Pivotal

STATISTICAL ANALYSIS PLAN

Study Code: APX005M-010

Protocol Version: Amendment 2

Protocol Date: 28 - December - 2020

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

Investigational Product	Sotigalimab (also known as APX005M)
Indication Studied	Unresectable or metastatic melanoma
EudraCT No	2018-003864-30
Phase of Study	Phase 2
Sponsor (company and address)	Apexigen America, Inc., 75 Shoreway Road, Suite C, San Carlos, CA 94070, U.S.A.

Pages Nº	60
SAP Version	1.0
SAP Date:	27-Oct-2022

Approvals

By signing this document, I acknowledge that I have read the Statistical Analysis Plan and approve of the planned statistical analysis described herein.

I agree that the planned statistical analyses are appropriate for the objective of the study and are consistent with the methodology described in the protocol, clinical development plan.

I also understand that any subsequent changes to the statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

PIVOTAL

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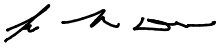

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STATISTICAL ANAYSIS PLAN VERSION

This section details the changes compared to previous version of the statistical analysis plan (SAP).

SAP Version	Date of SAP version	Author	Changes from the previous version
1.0	XX-XXX-XXXX	Elena Santiago	NA

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
APC	Antigen-presenting Cell
AST	Aspartate Aminotransferase
BOR	Best Overall Response
CD40	Cluster of Differentiation 40
CD40L	CD40 Ligand
CR	Complete Response
CRS	Cytokine release syndrome
DCs	Dendritic Cells
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOT	End of Treatment
iBOR	iRECIST Best Overall Response
ICF	Informed Consent Form
iCR	iRECIST Complete Response
iCPD	iRECIST Confirmed Progressive Disease
iPR	iRECIST Partial Response
iRECIST	Immune-related RECIST
iORR	iRECIST Overall Response Rate
iSD	iRECIST Stable disease
iUPD	iRECIST Unconfirmed Progressive Disease
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NK	Natural Killer
ORR	RECIST Overall Response Rate
PD	Progressive Disease/Disease Progression
PD-1	Programmed Death Receptor-1
PD-L1	Programmed Death-ligand 1
PET	Positron Emission Tomography
PK	Pharmacokinetics
PFS	Progression-free Survival
PP	Per protocol
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiation Therapy (or radiotherapy)
SAE	Serious Adverse Event

Abbreviation	Definition
SAF	Safety population
SAP	Statistical Analysis Plan
SBRT	Stereotactic Body Radiation Therapy
SD	Stable disease
SD	Standard deviation (only applicable in statistical results)
SOC	System Organ Class
TEAE	Treatment -emergent adverse event
TNFR	Tumor Necrosis Factor Receptor
ULN	Upper Limit of Normal

2. INTRODUCTION

The Statistical Analysis Plan (SAP) has been written based on the Clinical Protocol Amendment 2 (28 December 2020).

The purpose of this document is to describe the procedures and the statistical methods to be applied in the data analysis and to ensure that the statistical methodologies that will be used are complete and appropriate to the study objectives.

The focus of this SAP is for the planned primary, secondary, and exploratory analysis at the final analysis in the study.

Pivotal will perform the statistical analyses described in the protocol, except for the TFLs associated with the below exploratory objectives:

- 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)

Result of the analyses described in this SAP will be include in the Clinical Study Report (CSR).

2.1 Background & Rationale

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. 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.

Apexigen America, Inc. (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. CD40 is expressed by dendritic cells (DC), B cells, monocytes, and some non-lymphoid cells. 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. 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. Activation of CD40 on tumor cells results in tumor cell apoptosis and inhibition of tumor growth. 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.

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.

In several preclinical models the combination of RT with drugs that activate APCs results in synergistic anti-tumor effects. 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.

2.2 Study Objectives

2.2.1 Primary Objective

- Evaluate the Overall Response Rate (ORR) by RECIST 1.1 in each cohort.

2.2.2 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

2.2.3 Exploratory Objectives

2.2.3.1 Exploratory Objectives included in the protocol

- 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)

Pivotal will not be responsible for TLFs using data from the correlative laboratory samples. The current SAP will not include the analyses about the following endpoints: PK, ADA, the association between PDn markers and PK, and the association between biomarkers and anti-tumor activity. These analyses will be carried out by Apexigen, Inc. or a different provider.

2.2.3.2 Exploratory Objectives not included in the protocol

- Duration of stable disease (SD) in each cohort.

2.2.4 Subgroup Analysis not included in the protocol

2.2.4.1 Steroids during treatment- Subgroup

For subjects receiving steroids, the Best Overall Response (BOR) will be provided. We will consider two scenarios:

- Subjects receiving steroids during treatment. For the first dose, the window should be from screening to 5 days after the first dose - all other cycles should be +/-5 days from the APX005M
- Subjects receiving steroids for the first dose. The window should be from screening to 5 days after the first dose.

2.2.4.2 LDH pre-treatment values- Subgroup

Subjects will be classified according to their presenting Lactate Dehydrogenase (LDH) pre-treatment (screening or/and C1D1) values above the upper normal range vs. below the upper normal range.

- Best Overall Response, ORR and DCR will be presented in a table. (Overall and by cohort)
- PFS will be provided in a table. (Overall and by cohort)

2.2.4.3 LDH pre-treatment values and prior anti-CTLA4 - Subgroup

- Summary of Subjects prior anti-CTLA4 and elevated pre-treatment LDH and BOR.

A table of BOR will be included. For each level of response, the number of subjects who received prior-anti CTLA4, and the number of subjects with elevated pre-treatment LDH.

- The following variables will be provided for each subject in a listing.
  Subject ID, Time on Prior PD1(months), Prior anti-CTLA4 (yes/no), Elevated pre-treatment LDH (>ULN) (yes/no)), Pre-study anti-PD1 to study start (months) and Best Overall Response on Study.

2.3 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 who 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).

Subjects in all 3 cohorts with unconfirmed PD (iUPD, iRECIST) will be permitted to continue treatment as long as they meet the criteria in Section (3.2.6.2 Treatment beyond Progression)

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

They do not have confirmed PD as defined by iRECIST on a repeated tumor assessment 4-8 weeks later.

Study periods:

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

Screening period:

All subjects signing the informed consent form will enter the Screening Period

Treatment period:

Treatment period will start with the administration of 1st dose of APX005M ± SBRT and will continue for up to 12 months or until criteria Section 3.2.6.1 (Discontinuation of subjects from treatment) are met.

Follow-up period:

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 (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 lost to follow-up, death, or study termination by Apexigen.

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.

2.3.1 Eligibility and Randomization

This is an open-label study in three Parallel cohorts and there is no randomization or blinding needed.

2.3.2 Eligibility Criteria

2.3.2.1 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 109/L in absence of growth factor support
   b. ANC ≥1.0 x 109/L in absence of growth factor support
   c. Platelet count ≥100 x 109/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.

