
- Tumor assessment (for subjects that discontinue treatment before the first scheduled on study tumor assessment)

4.1.3 Follow-up Period

- Follow-up AEs related to APX005M until resolution, stabilization, until improvement is not expected, 30 days, death, or initiation of new anticancer therapy, whichever occurs first
- Record SAEs, pregnancies and AEs with potential immunologic etiology up to 90 days, death, or initiation of new anticancer therapy, whichever occurs first. Follow-up SAEs, pregnancies and AEs with potential immunologic etiology until resolution, stabilization, until improvement is not expected, 90 days from APX005M, death, or initiation of new anticancer therapy, whichever occurs first
- Record ConMeds
- Report date of death or progressive disease
- Record subsequent treatment and date
- For subjects continuing immediately following this study on a PD-1/PD-L1 containing regimen, the regimen and the response to that regimen should be documented.

4.2 Safety Assessments

4.2.1 Medical History

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

4.2.2 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.

4.2.3 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.

4.2.4 Vital Signs

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

- within 30 minutes prior to APX005M dose (pre-infusion)
- within 30 minutes after the end of the APX005M infusion
- 4 hours (±30 minutes) after the end of APX005M infusion (Cycles 1 and 2 only)
- 24 hours and 168h after the end of APX005M infusion (Cycles 1 and 2 only)
- On Day 1 of subsequent cycles (preinfusion, end of infusion)
- As medically indicated
- End of treatment visit

4.2.5 ECOG Performance Status

ECOG performance status should be assessed a time points indicated in Appendix A.

Table 4: ECOG Performance Criteria

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

It is recommended, where possible, that a patient's performance status will be assessed by the same person throughout the study.

4.2.6 Laboratory Tests

All clinical laboratory tests (e.g., urinalysis, serum chemistry, hematology, coagulation) will be performed at local laboratories. Assessments performed within 3 days (with results available) prior to the administration of study treatment could be used for Day 1 of any cycle.

4.2.6.1 Urinalysis

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

4.2.6.2 Serum Chemistry

The laboratory tests included in the full chemistry panel are:

- Albumin
- Alkaline phosphatase
- Bicarbonate
- Blood urea nitrogen
- Calcium
- Chloride
- Creatinine
- Creatinine clearance (calculated or measured)
- Glucose
- Lactate dehydrogenase
- Magnesium
- Phosphorous
- Potassium
- SGOT/AST
- SGPTALT
- Sodium
- Total bilirubin
- Total protein
- Uric acid
- 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

4.2.6.3 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.

4.2.6.4 Pregnancy Test

For WOCBP, a pregnancy test is required for eligibility determination and should be performed at the local laboratory. A WOCBP as a sexually mature woman who:

- has not undergone a hysterectomy or bilateral oophorectomy, or
- 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 prior to first dose of investigational therapy(ies), or a serum pregnancy test will be done within 3 days prior to first dose of investigational therapy(ies). Pregnancy testing should be conducted every other cycle and at the End of Treatment Visit. More frequent pregnancy tests may be conducted if required per local regulations.

4.3 Efficacy Assessments

Tumor assessment will be performed within 21 days prior to start of investigational therapy and during the Treatment Period (every 8 ± 1 week). Subject that discontinue treatment before the first scheduled on study tumor assessment (8 weeks following the first dose of APX005M) should have the tumor response evaluated at the end of treatment visit. Tumor assessments will follow RECIST 1.1 guidelines. Complete or partial responses should be confirmed at a subsequent time point 4 weeks later.

Subjects enrolled in Cohort 3 are required to have a minimum of 3 measurable target lesions. The lesions which are the first and second radiation therapy targets should be recorded.

4.3.1 Collection of Tumor Assessment Images

Copies of all diagnostic and post-treatment tumor assessment images may be collected and may be used to confirm disease responses.

4.3.2 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 [22]) will be used to assess tumor response for all treated subjects.

