Statistical Analysis Plan Version 2.0

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

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Pivotal

STATISTICAL ANALYSIS PLAN

Study Code:	APX005M-002
Protocol Version:	Amendment 4
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A Study to Evaluate the Safety and Efficacy of the CD40 Agonistic Antibody APX005M Administered in Combination with Nivolumab in Subjects with Non-Small Cell Lung Cancer and Subjects with Metastatic Melanoma

Investigational Product	APX005M and Nivolumab
Indication Studied	Non-small Cell Lung Cancer and Metastatic Melanoma
EudraCT No	2018-003866-14
Phase of Study	Phase 1b-2
Sponsor (company and address)	Apexigen Inc., 75 Shoreway Road, Suite C, San Carlos, CA 94070, USA.
Sponsor representative (name, title and company)	Ovidiu C. Trifan, MD, PhD

Approved by

Signature: 2/4/21

Name: Thomas Jahn, MD/PhD

Role: VP Clinical Development

Pages Nº	30
SAP Version	2.0
SAP Date	04-Feb-2021

Statement:

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, and all regulatory guidelines.

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.

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

CHANGES COMPARED TO PREVIOUS STATISTICAL ANALYSIS PLAN (SAP) VERSIONS

Previous SAP section	Change
V1.0 --30MAY2016	N.A.
V2.0 –01FEB2021	Exploratory, sensitivity and subgroups analyses requested by the Sponsor are included Phase 2 TFLs

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1. LIST OF ABBREVIATIONS

1.1 Abbreviations

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

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

2. INTRODUCTION

2.1 Background & Rationale

Among the promising approaches to activating therapeutic anti-tumor immunity is the modulation of host immune system. Immune modulation includes inhibitory or stimulatory pathways in the immune system that are crucial for activating the immune response, maintaining self-tolerance, and modulating the duration and amplitude of physiological immune responses. Modulation of immune checkpoints by antibodies against immune inhibitory molecules has shown clinical benefits for patients with various solid tumors such as melanoma, lung cancer, bladder cancer, renal cell carcinoma [1, 2, 3]. Currently, both antagonistic monoclonal antibodies (mAb) against immune inhibitory molecules such as cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed death receptor-1 (PD-1)/ programmed death-ligand 1 (PD-L1) and agonistic antibodies against immune costimulatory molecules such as CD40 and OX40 are under active development for different cancer indications and is believed that combination of such immunomodulatory agents could lead to a cure for cancer [4].

Apexigen has developed the mAb APX005M, which binds and activates CD40, a costimulatory molecule expressed by antigen presenting cells (APC). As such, APX005M is a CD40 agonistic antibody. The cell surface molecule CD40, a member of the tumor necrosis factor receptor (TNFR) superfamily, plays an important role in induction of tumor apoptosis and regulation of immune activation, especially in crosstalk between T cells and APCs [5]. CD40 is expressed by dendritic cells (DC), B cells, monocytes, and some non-lymphoid cells [6]. The natural ligand (CD40L) for CD40 is CD154, which is expressed on activated T cells and provides a major component of T cell “help” for immune response. Agonistic CD40 antibodies can substitute for the function of CD154 on T cells to boost immunity. Signaling through CD40 on APCs, including dendritic cells (DCs), monocytes, and B cells, can, in turn, enhance the T cell response via improvement in antigen processing and presentation and through the release of cytokines from activated APCs [7, 8][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 patients [11, 12, 13, 14].

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

2.2 Study Objectives and Analyses

This statistical analysis plan describes the methods and statistical models to be applied for the generation of the statistical report. As a reference, the Amendment 4 of the protocol (dated on 10 October 2019) has been used in order to prepare this document.

2.2.1 Primary Objective

- Determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of APX005M when given in combination with nivolumab (Phase 1b only)
- Evaluate the overall response rate (ORR) by RECIST v1.1 in each cohort/group (Phase 2 only)

2.2.2 Secondary Objectives

- Evaluate safety of the APX005M and nivolumab combination by analysing the incidence and severity of AEs and specific laboratory abnormalities graded according to NCI-CTCAE, v4.03
- Evaluate the 6-month progression-free survival (PFS) rate (PFSR) in each cohort/group (Phase 2 only)
- Evaluate duration of response (DoR) in each cohort/group by RECIST v1.1 (Phase 2 only)
- Evaluate the median PFS by cohort/group by RECIST v1.1 (Phase 2 only)

2.2.3 Exploratory Objectives

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

Note: 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, association between PDn markers and PK, and association between biomarkers and anti-tumor activity. These analyses will be carried out by Apexigen, Inc. or a different provider.