2.3.2.2 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
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.

2.3.3 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
- 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

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

2.3.4 Study treatment

2.3.4.1 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.

The APX005M infusion can be interrupted in the case of infusion reaction. 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

Administration of APX005M will continue for up to 12 months or until criteria in Protocol Section 3.2.6.1 (Discontinuation of Subjects from Treatment) are met.

2.3.4.2 Radiation Therapy

All subjects assigned to cohort 3 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.

2.3.4.3 Treatment beyond Progression

Accumulating evidence indicates that subjects 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 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
- 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.

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

2.3.5 Replacement of Subjects

Enrolled subjects assigned to a specific cohort who do not receive APX005M or are not evaluable for tumor response will be replaced in that cohort.

The decision to replace subjects will be made by the Sponsor.

Details of the replaced subjects will be listed in the FSR.

Note: Apexigen decided on 02-Nov-2021 that no more subjects would be replaced.

2.3.6 Follow up

Subjects who discontinue 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.

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.

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.

2.4 Modifications made in the Statistical Analysis Plan

The following modifications have been made to the analyses specified in Protocol Amendment 2 (28 December 2020):

Replacement of subjects:

Apexigen decided that no more subjects would be replaced after 02-Nov-2021.

Efficacy population definition:

The definition of the efficacy population has been updated.

Original definition:

Subjects evaluable for efficacy (tumor response) are defined as those who have at least one on-treatment (post baseline) tumor assessment.

Modified definition:

Subjects evaluable for efficacy (tumor response) are defined as those who have measurable disease and at least one evaluable (post-baseline) tumor assessment performed during the treatment period or within 30 days after the administration of the last dose of treatment.

> **Note:**
>
> If "Death" or "Clinical Progression" without confirmation has been reported as the end of treatment reason before the first scheduled tumor assessment (first tumor assessment will be evaluated approximately 8 ± 1 week following the first dose of APX005M.), the subject will be included in this population.
>
> Response for these subjects will be considered Not Evaluable.

Per Protocol Population definition:

The definition of the Per Protocol population has been added for sensitivity analysis.

Enrolled Population definition:

The definition of the Enrolled population has been added.

Disease control rate:

This variable is not included in the analysis within the protocol, it has been defined in the SAP and will be shown in the tables

Duration of Response and PFS

In addition to RECIST progressions and deaths, the clinical progressions have been considered an event in these analyses.

Exploratory analysis

The duration of Stable disease will be provided as exploratory analysis.

Subgroup analysis

Some subgroups analyses have been added.

- Steroids received during treatment.
- LDH pre-treatment values above the upper normal range vs. below upper normal range
- Elevated pre-treatment LDH and prior CTLA4

3. ANALYSIS POPULATIONS

The following analysis populations are described in the study protocol.

3.1 Efficacy population

Subjects evaluable for efficacy (tumor response) are defined as those who have measurable disease and at least one evaluable (post-baseline) tumor assessment performed during the treatment period or within 30 days after the administration of the last dose of treatment.

Note:

If “Death” or “Clinical Progression” without confirmation has been reported as the end of treatment reason before the first scheduled tumor assessment (first tumor assessment will be evaluated approximately 8 ± 1 week following the first dose of APX005M.), the subject will be included in this population.

These subjects will be considered not evaluable for the response.

3.2 Safety Population (SAF)

All subjects receiving any APX005M will be included in the safety population. The subjects will be analyzed in the received treatment group.

3.3 Other analysis sets

3.3.1 Screening population

The Screened population is defined as all screened subjects, including screening failures, who are in the database. A list will be included.

3.3.2 Screening Failure population

The Screening Failure population is defined as all Screened Failure subjects. A list will be included, with the number of subject and why it is considered a screening failure.

3.3.3 Enrolled (Intent-to-treat) population

The enrolled population is defined as all screened subjects that are assigned to a cohort.

3.3.4 Per Protocol population (PP)

The Per Protocol population (PP) is defined as all the subjects of the efficacy population who do not meet one or more of the following criteria that will potentially impact the primary efficacy objective:

- Deviations for the inclusion or exclusion criterion.
- Use of prohibited and/or restricted therapies.
- Patients who have clinical progression without any evidence of pathological or imaging data.

To assess the deviations that may result in the exclusion of subjects from the Per Protocol population, these will be reviewed and approved by the sponsor before database lock for analysis.

The Per Protocol population will be used for sensitivity analysis of the efficacy endpoints and will be considered supportive.

Table 1 Analysis population

	Efficacy	SAF	PP
DEMOGRAPHIC CHARACTERISTICS			
-Baseline characteristics	x	x	x
-Previous treatment	x		
EFFICACY (Primary & secondary endpoints)			
Primary endpoint: -ORR by RECIST in each cohort	x		x
Secondary endpoints: -Evaluate ORR by modified RECIST 1.1 for immune-based therapeutics (iRECIST) in each cohort -Evaluate median duration of response (DOR) by RECIST in each cohort	x		
SAFETY			
Secondary objective: -Evaluate the safety of APX005M alone or in combination with radiation therapy in each cohort -Treatment exposure		x	

	Efficacy	SAF	PP
Exploratory endpoints			
- PFS (by RECIST 1.1 and iRECIST) by cohort - Duration of stable disease by cohort.	x		
Subgroup analysis			
- Subjects receiving steroids during treatment period by cohort. - LDH pre-treatment values above the upper normal range vs. below upper normal range overall and by cohort - Elevated pre-treatment LDH and prior CTLA4 overall and by cohort	x		

4. STUDY ENDPOINTS AND DERIVED VARIABLES DEFINITION

4.1 General considerations

The following time unit conversion factors will be applied to convert days into weeks, months, or years

Table 2 Time unit conversion factors

1 week	7 days
1 month	30.4375 days
1 year	365.25 days

Study day: The date on which the first dose of APX005M is administered is considered as Day 1 of the study.

For the events occurring on or after this day, the study day is calculated as the event date minus the date of the first administration of APX005M plus 1 day.

For the events occurring before the start of treatment, study day is calculated as the event date minus the date of the first administration of APX005M.

Baseline: is define as the last non-missing value before treatment.

On treatment period is defined as the time elapsed (in months) from the first dose of APX005M and the date of End of Treatment reported at the End of Treatment form.

Follow up period is defined as the time elapsed (in months) from the date of the End of Treatment reported at the End of Treatment form and the date of the End of the Study reported at the End of the Study form.

4.2 Baseline and Demographics Characteristics

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

Age:

Is defined as the time elapsed (in years) between the birth date and the informed consent date. This variable is a derived variable that appears in the demographics form.

Previous diagnosis before the diagnosis of metastatic or advanced disease (Yes/No):

If the date of the first positive biopsy for the disease is before the diagnosis date of advanced or metastatic disease the subjects will be classified as subjects with previous diagnosis before the diagnosis of metastatic or advanced disease.