Subjects with RECIST 1.1-defined PD (iUPD [iRECIST]) 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 3.2.6.2 and they do not have confirmed PD as defined by iRECIST. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

4.4 Correlative Studies

Correlative laboratory samples will be obtained in relation to the APX005M infusion. End of infusion sample should be collected within the 10 minutes after the completion of the infusion (before flush). Other post infusion time points in the within the first 24 hours are ± 30 minutes. A ± 2 hours window is allowed for the 24 hours and 168-hour time point. If samples cannot be collected within the protocol-specified window they should be collected as soon as practicable.

4.4.1 APX005M Pharmacokinetic Assessments

Serum samples for pharmacokinetics (PK) will be obtained from all subjects in Cycles 1 and 2 Day 1 (preinfusion, end of infusion, 4 hours ± 30 min after end of infusion), Day 2 (24 ± 2 hours after the end of infusion), and in Cycles 3 and 5 Day 1 (preinfusion, end of infusion).

4.4.2 APX005M Anti-drug Antibodies

Serum samples will be collected for anti-drug antibody (ADA) analysis in Cycles 1, 2, 3 and 5 Day 1 (preinfusion) and at the EOT Visit.

4.4.3 Blood and Tumor Biomarkers

Whole blood and plasma will be collected from all participating subjects in Cycles 1 and 2 (Day 1 [preinfusion], Day 2 [24 ± 2 hours]) and Day 8 [168 ± 2 hours]), Cycles 3 and 6 Day 1 (preinfusion) for subjects in Cohort 1, Cycles 4 and 8 Day 1 (preinfusion) for subjects in Cohorts 2 and 3, time of 2nd tumor core biopsy (if applicable; see below) and at the EOT visit. Submission of archived formalin-fixed paraffin embedded tumor tissue or 15 unstained slides is mandatory. Tissues may be from the primary tumor, or a metastatic site (or site of local

recurrence or advancement) if the primary tumor is unavailable, or if possible, from both primary tumor and a metastatic site.

Subjects who enter Screening Period will be asked to consent to collection of paired fresh tumor tissue whenever possible. Up to 18 subjects (6 subjects within each cohort) should consent to fresh core biopsies.

Fresh tumor core biopsies will be collected from consenting subjects prior to the first dose of APX005M and prior to first scheduled tumor assessment (at approximately 8 weeks from first dose of APX005M).

For sampling procedures, storage conditions and shipment instructions, see the study Laboratory Manual.

Markers of inflammation, angiogenesis, tumor biology, tumor necrosis, vascularity, cell turnover, and expression of molecules in gene families and their signaling pathway molecules may be assessed in tissue and blood samples.

These data will also be used to derive new hypotheses about mechanisms of drug response, resistance, and safety.

4.4.4 Cytokines

Plasma samples for cytokine analysis will be obtained from all subjects in Cycles 1 and 2 Day 1 (preinfusion, end of infusion, 4 hour ± 30 min after end of infusion), Day 2 (24 ± 2 hours) and Day 8 (168 ± 2 hours) time of 2nd tumor core biopsy (if applicable; see below), and at EOT visit.

5. ADVERSE EVENTS

5.1 Definitions

The AE definitions and reporting procedures provided in this protocol comply with current 21 Code of Federal Regulations Part 312.32. The Apexigen Medical Monitor (or designee) must promptly review all information relevant to the safety of APX005M received from any source. The investigator or appropriately qualified designee (e.g., a certified nurse practitioner or physician's assistant) will carefully monitor each subject throughout the study for possible AEs, the designee must be properly listed on the Form FDA 1572.

5.1.1 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. Abnormal laboratory findings should be reported as AEs only if they are clinically relevant.

5.1.2 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.

5.1.3 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.

5.1.4 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.

5.1.5 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.

5.1.6 Overdose

For this trial, an overdose will be defined as a dose of APX005M that is >1 mg/kg body weight.

It is expected that an overdose of APX005M will be associated with severe cytokine release syndrome. 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).