2.2.4 Additional exploratory efficacy analyses (Phase 2 only)

Exploratory analyses of efficacy will be carried out including occurrences of unconfirmed responses:

- ORR - including unconfirmed response (efficacy and safety population)
- DoR - including unconfirmed response (efficacy and safety population)

Exploratory analysis: Characterization of progressive disease. (efficacy population)

2.2.5 Subgroup efficacy analyses (Phase 2 only)

Subgroup analyses by prior therapy:

- Subgroup analysis Cohort 1: Prior therapy - platinum-based vs other
- Subgroup analysis Cohort 1: Prior therapy - anti-EGFRi+TKI vs other

- Subgroup analysis Cohort 2: Prior therapy - pembrolizumab vs. nivolumab
- Subgroup analysis Cohort 2: Prior therapy - BRAF/MEK inhibition vs other
- Subgroup analysis Cohorts 3A+3B: Prior therapy - pembrolizumab vs. nivolumab

Subgroup analysis by LDH

- Subgroup analysis Cohort 2: LDH baseline values above the upper normal range vs normal/lower

Subgroup analysis by country

- Subgroup Analysis by country: US vs. non-US

2.2.6 Sensitivity efficacy analyses (Phase 2 only)

Parameters of Response by RECIST v1.1 in the safety population:

- ORR (RECIST v 1.1, safety population
- DoR (RECIST v1.1, safety population

2.3 Study Design

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

Phase 1b dose-escalation of APX005M:

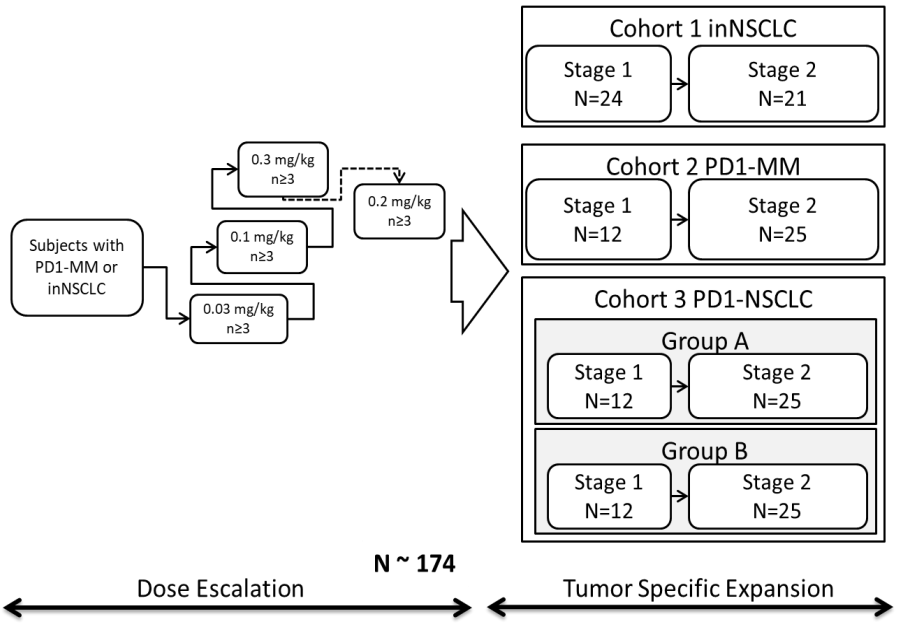
- Up to 4 dose levels of APX005M administered IV every 21 days
- In combination with nivolumab 360 mg IV every 21 days
- Participants with inNSCLC or PD1-MM

Phase 2 dose-expansion (Simon optimal 2-stage design):

- The RP2D dose of APX005M administered IV every 21 days in combination with nivolumab 360 mg IV
- 3 cohorts
  - Cohort 1: Participants with inNSCLC
  - Cohort 2: Participants with PD1-MM
  - Cohort 3: Participants with PD1-NSCLC
    - Group A: Participants with PD1-NSCLC with best response of progressive disease or with stable disease < 16 weeks while on previous PD-1/PD-L1 containing regimen
    - Group B: Participants with PD1-NSCLC with tumor response or with stable disease ≥ 16 weeks while on previous PD-1/PD-L1 containing regimen