Note:

If the difference between these dates is less than or equal to one month, the subject will be classified as first diagnosed metastatic or advanced disease.

Time from the first diagnosis to the diagnosis of advanced or metastatic disease:

Is defined as the time elapsed (in months) from the date of the first positive biopsy for this disease to the diagnosis date of advanced or metastatic disease.

Time from the diagnosis of advanced or metastatic disease to informed consent:

Is defined as the time elapsed (in months) from the date of the diagnosis of advanced or metastatic disease to the informed consent date.

Any metastatic sites at study entry (Yes/No)

If the subject has any reported metastases at study entry this variable will take the value 'Yes'.

4.3 Prior and Concomitant medications

Prior medications: are defined as medications that started and stopped before the first dose of any investigational product.

Concomitant medications: are defined as medication (including all prescription, over the counter, herbal supplements, and IV medications and fluids) that continued or started on or after the first dose of any investigational product, up to 30 days after the last dose of investigational product.

4.4 Efficacy Endpoints

For subjects included in Cohort 3, information on the lesions that are radiated will be recorded for follow-up purposes.

These radiated lesions will not be considered in the tumor evaluation of the subjects.

4.4.1 Best Overall Response

4.4.1.1 RECIST confirmed Best Overall Response (BOR)

The confirmed Best Overall Response (BOR) is defined as the best response presented according to RECIST v1.1 from the inclusion in the study to documented disease progression. (Only tumor assessments performed before the end of treatment visit date or within 30 days after the administration of the last dose of treatment will be considered in the assessment of BOR).

Partial and complete responses should be confirmed.

Table 3 Criteria for Best overall confirmation with RECIST 1.1

Overall response at previous time point	Overall response at current time-point	Best Overall Response
CR	CR	CR
CR/PR	PD	SD
PR	CR	PR
PR	PR	PR
SD	Any	SD

Non-evaluable subjects for BOR will be summarized by reason.

Table 4 BOR of NE reasons

BOR of non-evaluable reasons	BOR
No baseline tumor assessment	NE
No post baseline assessment	NE
All post baseline tumor Assessments have overall response NE.	NE
First tumor assessment with overall response as PD reported after 2 or more missing or NE on treatment tumor assessment (16 weeks or more from the first dose of treatment administered.)	NE

Note:

- Best response could be confirmed during the follow up period.
- Clinical progression /deterioration will not be considered as documented disease progression.

4.4.1.2 iRECIST Best Overall Response (iBOR)

The Best Overall Response according to iRECIST (iBOR) is the best response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation.

iUPD will not override a subsequent Best Overall Response of iSD, iPR, or iCR, meaning that iPR or iSD can be assigned, providing that the criteria for iCPD are not met.

4.4.2 Overall Response Rate

4.4.2.1 RECIST Overall Response Rate (ORR) - Primary Objective

The confirmed Overall Response Rate (ORR) is defined as the proportion of subjects having reached a confirmed Complete Response (CR) or Partial Response (PR) by RECIST 1.1, relative to the number of subjects belonging to the analysis population set.

4.4.2.2 iRECIST Overall Response Rate (iORR) - Secondary Objective

The immune Overall Response Rate (iORR) is defined as the proportion of subjects who show as Best Overall Response by iRECIST an immune confirmed Complete Response (iCR) or immune confirmed Partial Response (iPR).

4.4.3 Disease Control Rate

4.4.3.1 RECIST Disease Control Rate (DCR)

The confirmed Disease Control Rate (DCR) is defined as the proportion of subjects having reached a confirmed Complete Response (CR), Partial Response (PR), or Stable Disease (SD) by RECIST 1.1, relative to the number of subjects belonging to the analysis population set.

4.4.3.2 iRECIST Disease Control Rate (iDCR)

The immune Disease Control Rate (iDCR) is defined as the proportion of subjects who show as Best Overall Response by iRECIST an immune confirmed Complete Response (iCR), immune confirmed Partial Response (iPR), or immune SD (iSD).

4.4.4 Duration of Response

4.4.4.1 RECIST Duration of Response (DoR) - Secondary Objective

The Duration of Response (DoR) is defined as the time (in months) from the first evidence of confirmed objective response (CR or PR) to the event or censoring date.

$$\boldsymbol{DoR\ (months)} = \frac{(date\ of\ \text{event or censoring for DoR} - first\ date\ of\ PR\ or\ better) + 1}{30.4375}$$

An event is defined as the first documentation of progression disease (disease progression assessed based on tumor assessment or clinical progression) or death due to any cause, whichever occurs earlier.

The rules for censoring cases are defined as follows:

If a subject is discontinued or lost to follow up before reporting an event will be censored at the date of the last tumor assessment documenting the absence of PD.

Subjects who start other systemic anti-cancer therapy before an event will be censored at the date of the start of this therapy.

Subjects who die or progress during the follow up period after ≥2 consecutive missed from the last tumor assessment visits will be censored at the date of the last tumor assessment before the tumor assessment of progressive disease or death.

The censoring and event date rules for Duration of Response are presented below.

Table 5 Event and censoring dates for DoR analyses

Events scheme:

Scenario	Date of event
Objective progression.	First date at which progression criteria are met.
Death due to any cause.	Date of death.
Non-objective progression but discontinuation of treatment due to clinical progression.	Date the last tumor assessment before the clinical progression (if any). In case of not having any tumor assessment, the date of clinical progression should be considered.

Censoring scheme:

Scenario	Date of censoring
PD after 2 or more missed tumor assessments during the follow up period from the last tumor assessment	Date of the last tumor assessment before the event.
No PD and no Death.	Date of last tumor assessment documenting the absence of PD.

Receive any systemic therapy after treatment discontinuation.	Date of last tumor assessment documenting the absence of PD before starting systemic therapy

DoR analysis will be calculated for subjects with confirmed CR or PR as Best Overall Response.

4.4.5 Progression-Free survival

4.4.5.1 RECIST progression-free survival (PFS)-Exploratory Objective

The Progression-Free Survival (PFS) is defined as the time (in months) from the first administration of APX005M to the event or censoring date.

$$\boldsymbol{PFS\ (months)} = \frac{(\text{date of event or censoring for PFS} - \textit{date of first APX005M dose}) + 1}{30.4375}$$

An event is defined as the first documentation of progression disease (disease progression assessed based on tumor assessment or clinical progression) or death due to any cause, whichever occurs earlier.

The rules for censoring cases are defined as follows:

If a subject is discontinued or lost to follow up before reporting an event will be censored at the date of the last tumor assessment documenting the absence of PD.

Subjects who start other systemic anti-cancer therapy before reporting an event will be censored at the date of the start of this therapy.

Subjects who die or progress during the follow up period after ≥2 consecutive missed from the last tumor assessment visits will be censored at the date of the last tumor assessment before the tumor assessment of progressive disease or death.