5.2 Adverse Event Classification

5.2.1 Relationship to Investigational Therapy(ies)

The Investigator will assign attribution of the possible association of the event with use of the investigational therapy(ies) (APX005M and/or radiation), and this information will be entered into electronic data capture (EDC) system using the classification system listed below:

Related to Investigational Therapy(ies)

The event is suspected to be related if:

- There is a clinically plausible time sequence between the AE onset and administration of investigational therapy(ies)
- There is a biologically plausible mechanism for the investigational therapy(ies) to cause or contribute to the AE
- The event improves or diminishes upon temporary interruption of the investigational therapy(ies) 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 Therapy(ies)

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 therapy(ies)
- The event is not related to the investigational therapy(ies)

5.2.2 Severity

AE will be reported at the highest grade experienced. 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 5 should be used.

Table 5: Toxicity Grading for AEs Not Covered in NCI-CTCAE (Version 4.03)

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

Semi-colon indicates "or" within the description
Abbreviations: ADL = activities of daily living.
* 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.

5.3 AE Collection and Reporting

5.3.1 General AE Reporting

All AEs will be collected from the time the subject receives any investigational therapy(ies) through 30 days after receiving the last dose of investigational therapy(ies), death, or initiation of new anticancer therapy, whichever occurs first. SAEs, pregnancies and AEs with potential immunologic etiology will be recorded up to 90 days after the last dose of investigational therapy(ies), death, or initiation of new anticancer therapy, whichever occurs first. 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 therapy(ies).

Events that occur after the subject signs the informed consent but prior to the first dose of APX005M will be recorded as past medical history; events that start after the first dose of APX005M will be recorded as AEs.

All AEs must be promptly documented on the AE eCRF. The minimum information required for each AE includes event, duration (start and end dates), severity, seriousness, relationship to iAPX005M, 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 (See Section 5.3.3) and Cytokine Release Syndrome (See Section 5.3.3).

All AEs that are considered related to APX005M must be followed to resolution, stabilization, until improvement is not expected, 30 days after receiving the last dose of APX005M, death, or

initiation of new anticancer therapy, whichever occurs first. SSAR will be followed until resolution, stabilization, 90 days or until resolution is not anticipated.

AE will be reported at the highest grade experienced. AEs which completely resolve and then recur will be recorded as a new AE. All AEs that are considered related to investigational therapy(ies) must be followed to resolution, stabilization, until improvement is not expected, 30 days after receiving the last dose of investigational therapy(ies), 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 therapy(ies) 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 sub-investigators and must ensure that these sub- investigators are qualified to perform these duties under the supervision of the Investigator and that they are listed on the FDA Form 1572.

5.3.2 Intermittent Adverse Events

AEs which completely resolve and then recur will be recorded as a new AE.

5.3.3 Reporting Symptoms Versus Syndromes

The constellation of symptoms that comprise an APX005M infusion related reaction or cytokine release syndrome has not been completely defined, so it is important that all symptoms be reported and not just the all-inclusive event of infusion-related reaction or cytokine release syndrome. All AEs and the overall syndrome will be graded in accordance with NCI-CTCAE criteria.

5.3.4 Disease Progression

Progression of underlying malignancy is not reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST, or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the Investigator may elect not to perform further disease

assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

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 APX005M. 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.

5.3.5 Reporting Serious AEs

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: DrugSafety010@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). Apexigen (or designee) 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.

Apexigen (or designee) 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.

5.3.6 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.

5.3.7 Non-Serious AEs

The collection of AE information begins after subject's written consent to participate in the study. AEs should be followed to resolution, stabilization, a minimum of 30 days after the last dose of APX005M or reported as SAEs if they become serious.

5.3.8 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 APX005M discontinued, delayed, or interrupted
- Require the subject to receive specific corrective therapy
- Are clinically significant
- Meet the definition of an SAE/SSAR.

5.4 Pregnancy

Subjects will be instructed to notify the investigator as soon as possible after becoming pregnant (or suspecting pregnancy) or learning of the pregnancy or suspected pregnancy of a partner. If a subject or partner of a subject becomes pregnant during treatment or up to 90 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 therapy(ies), the investigational therapy(ies) will be permanently discontinued. Exceptions to the investigational therapy(ies) discontinuation may be considered for life-threatening conditions only after consultation with the Apexigen Medical Monitor (or designee). 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.