Participants will be evaluated for tumor response approximately every 8 weeks following the first dose of investigational product. An ORR of at least 22% (6 out if 24 response evaluable participants) in the inNSCLC cohort and 5% (1 out if 12 response evaluable participants) in the PD1-MM cohort or PD1-NSCLC (Group A or B) is required in Stage 1 for that cohort to proceed to Stage 2. Enrollment may continue into Stage 2 while the planned number of participants for Stage 1 are followed for efficacy.

Figure 1 APX005M-002 Study Design



2.3.1 Eligibility and Randomization

This is an open-label study, and there is no randomization or blinding needed.

2.3.2 Eligibility Criteria

2.3.2.1 Phase-Specific Criteria

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

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

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

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

Participants with ocular melanoma are excluded.

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

Based on response to previous PD-1/PD-L1 containing regimen, participants will be enrolled in one of the following groups:

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

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

2.3.2.2 General Inclusion Criteria

1. Subjects willing and able to provide written informed consent for this study
2. Male or female ≥18 years old at time of consent
3. Measurable disease by RECIST criteria v1.1
4. ECOG performance status of 0 or 1
5. Resolution of prior treatment-related toxicities to Grade 1 (check the protocol for some exceptions)
6. Adequate organ function within 14 days of first dose of investigational product (check protocol for appropriate parameters guidelines)
7. Women of childbearing potential (WOCBP) must have negative pregnancy test (check protocol for more details)
8. WOCBP and males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (check protocol for more details)
9. Available archived or fresh tumor tissue sample for PD-L1 and other biomarker analysis
10. For subjects that consent to collection of tumor biopsies at study entry and before the first scheduled tumor assessment, primary or metastatic tumor that can be safely biopsied. A minimum of 24 subjects (6 subjects with each cohort/group) must consent to fresh core biopsies.

2.3.2.3 General Exclusion Criteria

1. Previous exposure to any immunomodulatory agents (check exceptions in the protocol)
2. Second malignancy (solid or hematologic) within the past 3 years (check exceptions in the protocol)
3. Active, known, clinically serious infections (≥ Grade 2 according to NCI-CTCAE v4.03) within the 14 days prior to first dose of investigational product
4. Use of systemic corticosteroids or other systemic immunosuppressive drugs within the 28 days prior to first dose of investigational product (except inhaled corticosteroids); the use of physiologic doses of corticosteroids may be approved after consultation with the Apexigen Medical Monitor (or designee)

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

2.3.3 Withdrawals

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

- Disease progression by RECIST 1.1, or disease progression following treatment beyond progression
- Death
- Toxicity requiring discontinuation of both investigational products 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 investigational product (except Grade 2 alopecia and Grade 2 fatigue), unless the participant is benefiting from therapy and after discussion with and approval by Apexigen Medical Monitor (or designee)
- Failure to recover within 4 weeks of last dose of investigational product if AE is related to infusion reaction/cytokine release
- Inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks of last dose of investigational product and after discussion with and approval by Apexigen Medical Monitor (or designee)
- Participant's decision to withdraw for any reason from study treatment (participant withdraws consent)
- Pregnancy
- Any clinical AE, laboratory abnormality or coincident illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the participant
- Requirement for alternative therapy
- Noncompliance with study procedures, including use of prohibited medications
- Participant is lost to follow-up
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Study termination by Apexigen

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

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

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

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

For all participants receiving investigational products, the subsequent anticancer therapy will be documented. Once this information is collected, a participant is considered off-study.

2.3.4 Study treatment

In this study, the investigational products are APX005M and nivolumab.

Nivolumab is administered on Day 1 of each 3-week treatment cycle as a dose of 360 mg using a 30-minute IV infusion.

APX005M is administered on Day 1 of each 3-week treatment cycle approximately 30 minutes following nivolumab using a 60-minute IV infusion. Up to 4 dose levels of APX005M could be used in Phase 1b and the RP2D will be used for Phase 2, which will be determined during the Phase 1b of this study (between 0.03 and 0.3 mg/kg).