The censoring and event date options to be considered for PFS are listed below.

Table 6 Event and censoring dates for PFS analyses

Events scheme:

Scenario	Date of event
Objective progression.	First date at which progression criteria are met.
Death.	Date of death.
Non-objective progression but discontinuation of treatment by clinical progression.	Date the last tumor assessment before the clinical progression (if any). In case of not having any tumor assessment, the date of clinical progression should be considered.

Censoring scheme:

Scenario	Date of censoring
No tumor assessment after the baseline.	Date of the first dose.
PD after 2 or more missed tumor assessments during follow up period.	Date of the last tumor assessment before the event.
No PD and no Death.	Date of last tumor assessment documenting the absence of PD.
Receive any systemic therapy after treatment discontinuation.	Date of last tumor assessment documenting the absence of PD before starting systemic therapy

4.4.5.2 iRECIST progression-free survival (iPFS)-Exploratory Objective

The immune Progression-Free Survival (iPFS) is defined as the time (months) from the first administration of APX005M to the event or censoring date.

$$iPFS\ (months) = \frac{(date\ of\ event\ or\ censoring\ for\ iPFS) - date\ of\ first\ APX005M\ dose) + 1}{30.4375}$$

An event is defined as the first documentation of iCPD, clinical progression, or death due to any cause, whichever occurs earlier.

If subjects have iUPD which is confirmed at the next assessment as iCPD, then iPFS is the time from the first administration of APX005M to the first date of iUPD that is subsequently confirmed.

The rules for censoring cases are defined as follows:

If a subject is discontinued or lost to follow up before reporting an event will be censored at the last tumor assessment documenting the absence of PD.

Subjects who start other systemic anti-cancer therapy before reporting an event will be censored at the date of the start of this therapy.

Subjects who death or progress during the follow up period after ≥2 consecutive missed from the last tumor assessment visits will be censored at the date of the last evaluable tumor assessment before the tumor assessment of progressive disease or death.

The censoring and event date rules for Duration of Response are presented below.

Table 7 Event and censoring dates for iPFS analyses

Events scheme:

Scenario	Date of event
iUPD confirmed at the next assessment.	The first date of iUPD is subsequently confirmed.
If iUPD progression is not confirmed and there is no subsequent iSD, iPR, or iCR. The following scenarios may occur: 1.No further response assessments are done (Subject refusal, protocol noncompliance...). 2.The next timepoint response is iUPD, and iCPD never occurs.	The first date of iUPD is not subsequently confirmed.
Subject with non-objective progression but discontinuation of treatment by clinical progression.	Date of last tumor assessment Date of withdrawal discontinuation of treatment.
Death.	Date of death.

Censoring scheme:

Scenario	Date of censoring
No tumor assessment after the baseline.	Date of the first dose.
iPD after 2 or more missed tumor assessments during follow up period.	Date of the last tumor assessment before the event.
No iPD and no Death.	Date of last tumor assessment documenting the absence of iPD. If last response is iSD with no previous iPD, date of end of treatment.
Receive any systemic therapy after treatment discontinuation.	Date of last tumor assessment documenting the absence of PD before starting systemic therapy

4.5 Safety Endpoints

Safety will be assessed by cohort through summaries of AEs, incidence and severity of AEs, laboratory test results, specific laboratory abnormalities grades according to NCI-CTCAE, ECG, vital signs, APX005M exposure, and premedication prior to APX005M.

4.5.1 Treatment

4.5.1.1 Duration of treatment

The duration of treatment (in weeks) of each subject will be computed as:

$$\boldsymbol{Duration\ of\ treatment(weeks)} = \frac{(date\ of\ last\ dose - date\ of\ first\ dose\ of\ APX005M) + (\ 21\ \text{days (Cohort 1) or 14 days (Cohort2 or Cohort3)})}{7}$$

4.5.1.2 Duration of treatment at starting dose

The duration of treatment (in weeks) at starting dose will be computed as:

$$\boldsymbol{Duration\ of\ treatment\ at\ starting\ dose(weeks)} = \frac{(date\ of\ last\ starting\ dose - date\ of\ first\ dose\ of\ APX005M) + (\ 21\ \text{days (Cohort 1) or 14 days (Cohort2 or Cohort3)})}{7}$$

*Starting dose=0.3 mg/kg

4.5.1.3 Dose intensity (DI)

Dose intensity (DI) is defined as the APX005M dose delivered per time unit and is expressed as mg/kg per week.

The weight registered for each cycle will be used to calculate the administered dose in mg/kg (in case a cycle's weight is missing it will be imputed via the LOCF –last observation carried forward– method).

4.5.1.4 Relative dose intensity (RDI)

Relative dose intensity (RDI) is defined as the ratio of administered dose intensity to planned (reference) dose intensity, expressed as a percentage:

$$\boldsymbol{RDI}\ (\%) = \frac{Delivered\ dose\ intensity}{Target\ Dose\ Intensity} * 100$$

4.5.1.5 Number of cycles

The absolute and relative frequencies of the cycles administered per subject will be described. (Only cycles with doses greater than 0 are taken into account).

4.5.1.6 Dose delay, interruptions, and reduction

Dose delays, interruptions, and reductions per subject and the reasons for these dose modifications will be described by subject. Information on delays and dose reductions reported in the study database will be considered.

4.5.2 Safety

4.5.2.1 Medical history, TEAEs and SAEs

TEAE is an AE occurs after administration of the first dose of the investigational product and through 30 days after the last dose of the investigational product, death, or initiation of new anticancer therapy, whichever occurs first.

SAEs, pregnancies, and TEAEs with potential immunologic etiology will be recorded up to 90 days after the last dose of investigational product, death, or initiation of new anticancer therapy, whichever occurs first. These SAEs / AEs will be considered TEAEs in the safety analysis.

In addition, the investigator should report any AEs that may occur after this period which are assessed to have a reasonable possibility of being associated with investigational therapy(ies). These AEs will be considered TEAEs in the safety analysis.

Notes:

- All AEs occurring after administration of first dose of investigational product will be considered as TEAEs in the analysis.
- If an AE date of onset is incomplete, an imputation rule will be used to classify the AE as treatment-emergent or not. The algorithm for imputing date of onset is provided in the section Handling of Missing Data.

Medical history: 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.

4.5.2.2 Cytokine release syndrome / infusion reaction

Cytokine release syndrome/infusion reactions have been recorded as an adverse event.
In addition, all associated symptoms have been described as adverse events independently.

- For AE terms coded as ‘’Cytokine release syndrome” or “Infusion reaction” it should be selected that it is not a symptom of a ‘’Cytokine release syndrome” or “Infusion reaction”.
- All the symptoms associated with each “Cytokine release syndrome” or “Infusion reaction” should be reported. For these symptoms, it has been indicated that it is a symptom of a “Cytokine release syndrome” or “Infusion reaction”.