6. STATISTICS

6.1 Sample Size Determination

This is an exploratory Phase 2 study. Cohorts 1 and 2 will enroll 11 subjects each. Assuming a true response rate of about 18.2% (2 subjects with tumor response out of 11 subjects) in each of these cohorts, the estimated standard error of the response rate in each of these cohorts will be 11.6%. Cohort 3 will enroll 18 subjects. Assuming a true response rate in this cohort of about 16.7% (3 responders out of 18 patients) the estimated standard error will be 8.8%.

6.2 Populations for Analyses

Analysis Population	Description
Safety	All subjects receiving any APX005M
Efficacy Evaluable	All who have at least one on treatment (post baseline) tumor assessment

6.3 Endpoint Definitions

Endpoint	Description
Primary	• ORR (rate of CR and PR) by RECIST 1.1 in each cohort
Secondary	• Incidence and severity of AEs and specific laboratory abnormalities graded according to NCI-CTCAE, v4.03 • Changes from baseline of vital signs and clinical laboratory results during and following investigational therapy(ies) administration • ORR (rate of CR and PR) by iRECIST in each cohort • DOR (by RECIST 1.1) by cohort, defined as the time from the first evidence of confirmed PR or better to disease progression or death due to any cause • DOR (by iRECIST) by cohort, defined as the time from the first evidence of confirmed PR or better to disease progression or death due to any cause
Exploratory	• PFS (by RECIST 1.1) by cohort, defined as time from first dose of investigational therapy(ies) to the earlier of PD or death due to any cause • PFS (by iRECIST) by cohort, defined as time from first dose of investigational therapy(ies) to the earlier of PD or death due to any cause • Association between potential tumor and/or blood biomarkers and antitumor activity and/or resistance to treatment • Presence and titer of anti-APX005M antibodies

6.4 Analyses

6.4.1 Demographics and Baseline Characteristics

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

6.4.2 Safety Analyses

Safety will be assessed by cohort through summaries of AEs, 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.

6.4.3 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 and for each tumor assessment method. Additional details will be provided in the Statistical Analysis Plan.

6.4.4 Exploratory Analyses

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

7. ADMINISTRATIVE SECTION

7.1 Ethics

7.1.1 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:

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

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

7.1.2 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.

7.1.3 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.

7.2 Study Materials

The following study materials will be provided at study start:

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

7.3 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).

7.3.1 APX005M

APX005M study drug packaging will bear a label with the identification required by local law, including the protocol number, drug identification, dosage, and expiry date. The study drug must be stored according to the details on the product label. Local packaging in some countries may be different.

Upon arrival of investigational therapy at the site, site personnel should check the shipment for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the Apexigen (or designee) upon discovery.

7.3.1.1 Assessment of Compliance

Compliance will be assessed by maintaining adequate study drug dispensing records. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator.

The Investigator is responsible for the control of APX005M under investigation. Adequate records for the receipts (e.g. Drug Receipt Record) and disposition (e.g. Drug Dispensing Log) of the study drug must be maintained. Accountability and patient compliance will be assessed by maintaining adequate "drug dispensing" and return records. All records and drug supplies must be available for inspection by the Monitor at every monitoring visit. These records must contain the following information:

- Documentation of drug shipments received from the Sponsor (date received, quantity, and batch numbers).
- Disposition of unused study drug not dispensed for patient.

A Drug Dispensing Log must be kept current and should contain the following information:

- The identification of the patient for whom the study treatment was dispensed.
- The date(s), quantity, and batch numbers of the study treatment dispensed.

This inventory must be available for inspection by the Monitor. All supplies, including partially used or empty containers and copies of the dispensing and inventory logs, must be returned to Apexigen (or designee) at the end of the study, unless alternate destruction has been authorized by Apexigen (or designee), or required by local or institutional regulations (See Pharmacy Manual).

The Pharmacy Manual contains further detailed information about packaging, labeling, storage, dispensing, preparation and administration of APX005M.

7.3.1.2 Destruction of the APX005M Investigational Therapy

Local or institutional regulations may require immediate destruction of used APX005M for safety reasons e.g., cytotoxicity. In these cases, it may be acceptable for investigational site staff to destroy dispensed APX005M before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the Apexigen at study start up before destruction.