2.3.5 Replacement of Patients

- For Phase 1b of the study, all participants that are not DLT-evaluable will be replaced for the purpose of establishing MTD.
- For Phase 2 of the study, participants will be evaluated for tumor response approximately every 8 weeks following the first dose of investigational product. Participants that are non-evaluable for tumor response will be replaced.

3. STUDY POPULATIONS

3.1 Screened Population

The screened population is defined as all screened participants, including screen failures. Screen failures will be captured and listed, including the reason for screen failure.

3.2 Safety Population

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

3.3 DLT-Evaluable Population

The DLT-evaluable population is defined as all participants of Phase 1b who met all eligibility criteria, received the entire planned dose of APX005M and nivolumab during the DLT observation period and have completed a follow-up period after administration of study drug for at least 21 days (one full treatment cycle; i.e., participant does not come off study for reasons other than toxicity).

3.4 Efficacy Population

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

4. DEFINITION OF STUDY ENDPOINTS AND DERIVED VARIABLES

4.1 Baseline and Demographics Characteristics

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

- Time from diagnosis is defined as the time elapsed (in months) since the date of first positive biopsy for this disease until the informed consent date.

4.2 Efficacy Endpoint

- The Progression-Free Survival (PFS) is defined as the time from first dose of investigational product to the earlier of PD (by RECIST 1.1 and iRECIST) or death due to any cause.
  PFS will be calculated as time in months between (first date of PD or death due to any cause – date of first dose).
  - For participants with no baseline assessment, PFS will be censored on the date of first dose.
  - For alive participants with no post baseline tumor assessment will be censored on the date of first dose however they will be considered an event in case of record end of treatment by clinical progression within eight weeks of first treatment dose (before the first tumor assessment schedule)
  - For participants who have at least 1 post baseline tumor assessment, if they do not have PD or do not die, PFS will be censored on the date of last tumor assessment documenting the absence of PD.

  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 (Brookmeyer and Crowley method). PFS by RECIST 1.1 and by iRECIST will be summarized by dose level and overall in each tumor type for Phase 1b and by cohort for Phase 2 (including participants treated at RP2D in Phase 1b) in 2 separate tables. A graph of the Kaplan Meier curve will be presented for Phase 2 (including participants treated at RP2D in Phase 1b).

- The Best Overall Response (BOR) is defined as the best response presented according to RECIST v1.1 from the inclusion in the study to progressive disease (PD).
- The Objective Response Rate (ORR) is defined as the incidence of patients who show as best overall response a complete response (CR) or partial response (PR). The ORR can be calculated based on two tumor assessment methods, RECIST 1.1 and iRECIST.

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

- The Duration of Response (DoR) is defined as the time in months from the first evidence of confirmed PR or better to disease progression or death due to any cause, whichever occurs earlier (by RECIST 1.1 and iRECIST). DoR will be calculated for the participants with a response of PR or better. If participants do not have PD or do not die, DoR will be censored on the date of last tumor assessment documenting the absence of PD.

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 (Brookmeyer and Crowley method). The DoR by RECIST 1.1 and iRECIST will be summarized by dose level and overall for Phase 1b and by cohort for Phase 2 (including participants treated at RP2D in Phase 1b) in 2 separate tables. A graph of the Kaplan Meier curve will be presented for Phase 2 (including participants treated at RP2D in Phase 1b).

- The 6-month Progression-Free Survival Rate (PFSR) is defined as the proportion of participants that did not have disease progression (by RECIST 1.1) or died due to any cause at 6 months from the first dose of investigational product. It will be depicted in a Kaplan Meier survival curve.

4.3 Safety Endpoints

Safety will be assessed through summaries of DLTs, incidence and severity of AEs, specific laboratory abnormalities graded according to NCI-CTCAE, ECG, vital signs, and APX005M exposure.

All AE data collected will be listed by study site, cohort, participant number, and cycle day.

4.3.1 Extent of exposure and compliance

- The MTD is maximum dose for which <33% of DLT-evaluable participants experience a DLT (only Phase 1b)
- The RP2D will be stablished taking into account the MTD of APX005M (if applicable), as well as the nature, severity and causal relationship for all AEs. Prior to establishing the RP2D all participants enrolled in the Phase 1b portion of the study must be followed until PD, study discontinuation due to toxicity or at least 2 cycles
- The duration of treatment of each patient will be computed as the time in weeks from the date of the first dose of any investigational product until the last dose administration (APX005M or nivolumab)+ (21 days, one cycle)/7.