4.6 Other Derived Variables

In the case that more derived variables than the ones described in this document are required for the analysis, they will be defined and described in the statistical report.

5. GENERAL STATISTICAL METHODS

5.1 Sample Size

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 subjects) the estimated standard error will be 8.8%.

5.2 Subject´s Disposition

For subject study status, the number and percentage of subjects for each one of the following categories will be presented.

- Screened subjects, including screened failures (the number only)
- Screened-failure subjects (the number only)
- Enrolled subjects (the number only)
- Enrolled and treated subjects
- Subjects in Efficacy Population
- Subjects in Safety Population
- Subjects in Per protocol Population.
- Subjects who discontinued study treatment by primary reason
- Subjects who discontinued study by primary reason

For all categories of subjects, percentages will be calculated using the number of enrolled subjects.
The data for subject disposition, protocol deviation, eligibility, and whether a subject is included in the analysis populations will be listed.
End of treatment and end of study reasons will be displayed in a listing.

5.2.1 Protocol Deviations

All protocol deviations will be collected separately from the clinical database. They will be recorded and categorized by the Pivotal study monitors in Danah, a specific clinical trial management system provided by Pivotal.
A listing of all patients with protocol deviations will be maintained by Pivotal and periodically reviewed by the Sponsor. The Sponsor may upgrade or downgrade the category of the protocol deviation, always based on the approved Deviation Plan.

All protocol deviations will be listed by category and deviation type.
The final list of protocol deviations will be reviewed before the database lock and provided to the biostatistician.

Some major deviations from the protocol that will potentially impact the primary efficacy objective and may lead to the exclusion of a subject from the per protocol population.

5.3 Summary of Statistical Methods

All subjects entered in the database will be included in subject data listings. The listings will be generally sorted by cohort and then Subject ID unless specified otherwise. All relevant subject data will be included in listings.

All applicable data will be summarized by cohort unless specified otherwise. In addition, data will be summarized by visit and/or time-point when appropriate. Unscheduled or repeat assessments will not be included in summary tables but will be included in listings.

Continuous variables will be summarized using the number of observations (n), the number of subjects with non-missing values, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum along with the total number of subjects contributing values.

Descriptive statistics for categorical/qualitative data will include frequency counts and percentages. The total number of subjects in the cohort (N) will be used as the denominator for percent calculations unless stated otherwise in the table footnote.

Time to event distributions (eg, PFS and DoR) will be estimated using the Kaplan-Meier methodology. In these analyses, in addition to the Kaplan-Meier curve, the median, Q1, Q3, and their corresponding CI 90% (if estimable), the number of events and censored cases distribution will be shown.

5.3.1 Demographics, Other Baseline Characteristics and Medication

Listings will also be presented for the demographic characteristics and disease history, respectively.

5.3.1.1 Demographic Characteristics

The following variables for demographics characteristics will be summarized by cohort and overall:

- Gender (Male/ Female)
- Age (years)
- Race (American Indian or Alaska Native Asian/ Black or African American/ Native Hawaiian or other Pacific Islander/ White or Caucasian/Other) and Ethnicity (Hispanic or Latino/Not Hispanic or Latino/Unknown). Only categories with any occurrence will be listed.
- Height (cm) and weight (kg)
- ECOG performance status (0/ 1/ 2/ 3/ 4/ 5). Only categories with any occurrence will be listed.

5.3.1.2 Disease characteristics

The following variables for disease history will be summarized by cohort and overall:

Subjects with disease prior to advance or metastatic disease.
For these subjects:

- Time (months) from the first biopsy of disease and diagnosis date of advanced or metastatic disease.

For all subjects

- Time (months) from diagnosis of advanced or metastatic disease and date of informed consent
- Histology (Superficial spreading malignant melanoma/Nodular malignant melanoma/Lentigo malignant melanoma/Acral lentiginous melanoma/Amelanotic melanoma/Oral/Mucosal/Skin-Limbs (upper)/Skin- Limbs (lower)/Skin- Trunk/Missing). Only categories with any occurrence will be listed.
- Histological grade (G1 – well differentiated/ G2 -moderately differentiated / G3 – poorly differentiated/ G4 -undifferentiated/ GX -grade cannot be assessed or Not Applicable /Missing). Only categories with any occurrence will be listed.
- Metastatic sites at study entry
  Any metastatic sites at study entry? (Yes/No), in case of No a note will be included in the table footnote.
  Subjects with a metastatic lesion at the time of study entry will be shown.
  Specific metastatic sites
  (Bone/ CNS/ Distant Lymph Nodes/ Liver/ Local or Regional Lymph Nodes/ Lung/ Skin or Subcutaneous/ Other)
- Unresectable/metastatic
- PD-L1 Status (Positive/Negative/Unknown)

5.3.1.3 Medical History

Medical history abnormalities will be coded to Medical Dictionary for Regulatory Activities (MedDRA) terms. The version used will be specified in the data display footnote.

The medical history will only be listed but not summarized.

5.3.1.4 Prior Systemic Therapy

A table with the maximum number of prior therapies by cohort will be summarized.

A table with the prior treatment regimen by cohort and by the number of lines will be summarized.

A table with the prior immunotherapy treatment by cohort will be summarized.

A listing will be provided for the Prior Systemic Therapy.

5.3.1.5 Prior Radiation

A listing will be provided for the Prior Radiation.

5.3.1.6 Prior Surgery

A listing will be provided for the Prior Surgery.

5.3.1.7 Prior and Concomitant Medications

Prior and concomitant medications will be listed in the same table but not summarized; a column will be included in the listing to indicate if the medication is prior or concomitant.

The premedication information will be included in the safety analysis.

5.3.1.8 Concomitant Procedures

A listing will be provided for the concomitant procedures performed.

5.3.2 Efficacy Analyses

5.3.2.1 Primary efficacy endpoint (ORR by RECIST 1.1)

The primary efficacy endpoint is **ORR by RECIST 1.1**, as defined in Section 4.4.2, is based on tumor assessments which will be performed by RECIST1.1 at Screening, about every 8 weeks during Treatment Phase.

The point estimate of the ORR will be presented along with an exact two-sided 90% confidence interval (CI) using the exact (Clopper-Pearson) method.

The ORR by RECIST 1.1 will be estimated for each cohort and overall.

In addition, swimmer, spider, and waterfall plots will be provided.

5.3.2.2 Secondary efficacy endpoints:

ORR by iRECIST (and 90% confidence interval by exact distribution) will be estimated for each cohort and overall, as a secondary efficacy objective.

DoR will be estimated for each cohort and each tumor assessment method (by RECIST 1.1 and iRECIST). The DOR will be summarized using the Kaplan Meier method; the median event time (if appropriate) and two-sided 90%CI for the median will be provided.