Written documentation of destruction must contain the following:

- Identity (batch numbers and patient numbers) of investigational therapy destroyed
- Quantity of investigational therapy destroyed
- Date of destruction (date discarded in designated hazardous container for destruction)
- Method of destruction (the site must provide the Sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)

- Name and signature of responsible person who discarded the investigational therapy in a hazardous container for destruction.

7.4 Confidentiality

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

Subject names will not be supplied to Apexigen. 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 Apexigen, 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.

7.5 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 investigative site 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.

7.6 Data Collection and Handling

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.

7.7 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.

8. 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
AST	Aspartate Aminotransferase
$AUC_{0-\infty}$	Area Under the Curve Extrapolated to Infinity
BRAF	Human Proto-oncogene Encoding B-Raf Protein
CBCT	Cone-beam Computed Tomography
CD40	Cluster of Differentiation 40
CD40L	CD40 Ligand
C_{max}	Maximum Serum Concentration
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CTLA-4	Cytotoxic T-lymphocyte Associated Protein 4
CTV	Clinical Target Volume
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
FOV	Field of Vision
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GTV	Gross Tumor Volume
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

Abbreviation	Definition
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IGRT	Image-guided Radiation Therapy
IMRT	Intensity Modulated Radiotherapy
IND	Investigational New Drug Application
INR	International Normalized Ratio
IRB	Institutional Review Board
iRECIST	Immune-related RECIST
iUPD	iRECIST Unconfirmed Progressive Disease
ISR	IND Safety Report
ITV	Internal Target Volume
IV	Intravenous
K_d	Dissociation Constant
mAb	Monoclonal Antibody
mL	Milliliter
MLC	Multi-leaf Collimator
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MV	Megavolt
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NOAEL	No Observed Adverse Effect Level
OAR	Organ at Risk
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
PDn	Pharmacodynamics
PET	Positron Emission Tomography
PK	Pharmacokinetics
PFS	Progression-free Survival
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PTV	Planning Target Volume
QA	Quality Assurance
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Definition
RT	Radiation Therapy (or radiotherapy)
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SBRT	Stereotactic Body Radiation Therapy
SEP	Subject Eligibility Packet
SSAR	Serious Suspected Adverse Reaction
TNFR	Tumor Necrosis Factor Receptor
ULN	Upper Limit of Normal
VMAT	Volumetric Modulated Arc Therapy
WOCBP	Women of Childbearing Potential

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APPENDIX A: STUDY APX005M-010 SCHEDULE OF EVENTS

		Treatment Period								
		Cycles 1 & 2			Cycle 3+					
	Screening Period	Day 1	Day 2(24h)	Day 8(168h)	Day 1	Optional Visit	Tumor Assmnt	2nd Biopsy	EOT	Follow-up
Eligibility	X	X								
Demographics & Med History	X									
Physical Examination	X	X			X				X	
12-lead ECG	X									
Height	X									
Weight	X	X			X				X	
Vital Signs[1]	X	X	X	X	X	X			X	
ECOG Performance Status	X	X			X				X	
Urinalysis	X									
Serum Chemistry	X	X	X	X	X	X		X	X	
Hematology	X	X	X	X	X	X		X	X	
Coagulation	X	X	X	X	X				X	
Pregnancy Test (if applicable)[2]	X				X				X	
Tumor Assessment[3]	X						X		X	
AEs and ConMeds		X	X	X	X	X		X	X	
SBRT[4]		X			X					
Premedication		X			X					
APX005M Administration[5]		X			X					
PK[6]		X	X		X					
ADA[7]		X			X				X	
Whole Blood and Plasma for Biomarkers[8]		X	X	X	X			X	X	
Cytokines[9]		X	X	X				X	X	
Archived Tumor Tissue Sample[10]	X									
Fresh Tumor Tissue Sample[11]	X							X		
Date of PD and Subsequent Treatment										X