- The relative dose intensity (RDI) and its components will be described for each of the drugs administered in the study

- Dose intensity (DI) is defined as the drug dose delivered per time unit and is expressed as mg/kg (for APX005M) or mg (for nivolumab) per week. In the case of APX005M, 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)
- Target dose intensity (TDI)
- Relative dose intensity (RDI) is the ratio of DI and TDI, and can be expressed as a percentage:

  RDI (%) = (DI/TDI) * 100

- Number of cycles administered per patient will be described
- Dose delays and dose reductions per patient and the reasons for these dose modifications will be described by patient.

4.4 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. Once the variables are created, it will be checked that their values are correct and that they represent exactly what it is expected.

5. GENERAL STATISTICAL METHODS

5.1 Sample Size

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

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

- Cohort 1 (inNSCLC): Assuming a false positive rate (α) of 0.1 (one-sided), a false negative rate (β) of 0.1, a response probability of poor drug (P0) of 22% and a response probability of good drug (P1) of 40%, first stage sample size (n1) is 24 and the maximum sample size (n) is 45 response evaluable participants.
  - In the first stage, if there are 5 or less responses in 24 participants, the enrollment in this cohort will be stopped. Otherwise, if 6 or more responses are observed, 21 additional participants will be accrued in Stage 2 for total of 45. Enrollment may continue into Stage 2 while the planned number of participants for Stage 1 are followed for efficacy.
  - By the end of Stage 2, if 13 or less responses are observed in 45 participants, then no further investigation is warranted. If 14 or more responses are observed, the null hypothesis will be rejected, and true RR is 40%.
  - The sample size of 45 participants, provides 97% power to statistically test the null hypothesis of historical 6-month PFS rate (PFSR) of 60% versus the alternative hypothesis of 6-month PFSR rate of 80%. This calculation assumes exponential PFS, 1-sided 5% type I error rate, enrollment of participants for 8 months with 6 months of follow-up prior to conducting the final analysis.
- Cohort 2 (PD1-MM): Assuming α of 0.1 (one-sided), β of 0.1, P0 5% and P1 of 20%, n1 is 12 and n is 37 response evaluable participants.
  - In the first stage, if there are no responses in 12 participants, the enrollment in this cohort will be stopped. Otherwise, if 1 or more responses are observed, 25 additional participants will be accrued in Stage 2 for total of 37. Enrollment may continue into Stage 2 while the planned number of participants for Stage 1 are followed for efficacy.
  - By the end of Stage 2, if 3 or less responses are observed in 37 participants, then no further investigation is warranted. If 4 or more responses are observed, the null hypothesis will be rejected and true RR is 20%.
  - The sample size of 37 participants, provides 92% power to statistically test the null hypothesis of historical 6-month PFSR of 19% (estimated for ipilimumab following nivolumab or pembrolizumab) versus the alternative hypothesis of 6-month PFSR rate of 38%. This calculation assumes exponential PFS, 1-sided 5% type I error rate, enrollment of participants for 8 months with 6 months of follow-up prior to conducting the final analysis.
- Cohort 3 (PD1-NSCLC) Group A and Group B: Assuming α of 0.1 (one-sided), β of 0.1, P0 5% and P1 of 20%, n1 is 12 and n is 37 response evaluable participants.
  - In the first stage, if there are no responses in 12 participants, the enrollment in that group will be stopped. Otherwise, if 1 or more responses are observed, 25 additional participants will be

accrued in Stage 2 for total of 37 per group. Enrollment may continue into Stage 2 while the planned number of participants for Stage 1 are followed for efficacy.

- By the end of Stage 2, if 3 or less responses are observed in 37 participants, then no further investigation is warranted. If 4 or more responses are observed, the null hypothesis will be rejected, and true RR is 20%.
- The sample size of 37 participants/group, provides 94% power to statistically test the null hypothesis of historical 6-month PFSR of 22% (estimated for chemotherapy regimens) versus the alternative hypothesis of 6-month PFSR rate of 43%. This calculation assumes exponential PFS, 1-sided 5% type I error rate, enrollment of participants for 8 months with 6 months of follow-up prior to conducting the final analysis.