The by-subject listings will be generated for the detailed tumor assessment, the response assessment by RECIST1.1 and iRECIST, and the derived DoR and PFS.

5.3.2.3 Exploratory efficacy endpoints:

PFS will be summarized using the Kaplan-Meier method; the median event time (if appropriate) and two-sided 90%- CI for the median will be provided. The corresponding Kaplan Meier curve will also be presented.

PFS will be estimated for each cohort and overall either RECIST 1.1 and iRECIST criteria.

Note:

Pivotal will not perform the TFLs associated with the below exploratory objectives:

- Evaluate the association between potential tumor and blood biomarkers and antitumor activity and/or resistance
- Determine the presence and titre of anti-APX005M antibodies (ADA).

5.3.3 Safety Analyses

The population used for safety analyses will be the Safety Population.

Safety of APX005M will be assessed by cohort through summaries of TEAEs, the incidence, and severity of TEAEs, laboratory test results, specific laboratory abnormalities grades according to NCI-CTCAE, ECG, vital signs, APX005M exposure, and premedication administered prior to APX005M.

5.3.3.1 Treatment Exposure and pre-medication

5.3.3.1.1 APX005M

Exposure of the APX005M will be summarized by cohort and overall. The following variables will be summarized:

- Maximum number of cycles started (Mean, SD, Median, Q1, Q3, Min and Max)
- Number of subjects who started the maximum cycle of 1, 2, 3, 4, and so on (number and percentage)
- Duration of treatment (weeks) (Mean, SD, Median, Q1, Q3, Min and Max)

The following variables will be summarized by cohort and overall.

- Number of infusions administered per subject (Mean, SD, Median, Q1, Q3, Min and Max)
- Number of subjects with dose reductions (number and percentage)
- Number of subjects with dose interruptions (number and percentage)
- Number of subjects with dose delivered off schedule (number and percentage)

In addition, the following variables will be summarized in the APX005M exposure table mentioned above.

- Dose intensity (mg/kg/week) (Mean, SD, Median, Q1, Q3, Min and Max)
- Relative dose intensity (%) (Mean, SD, Median, Q1, Q3, Min and Max)

Treatment assignment will be listed by subject, a listing of APX005M infusion information will be provided per subject and cycle.

The maximum number of cycles started, duration of treatment(weeks), and total dose will be listed per subject.

In addition, a separate listing will be provided for the pre-medications prior to the administration of investigational products.

5.3.3.1.2 Radiotherapy

Subjects included in cohort 3 receive treatment with radiotherapy.

- Maximum number of cycles started (Mean, SD, Median, Q1, Q3, Min and Max)
- Number of subjects who started the maximum cycle of 1, 2, 3, 4, and so on (number and percentage)
- Duration of treatment (weeks) (Mean, SD, Median, Q1, Q3, Min and Max)
- Total dose administered. (Mean, SD, Median, Q1, Q3, Min and Max)

In addition, a separate listing will be provided for the date of the session time of session and dose per cycle and subject.

5.3.3.2 Treatment Emergent Adverse Events

All TEAEs will be coded to System Organ Class (SOC) and Preferred Term (PT) using the MedDRA dictionary v24.0. or later.

Related Adverse Events to APX005M: adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with APX005M = Related) reported by the investigator and those of missing or unknown relationship.

Related Adverse Events to Radiotherapy: adverse events with relationship to radiotherapy (as recorded on the AE eCRF page, Relationship with Radiotherapy = Related) reported by the investigator and those of missing or unknown relationship.

Serious Adverse Events (SAE): serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).

Adverse Events Leading to Treatment Discontinuation: adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug withdrawn).

Adverse Events Leading to Death: adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal, as well as AEs of Grade 5).

Immune mediated Adverse Events: immune mediated adverse events (as recorded on the AE eCRF page, Immune mediated adverse event= Yes).

Infusion Reactions and or Cytokine Release Syndrome: are identified based on an AE term coded as 'Cytokine release syndrome' or 'Infusion Reaction'

The constellation of symptoms that comprise an APX005M infusion related reaction or cytokine release syndrome will be described.

The NCI-CTCAE version 4.03 will be used to assess the severity grade of TEAEs.

5.3.3.2.1 TEAEs – Overview

An overall summary table will be provided showing the number of TEAEs, the number, and proportion of subjects who presented:

- Any TEAE.
- Any TEAE grade 3 or higher.
- Any TEAE grade 3.
- Any TEAE grade 4.
- Any TEAE grade 5.

- Any TEAE related to APX005M.
- Any TEAE related to APX005M grade 3 or higher.
- Any TEAE related to APX005M grade 3.
- Any TEAE related to APX005M grade 4.
- Any TEAE related to APX005M grade 5.
- Any TEAE related to APX005M only

- Any TEAE leading to dose reduction (APX005M).

- Any TEAE leading to dose delay (APX005M)
- Any TEAE leading to treatment interruption (APX005M)
- Any TEAE leading to treatment discontinuation (APX005M).

- Any TEAE related to Radiotherapy (applicable to Cohort 3)
- Any TEAE related to Radiotherapy only (applicable to Cohort 3)

- Any TEAE leading to radiation discontinuation (only applicable in Cohort 3)

- Any TEAE Immune Mediated.

- Any TEAE Infusion reaction/ cytokine release syndrome.

- Any Serious TEAE.
- Any Serious TEAE with a fatal outcome.
- Any Serious TEAE related to APX005M.
- Any Serious TEAE related to APX005M with fatal outcome.
- Any Serious TEAE related to APX005M only
- Any Serious TEAE related to Radiotherapy (applicable to Cohort 3)
- Any Serious TEAE related to Radiotherapy only (applicable to Cohort 3)

This information will be presented by cohort and overall.

Separate listings will be produced for:

- TEAEs
- TEAEs excluding events marked as a symptom of CRS/IRR
- Serious TEAEs
- TEAEs leading to APX005M discontinuation
- TEAEs leading to APX0005M delay
- TEAEs leading to APX005M reductions
- TEAEs leading to infusion interruption
- TEAEs with fatal outcome
- TEAEs immune-mediated events
- TEAEs marked as a symptom of CRS / IRR

The listings will be sorted by Subject ID.

5.3.3.2.2 TEAEs.

Treatment Emergent Adverse Events will be summarized in different approaches:

- By worst grade according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTAE version 4.03) per subject, using the latest version of MedDRA as event category.

  When calculating the incidence of TEAEs by grade each subject will only be counted once (corresponding to the maximum toxicity grade), and any repetitions of adverse events will be ignored; the denominator will be the corresponding total Safety population Overall.
- By cohort

  When calculating the incidence of TEAEs by cohort each subject will only be counted once, and any repetitions of adverse events will be ignored; the denominator will be the corresponding total Safety population Overall.