1. Vital signs in Day 1 in Cycles 1 & 2 should be collected preinfusion, at the end of infusion, 4, 24, 168 hours after end of infusion, and as medically indicated. On Day 1 of subsequent cycles, vital signs should be collected preinfusion and at the end of infusion and as medically indicated.
2. Serum pregnancy test will be done within 7 days followed by a urine pregnancy test within 3 days prior to first dose of investigational therapy(ies), or a serum pregnancy test will be done within 3 days prior to first dose of investigational therapy(ies). Pregnancy testing should be conducted every other cycle and at EOT. More frequent pregnancy tests may be conducted if required per local regulations.
3. Tumor assessment will be performed within 21 days prior to start of investigational therapy(ies) and during Treatment Phase every 8 ± 1 weeks. Subjects that discontinue treatment before the first scheduled on study tumor assessment (8 weeks following the first dose of investigational therapy(ies)) should have the tumor response evaluated at the EOT visit.
4. Cohort 3: SBRT will be administered the same day, prior to APX005M administration.
5. APX005M may be administered up to 3 days after the scheduled Day 1 of Cycles 2 and beyond in 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).
6. PK serum samples will be obtained in Cycles 1 and 2 Day 1 (preinfusion, end of infusion, 4 hours ± 30 min after end of infusion) and Day 2 (24 ± 2 hours after the end of infusion), Cycles 3 and 5 Day 1 (preinfusion, end of infusion)
7. ADA serum samples will be collected in Cycles 1, 2, 3, and 5 Day 1 (preinfusion) and at the EOT visit.
8. Whole blood and plasma will be collected from all participating subjects in Cycles 1 and 2 (Day 1 [preinfusion], Day 2 [24 ± 2 hours] and Day 8 [168 ± 2 hours]), Cycles 3 and 6 Day 1 (preinfusion) for subjects in Cohort 1, Cycles 4 and 8 Day 1 (preinfusion) for subjects in Cohorts 2 and 3, time of 2nd tumor core biopsy (if applicable) and at the EOT.
9. Cytokine plasma samples will be obtained in Cycles 1 and 2 Day 1 (preinfusion, end of infusion, 4 hour ± 30 min after end of infusion), Day 2 (24 ± 2 hours) and Day 8 (168 ± 2 hours), time of 2nd tumor biopsy (if applicable) and at EOT.
10. Submission of archived formalin-fixed paraffin embedded tumor tissue or 15 unstained slides is mandatory.
11. Fresh tumor core biopsies will be collected from consenting subjects prior to first dose of investigational therapy(ies) and prior to first scheduled tumor assessment (at approximately 7–8 weeks from first dose of investigational therapy(ies)).

APPENDIX B: VITAL SIGNS AND CORRELATIVE LAB SCHEDULE

	Cycle 1			Cycle 2			Cycle 3	Cycle 4	Cycle 5	Cycle 6+	2nd Bx	EOT
	Day 1	**Day 2**	**Day 8**	**Day 1**	**Day 2**	**Day 8**	**Day 1**	**Day 1**	**Day 1**	**Day 1**		
Vital Signs												X
Preinfusion	X			X			X	X	X	X		
End of Infusion	X			X			X	X	X	X		
4 Hours After the End of Infusion	X			X								
24 Hours After the End of Infusion		X			X							
168 Hours After the End of Infusion			X			X						
Pharmacokinetics (PK)												
Preinfusion	X			X			X		X			
End of Infusion	X			X			X		X			
4 Hours After the End of Infusion	X			X								
24 Hours After the End of Infusion		X			X							
Anti-drug Antibodies (ADA)												X
Preinfusion	X			X			X		X			
Whole Blood and Plasma for Biomarkers	X	X	X	X	X	X	X[a]	X[a]		X[a]	X	X
Cytokines												X
Preinfusion	X			X								
End of Infusion	X			X								
4 Hours After the End of Infusion	X			X								
24 Hours After the End of Infusion		X			X							
168 Hours After the End of Infusion			X			X						

[a] Cycles 3 and 6 Day 1 (preinfusion) for subjects in Cohort 1, Cycles 4 and 8 Day 1 (preinfusion) for subjects in Cohorts 2 and 3.

APPENDIX C: METHODS OF CONTRACEPTION

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