5.2 Disposition of Study Participants

For participant study status, the number and percentage of participants for each one of the following categories will be presented by dose level and overall for Phase 1b and by cohort and overall for Phase 2 (including participants treated at RP2D in Phase 1b) in separate tables.

- Participants in Screened Population (the number only)
- Screen-failure participants (the number only)
- Enrolled participants (the number only)
- Participants in Safety Population
- Participants in Efficacy Population
- Participants in DLT Evaluable Population
- Participants who discontinued study treatment by primary reason
- Participants who discontinued study participation by primary reason

The data for participant disposition, protocol deviation, eligibility, and whether a participant is included in the analysis populations will be listed. Patients who discontinue treatment prematurely will be displayed in a listing, indicating the reason for such discontinuation.

5.3 Protocol Deviations

Deviations from the protocol, including violations of inclusion/exclusion criteria, will be assessed as “minor” or “major” by the clinical team. All protocol deviations will be collected separately from the database and listed.

All protocol deviations will be listed and major deviations from the protocol will lead to the exclusion of a patient from the EP.

5.4 Summary of Statistical Methods

Participants treated at the RP2D in Phase 1b will be included in Stage 1 of the relevant disease-specific cohort for Phase 2. All the data (e.g., safety and efficacy) from these participants will be used in the relevant summary tables and listings for both Phase 1b and Phase 2 (including participants treated at RP2D in Phase 1b).

All relevant participant data will be included in listings. All participants entered into the database will be included in participant data listings. The listings will be generally sorted by first dose level (Phase 1b) or

cohort (Phase 2, including participants treated at RP2D in Phase 1b) and then Participant ID, unless specified otherwise.

All applicable data will be summarized by dose level and overall for Phase 1b, and by cohort and overall for Phase 2 (including participants treated at RP2D in Phase 1b), 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), mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum along with the total number of patients contributing values.

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

Kaplan-Meier model will be used to analyze duration of response, PFS and OS. In all these analyses, in addition to the Kaplan-Meier curve, median, Q1, Q3 and their corresponding CI 95%, number of events and censored cases distribution will be shown.

5.4.1 Demographics, Other Baseline Characteristics and Medication

5.4.1.1 Demographic Characteristics

Descriptive statistics will be summarized for the demographic characteristics and disease history based on the safety population and efficacy population. Listings will also be presented for the demographic characteristics and disease history, respectively.

The following variables will be described by dose level and overall for Phase 1b and by cohort and overall for Phase 2 (including participants treated at RP2D in Phase 1b) in separate tables: age (years), sex, race, ethnicity, height (cm), weight (kg), and baseline ECOG performance status.

5.4.1.2 Disease History

The following variables for disease history will be summarized by dose level and overall for Phase 1b and by cohort and overall for Phase 2 (including participants treated at RP2D in Phase 1b) in separate tables:

- Primary diagnosis
- Time (months) from the first positive biopsy for this disease to the date of first dose. This will be defined as the number of months between the date of first dose and date of first positive biopsy.
- Histology
- Histological grade
- Metastatic sites at study entry

5.4.1.3 Medical & Smoking History

Medical history will only be listed but not summarized.

The smoking history of each patient will also be described.

5.4.1.4 Prior Systemic Therapy

A listing will be provided for the prior systemic therapy by verbatim term, WhoDrug codification won't be performed.

5.4.1.5 Prior Radiation

A listing will be provided for the prior radiation.

5.4.1.6 Prior Surgery

A listing will be provided for the prior surgery.

5.4.1.7 Subsequent Systemic Therapy

A listing will be provided for the subsequent systemic therapy by verbatim term, WhoDrug codification won't be performed.

5.4.1.8 Subsequent Radiation

A listing will be provided for the subsequent radiation.

5.4.1.9 Subsequent Surgery

A listing will be provided for the subsequent surgery.

5.4.1.10 Prior and Concomitant Medications

All medications, including all prescription, over the counter, herbal supplements and IV medications and fluids, will be recorded on the electronic case report form (eCRF). No coding will be performed for medications.