The following tables will be created:

TEAEs: by cohort:

- Incidence of TEAEs will be tabulated by Primary System Organ Class (SOC) and Preferred Term (PT), showing the total incidence of SOC and PT within SOC.
- Incidence of TEAEs will be tabulated by Preferred Term (PT), in order of highest number of subjects.

TEAEs: Worst grade by subject (by cohort):

- Incidence of TEAEs will be tabulated by Primary System Organ Class (SOC), Preferred Term (PT) and maximum CTCAE grade, showing the total incidence of SOC and PT within SOC. A table will be included for each cohort.
- Incidence of TEAEs will be tabulated by Preferred Term (PT) and maximum CTCAE grade, in order of highest number of subjects. A table will be included for each cohort.

TEAEs: Worst grade by subject grade 3 or higher (by cohort):

- Incidence of TEAEs grade 3 or higher will be tabulated by SOC, PT and maximum CTCAE grade, showing the total incidence of SOC and PT within SOC. A table will be included for each cohort.
- Incidence of TEAEs grade 3 or higher will be tabulated by PT and maximum CTCAE grade, in order of highest number of subjects. A table will be included for each cohort.

TEAEs: Worst grade by subject related to APX005M (by cohort):

- Incidence of TEAEs related to APX005M will be tabulated by SOC, PT and maximum CTCAE grade, showing the total incidence of SOC and PT within SOC. A table will be included for each cohort.
- Incidence of TEAEs related to APX005M will be tabulated by PT and maximum CTCAE grade, in order of highest number of subjects. A table will be included for each cohort.

TEAEs: Worst grade by subject related to Radiotherapy (only cohort 3)

- Incidence of TEAEs related to radiotherapy will be tabulated by SOC, PT and maximum CTCAE grade, showing the total incidence of SOC and PT within SOC.
- Incidence of TEAEs related to radiotherapy will be tabulated by PT, and maximum CTCAE grade, in order of highest number of subjects.

TEAEs: Leading to treatment discontinuation (by cohort)

- Incidence of TEAEs leading to treatment discontinuation will be tabulated by SOC and PT and cohort, showing the total incidence of SOC and PT within SOC.
- Incidence of TEAEs leading to treatment discontinuation will be tabulated by PT and cohort in order of highest number of subjects.

TEAEs: Worst grade by subject Immune mediated:

- Incidence of TEAEs immune mediated will be tabulated by SOC, PT and maximum CTCAE grade, showing the total incidence of SOC and PT within SOC.
- Incidence of TEAEs immune mediated will be tabulated by PT and maximum CTCAE grade, in order of highest number of subjects.

TEAEs: Worst grade by subject of symptoms that compromise an APX005M Infusion reaction and/or cytokine release syndrome:

- Incidence of TEAEs considered symptoms that compromise an APX005M infusion reaction and/or cytokine release syndrome will be tabulated by SOC, PT and maximum CTCAE grade, showing the total incidence of SOC and PT within SOC.
- Incidence of TEAEs considered symptoms that compromise an APX005M infusion reaction and/or cytokine release syndrome will be tabulated by PT and maximum CTCAE grade, in order of highest number of subjects.

Serious Adverse events (by cohort):

- Incidence of SAEs will be tabulated by SOC, PT and cohort, showing the total incidence of SOC and PT within SOC.
- Incidence of SAEs will be tabulated by PT and cohort, in order of highest number of subjects.

Serious Adverse events related to APX005M (by cohort):

- Incidence of SAEs related to APX005M will be tabulated by SOC, PT and cohort, showing the total incidence of SOC and PT within SOC.
- Incidence of SAEs related to APX005M will be tabulated by Preferred Term (PT) in order of highest number of subjects.

Adverse events with fatal outcome (by cohort):

- Incidence of TEAEs with fatal outcome will be tabulated by SOC, PT and cohort, showing the total incidence of SOC and PT within SOC.
- Incidence of TEAEs with fatal outcome will be tabulated by Preferred Term (PT) in order of highest number of subjects.

5.3.3.3 Deaths

The primary cause of death will be described for safety population (Death due to disease / Death due to AE / Death, cause unknown / Other).

A listing of deaths will be provided.

5.3.3.4 Clinical Laboratory Evaluation

To evaluate the safety profile the following laboratory tests will be performed locally:

- Serum chemistry
- Hematology
- Coagulation
- Urinalysis
- Pregnancy.

For each quantitative laboratory parameter, the values, and changes from baseline will be summarized (including number, mean, SD, median, Q1, Q3, minimum, and maximum) will be calculated for each visit or study assessment by cohort.

The frequency of subjects with clinically significant abnormal laboratory values will be tabulated for baseline and each scheduled post baseline visit, by cohort and overall.

The shift tables for baseline versus all visits will be presented for all chemistry and hematology laboratory parameters based on categories of below, within and above normal range.

Lab Original results with ND/ NA/ NE/ UNK/ NQ/ UN etc: will not be evaluated or used for the analysis purpose.

All serum chemistry, hematology, coagulation, and urinalysis data will be listed by subject; the clinically significant abnormal values will be flagged.

Notes:

- Clinical laboratory data will be analysed using standardized values.
- Repeated or unscheduled tests will not be summarized for each scheduled visit but will be included in the listing.
- The tables will include the visits until the number of patients will be representative.
- Only evaluable data will be used, and missing data will not be imputed.

The pregnancy results will also be listed only.

5.3.3.4.1 Selected laboratory parameters

Selected laboratory parameters will be graded according to CTCAE Version 4.03, the worst CTCAE grade will be summarized. All values will be considered, regardless of whether it is considered clinically significant or not.

For each test, subjects will be characterized based on their worst severity grade observed during on treatment period.

5.3.3.4.1.1 Hematology

In hematology, a table with the following abnormalities of laboratory parameters will be described:

- White Blood Cells decreased
- Neutrophil count decreased
- Platelet count decreased
- Lymphocyte count decreased
- Hemoglobin decreased.
- White Blood Cells increased
- Lymphocyte count increased

Note:

Repeated or unscheduled tests will be considered in calculating this information.