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

Prior and concomitant medications will be listed by verbatim term, WhoDrug codification won't be performed, therefore they will not be summarized; a column will be included in the listing to indicate if the medication is prior or concomitant.

5.4.1.11 Concomitant Procedures

A listing will be provided for the concomitant procedures performed.

5.4.2 Efficacy Analyses

The efficacy analysis is based on tumor assessments, which will be performed with two methods (RECIST 1.1 and iRECIST) at Screening, about every 8 weeks during Treatment Phase and Follow-up. The efficacy analysis will be performed for Efficacy Population.

ORR (and 90% confidence interval by exact distribution), DoR and PFS (Kaplan-Meier estimate) will be estimated for each cohort/group and for each tumor assessment method (by RECIST 1.1 and iRECIST).

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

5.4.3 Safety Analyses

The population used for safety analyses will be the Safety Population. Safety of APX005M in combination with nivolumab will be assessed on the basis of the exposures of investigational products, DLT, AE, laboratory data, vital signs, electrocardiogram (ECG), physical examinations, and Eastern Cooperative Oncology Group (ECOG) performance status.

A TEAE is an AE that occurs after administration of the first dose of the investigational product or a worsening (by CTCAE Grade) of a pre-existent condition, and through 30 days after the last dose of the investigational product, death or initiation of new anticancer therapy, whichever occurs first. SAEs and AEs with potential immunologic etiology will be recorded up to 100 days and pregnancies up to 120 days after the last dose of investigational product, death, or initiation of new anticancer therapy, whichever occurs first.

For AEs, events that occur prior to the first dose of investigational product will be recorded as medical history; events that start after the first dose of investigational product will be recorded on the AE eCRF pages. Thus, all AEs collected from AE eCRF pages are considered as TEAEs.

5.4.3.1 Treatment Exposure

Exposure of the investigational products (APX005M and nivolumab) will be summarized for Phase 1b (by dose level and total) and for Phase 2 (by cohort and total, including participants treated at RP2D in Phase 1b). The following variables will be summarized:

- Maximum number of cycles started
- Number of participants who started the maximum cycle of 1, 2, 3, 4, and so on
- Duration of treatment (weeks)

The following variables will be summarized separately for each investigational product (APX005M or nivolumab) by dose level and overall for Phase 1b and by cohort and overall for Phase 2 (including participants treated at RP2D in Phase 1b).

- Number of infusions administered per participant
- Number of participants with dose reductions
- Number of participants with dose interruptions
- Number of participants with dose delivered off schedule

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

- Dose intensity (mg/kg/week)

- Relative dose intensity (%)

Treatment assignment will be listed by participant. A listing of investigational product infusion data will be provided; a separate listing will be presented for cumulative actual dose, cumulative target dose, and relative dose intensity (%). In addition, separate listings will be provided for the pre-medications prior to administration of investigational products.

5.4.3.2 Dose Limiting Toxicities

Dose-limiting toxicities (DLTs) are defined in the study protocol. In brief, DLTs are defined events attributed to APX005M and nivolumab combination treatment (e.g., AEs that are not clearly attributable to extraneous causes occurring during the first 21-day following the administration of APX005M and nivolumab (the first 3 weeks-cycle). DLTs will be identified using a checkbox on the AE eCRF pages. The medical monitor will review all AEs and ensure that DLTs are appropriately checked as such in the EDC.

DLTs will be summarized for participants in DLT Evaluable Population, by dose level and overall for Phase 1b. In addition, DLT will be listed for Phase 1b.

5.4.3.3 Adverse Events

All AEs will be collected in the eCRF from the time the participant signs informed consent through 30 days after the last dose of investigational product, death, or initiation of new anticancer therapy, whichever occurs first. AEs will be coded to system organ (SOC) and preferred term (PT) using the MedDRA dictionary v18.0.

The NCI-CTCAE will be used to assess the severity of AEs.

The relationship of each AE to the investigational product will be classified as related or unrelated. If relationship is missing, the event will be listed as missing relationship but summarized as related.

Summaries will focus on the TEAEs. They will be summarized by dose level and overall for Phase 1b and by cohort and overall for Phase 2 (including participants treated at RP2D in Phase 1b). The following summary tables will be provided:

- An overall summary of the frequency of participants reporting all TEAEs, serious TEAEs, TEAEs with CTCAE grade 3 or higher, treatment-related TEAEs (separately for APX005M and nivolumab), and TEAEs leading to treatment discontinuation (separately for APX005M and nivolumab), TEAEs with fatal outcome.
- TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- TEAEs with CTCAE grade 3 or higher by SOC and PT
- Treatment-related TEAEs by SOC and PT (separately for APX005M and nivolumab)
- TEAEs leading to treatment discontinuation by SOC and PT (separately for APX005M and nivolumab)
- TEAEs with fatal outcome by SOC and PT
- TEAEs by SOC and PT, and by maximum CTCAE grade

All AEs will be listed by dose level (Phase 1b)/cohort (Phase 2, including participants treated at RP2D in Phase 1b), and then study site, participant number, and cycle day. Separate listings will be produced for TEAEs, serious TEAEs, TEAEs leading to APX005M discontinuation, delay, and interruption, and TEAEs with fatal outcome. Separate listings will be generated for immune-mediated events.

5.4.3.4 Clinical Laboratory Evaluation

The following laboratory tests will be performed locally to evaluate the safety profile: serum chemistry (including thyroid tests), hematology (including coagulation), urinalysis, and pregnancy. Except for urinalysis and pregnancy tests which are scheduled at Screening only, the other tests will be performed at Screening, Treatment Phase and End of Treatment (EOT).

For each laboratory parameter, the actual will be summarized and the frequency of participants with clinically significant abnormal laboratory values will be tabulated for baseline and each scheduled post baseline visit, by dose level and overall for Phase 1b and by cohort and overall for Phase 2.

All serum chemistry, hematology and urinalysis data will be listed by participant; the clinically significant abnormal values will be flagged. The pregnancy results will also be listed.

5.4.3.5 Vital Signs

Vital sign measurements, including blood pressure (systolic/diastolic), pulse rate, respiration rate, 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 participant.

5.4.3.6 12-Lead Electrocardiogram (ECG)

12-lead ECG measurements will be conducted locally, including the heart rate, RR Interval, PR interval, QRS interval, QT interval. ECG overall interpretation will also be collected on eCRF. 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 participant.

5.4.3.7 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 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 participant.

5.4.3.8 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 participant.

5.4.4 Exploratory Analyses

Blood samples will be collected from all participants for determination of serum concentrations of APX005M at time points specified in the protocol. PK parameters of APX005M will be determined using model-independent methods.

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

The analyses about pharmacokinetics (PK), immune pharmacodynamics (PDn), cytokines, APX005M anti-drug antibody (ADA), and tumor biomarkers will be carried out by Apexigen or a different provider.

Only listings will be produced for archival tumor tissue samples and fresh tumor biopsy.

5.4.5 Interim Analyses

No formal interim analyses are considered in the protocol.

However, a brief report with the main results of efficacy and safety will be prepared when each cohort completes the Stage 1 expected recruitment to check if the study continues.

The monthly generated outputs (mainly for safety) will provide enough information for the decision-making processes during the study.

5.4.6 Missing Data

5.4.6.1 General imputation method

Missing data will not be imputed, and it will be considered as missing values for the analysis.

5.4.6.2 Specific imputations

5.4.6.2.1 Partial dates

Only in case of any incomplete dates (missing day) necessary for the analysis, the 15th day of the month and year indicated in each case will be imputed.

Only in case of any incomplete dates (missing day and month) necessary for the analysis, the 15th day of the January year indicated in each case will be imputed.

For instance, Partial AE onset dates will be imputed so that if the partial AE onset date information does not indicate that the AE started prior to treatment or after the TEAE period, the AE will be classified as treatment-emergent.

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

5.4.6.2.2 Weight

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

5.4.7 Reporting Conventions

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

5.4.8 Study Timelines

- Date first participant enrolled: 17-May-2017
- Estimated date last participant enrolled: Q2-2020. The primary analysis of safety and efficacy is planned after all participants complete the final study visit or terminate early from the study.

5.4.9 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.

5.4.10 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

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7. TABLES, LISTINGS AND FIGURES

This information has been detailed and collected in an external document with the following file name: APX002 - Statistical Analysis Plan TFLs v2.0 -04FEB2021.docx

Note: The final report of phase 1b was performed based on the SAP and TFLs version 1.0 (30MAY2016)