Table 8 Grading of selected laboratory parameters - Hematology

Laboratory abnormality	CTCA V4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytes (Low)	White Blood Cells decreased	<LLN-3000/mm3; <LLN-3.0x10e9/L	<3000-2000/mm3; <3.0-2.0x10e9/	<2000-1000/mm3; <2.0-1.0x10e9/L	<1000/mm3; <1.0x10e9/L
Neutrophil (Low)	Neutrophil count decreased	<LLN-1500/mm3; <LLN-1.5 x 10e9/L	<1500-1000/mm3; <1.5-1.0 x10e9/L	<1000-500/mm3; <1.0-0.5x10e9/L	<500/mm3; <0.5x10e9/L
Platelet (Low)	Platelet count decreased	<LLN-75000/mm3; <LLN-75.0x10e9/L	<75000-50000/mm3; <75.0-50.0x10e9/L	<50000-25000/mm3; <50.0-25.0x10e9/L	<25000/mm3; <25.0x10e9/L
Lymphocyte (Low)	Lymphocyte count decreased	<LLN-800/mm3; <LLN-0.8 x10e9/L	<800-500/mm3; <0.8-0.5 x10e9/L	<500-200/mm3; <0.5-0.2x10e9/L	<200/mm3; <0.2x10e9/L
Hemoglobin (Low)	Anemia	<LLN - 10.0 g/dL; <LLN- 6.2 mmol/L; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L;	__
White Blood Cells (High)	Leukocytosis	__	__	> 100000/mm3;	__
Lymphocyte (High)	Lymphocyte count increased	__	>4000-20000/mm3	>20000/mm3;	__

5.3.3.4.1.2 Serum chemistry

In serum chemistry, a table with the following abnormalities of laboratory parameters will be described:

- AST increased
- ALT increased
- Total bilirubin increased
- Alkaline phosphatase increased
- Concurrent (AST or ALT) and Total Bilirubin (Hy's law)

Note:

- Repeated or unscheduled tests will be considered in calculating this information.

Table 9 Grading of selected laboratory parameters – Serum chemistry

Laboratory abnormality	CTCA V4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
Aspartate Aminotransferase (High)	Aspartate Aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alanine Aminotransferase (High)	Alanine Aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Total bilirrubin (High)	Blood bilirubin Increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Alkaline Phospatase (High)	Alkaline Phospatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20 x ULN

Hy's law

Concurrent (AST or ALT) and Total Bilirubin.

- The number of subjects and events reported per cohort will be included
- eDISH plots will be provided. (Scatter plots of peak ALT/AST versus peak Total bilirubin in the same date)

5.3.3.5 Vital Signs

Vital sign measurements, including blood pressure (Systolic/Diastolic) (mmHg), Pulse Rate (beats/minute), Respiration Rate (breaths/min), and Temperature, will be performed at Screening, during and after the investigational product infusion within Treatment Phase, and at EOT.

All vital signs measurements will be listed by subject.

5.3.3.6 12-Lead Electrocardiogram (ECG)

12-lead ECG measurements will be conducted locally, including RR Interval (msec), PR interval (msec), QRS interval (msec), QT interval (msec).

ECG overall interpretation will also be collected on eCRF (Normal / Abnormal NCS / Abnormal CS).

The ECG measurements are required at Screening only; additional ECGs can be performed as clinically indicated.

All ECG measurements and overall interpretation results will be listed by subject.

5.3.3.7 Physical Examination

A physical examination (including examination of the skin, head and neck, chest (heart and lungs), abdomen, limbs, and a brief neurological examination) will be assessed at the Screening, Treatment Phase, and EOT.

Any clinically significant abnormality at Screening will be recorded on eCRF pages for medical history; any clinically significant abnormality at all other visits will be recorded on AE forms.

Data from examinations will be listed by subject.

5.3.3.8 ECOG Performance Status

The six-grade ECOG Performance Status will be recorded at Screening, Treatment Phase, and EOT.

All ECOG performance status data will be listed by subject.

5.3.4 Subgroup analysis

5.3.4.1 Steroids during treatment- Subgroup

For subjects receiving steroids for each dose of APX005M, the BOR will be provided. It will be summarized in different approaches:

- Subjects receiving steroids during treatment: For the first dose, the window should be from screening to 5 days after the first dose - all other cycles should be +/-5 days from the APX005M
- Subjects receiving steroids for the first dose: the window should be from screening to 5 days after the first dose of APX005M.

5.3.4.2 LDH pre-treatment values- Subgroup

Subjects will be classified according to their presenting Lactate Dehydrogenase (LDH) pre-treatment (screening or C1D1) values above the upper normal range vs. below the upper normal range.

- Best Overall Response, ORR and DCR will be presented in a table. (Overall and by cohort)
- PFS will be provided in a table. (Overall and by cohort)

5.3.4.3 LDH pre-treatment values and prior anti-CTLA4 - Subgroup

- Summary of Subjects prior anti-CTLA4 and elevated pre-treatment LDH and BOR.
  A table of BOR will be included. For each level of response, the number of subjects who received prior-anti CTLA4, and the number of subjects with elevated pre-treatment LDH.
- The following variables will be provided for each subject in a listing.
  Subject ID, Time on Prior PD1(months), Prior anti-CTLA4 (yes/no), Elevated pre-treatment LDH (>ULN) (yes/no)), Pre-study anti-PD1 to study start (months) and Best Overall Response on Study.

5.3.5 Interim Analyses

No formal interim analyses are considered in the protocol.

Support material has been provided for the regular meetings during the life of the study.

Safety Assessment Committee meetings are organized every three months (approximately).

Medical Monitoring Meetings are organized regularly (approximately every month).

5.3.6 Handling of Missing Data

General imputation method: missing data will not be imputed, and it will be considered as missing values for the analysis.

Specific imputations:

Weight

In case a cycle's weight is missing it will be imputed via the LOCF–last observation carried forward–method.

Partial dates

Only in case of any incomplete date necessary for the analysis:

- Missing day: day 15 th of the month and year indicated in each case will be imputed.
- Missing day and month: day15th of January of the year indicated.
- If the date is completely missing, no imputation will be performed.

Just in case the previous imputation generated an incoherence considering the rest of dates reported for any subject, the day imputed would be the corresponding day according to the rest of dates for the same subject.

These data imputations are for analysis purpose only and will not be used in listings.

TEAEs severity.

If severity is missing, the event will be listed as missing severity but summarized as a CTCAE grade 3.

TEAEs relationship

If relationship is missing or unknown, the event will be listed as missing or unknown relationship but summarized as related.

5.3.7 Reporting Conventions

Descriptive statistics will be reported to 2 decimal places.

Estimated parameters, such as regression coefficients will be reported to 3 decimal places.

Percentages should be rounded to 2 decimal places.

P-values ≥0.0001 will be reported to 4 decimal places; p-values less than 0.0001 will be reported as "<0.0001".

Listings will be presented and sorted by subject ID, and cohort, when available, listings will also sort by visit.

5.3.8 Study Timelines

Date first subject enrolled: 16-Dec-2019

Date last subject enrolled: 21-Oct-2021

5.3.9 Technical Details

The most updated study protocol has been used as a reference for this document.

SAS programs, SAS Logs and SAS outputs generated during the creation of the Statistical Report will be archived in the PIVOTAL's File System.

5.3.10 Software

The statistical analysis will be performed using the scientific software SAS® V9.4 or later releases and SAS® Enterprise Guide V7.15 or later releases.

6. REFERENCES

Study protocol, Amendment A2 of the protocol (dated on 28 Dec 2020) has been used to prepare this document.

7. TABLES, LISTINGS AND FIGURES

This information has been detailed and collected in an external document with the following file name: APX010 - Statistical Analysis Plan - TFLs v1_0