Statistical Analysis Plan (SAP)

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Protocol NET-202

A Phase 2 multi-center, open-label, single arm study of nab-sirolimus in patients with well-differentiated neuroendocrine tumors (NETs) of the gastrointestinal tract, lung, or pancreas who have not received prior treatment with mTOR inhibitors

Approved by	Name	Signature
Vice President, Clinical Development	Yoichiro Inagaki	Signed by: Yoichiro Inagaki Signer Name: Yoichiro Inagaki Signing Reason: I approve this document Signing Time: 08-10-2025 | 4:07 午後 EDT 42DEABC187794D4EB989DBE76BF89520

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List of Abbreviations

Ab	antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase (SGPT)
AST	aspartate transaminase (SGOT)
BOR	Best overall response
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CM	Concomitant Medication
CR	complete response
CT	computed tomography
DCR	Disease control rate
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IP	investigational product
IRR	Independent Radiographic Review
IV	intravenously
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
nab	nano-particle albumin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not Evaluable
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PE	Physical Examination
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event

SAP	Statistical Analysis Plan
SD	Stable disease
SI	International System of Units
SOC	system organ class
TTR	time to response
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

1. Introduction

This is a prospective Phase 2 single arm, open-label, multi-institutional study to determine the efficacy and safety profile of *nab*-sirolimus administered by intravenous (IV) infusion in patients with functional or non-functional, well-differentiated, locally advanced unresectable or metastatic NETs of the GI tract, lung, or pancreas.

The study will enroll up to 21 efficacy evaluable patients at approximately 3 centers in the United States (US) according to the protocol (Version 2). If a patient discontinues the study before post baseline radiographic assessment, he/she will be replaced.

The study is terminated early due to low observed response. Total 12 out of 21 planned patients are treated by the time of early stopping.

A cycle will consist of 21 days. Patients will receive *nab*-sirolimus by IV infusion over 30 minutes (+10 minutes window allowed, ie, 30- to 40 minutes infusion) on Days 1 and 8 of every 21-day cycle. *Nab*-Sirolimus will be administered at 100 mg/m^2. Patients will be monitored for at least 2 hours following completion of the first infusion, and as clinically indicated for each subsequent infusion. Three sequential dose reductions for the management of AEs are allowed: 75, 56, and 45 mg/m^2.

The study is expected to take approximately 12 to 18 months from first patient enrolled to last patient follow-up, including approximately 6 months of enrollment period (from first to last patient in), allowing a minimum of 6 months of treatment for all enrolled patients, a 28-day screening, and a 28-day (4 week) safety follow-up after the last dose.

Patients will be assessed for response by investigator using computed tomography (CT) or magnetic resonance imaging (MRI) scan with contrast using RECIST v1.1.

Patients will continue treatment until PD, or unacceptable toxicity, or until in the opinion of the Investigator the patient is no longer benefiting from therapy, or at patient discretion.

The study will be conducted in compliance with the International Council for Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

This Statistical Analysis Plan (SAP) describes the methods, conduct, and content of statistical analyses for all prespecified endpoints in the protocol in detail. Any deviations from this SAP will be documented in the clinical study report.

2. Study Objectives and endpoints

2.1. Objectives

2.1.1. Primary Objectives

- To evaluate the efficacy of *nab*-sirolimus in patients with well-differentiated, and locally advanced unresectable or metastatic NETs of the gastrointestinal (GI)

tract, lung, or pancreas who have measurable disease per Response Evaluation Criteria in Solid Tumors Version v1.1 (RECIST v1.1).

2.1.2. Secondary Objectives

- To evaluate clinical benefit as defined by the duration of response (DOR), disease control rate (DCR), time to response (TTR), and progression-free survival (PFS) via Investigator assessment, and overall survival (OS) of *nab*-sirolimus.
- To describe the safety and tolerability of *nab*-sirolimus.

2.1.3. Exploratory Objectives

- To measure Chromogranin A levels and evaluate correlation with response to treatment and disease progression.
- To evaluate baseline molecular biomarkers and genomics and the association between genomic alterations and clinical outcome, as well as genomic changes during and/or after treatment.

2.2. Endpoint*s*

2.2.1. Primary Endpoint

- Overall Response Rate (ORR), defined as the proportion of patients with best overall response (BOR) of confirmed partial response (PR) or complete response (CR) from the time of study treatment initiation until progression of disease (PD) as determined by the Investigator using RECIST v1.1.)

2.2.2. Secondary Endpoints

- DOR: *Determined for patients with BOR of confirmed CR or PR defined as time from scan first showing response by RECIST v1.1 to PD or death.*
- DCR: BOR of confirmed CR or PR (either of any duration) or stable disease (SD) ≥12 weeks following study treatment initiation
- TTR: Time from first dose of study drug to initial measurement of CR or PR, where CR or PR is subsequently confirmed according to RECIST v1.1.
- PFS: Number of months from study treatment initiation to the date of disease progression (by IRR) or death due to any cause
- OS: Number of months from study treatment initiation to the date of death due to any cause
- Incidence and severity of treatment-emergent and treatment-related adverse events (AEs) as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0

2.2.3. Exploratory Endpoints

- Chromogranin A (CgA) levels

- Tumor Sequencing for mutations: From baseline tumor tissue (archival or fresh biopsy, if available) and blood (peripheral blood mononuclear cells, [PBMCs]):
    - To understand the concomitant alterations and allele frequency at baseline via a standardized method (secondary confirmation) (using next generation sequencing [NGS]).
    - To evaluate the association between mutational profile and clinical outcome.
- To evaluate the expression of pS6 and other relevant markers via immunohistochemistry.

3. Overall Study Design

3.1. Study Design

NET-202 is a prospective Phase 2 single arm, open-label, multi-institutional study to determine the efficacy and safety profile of *nab*-sirolimus administered by intravenous (IV) infusion in patients with functional or non-functional, well-differentiated, locally advanced unresectable or metastatic NETs of the GI tract, lung, or pancreas.

The study will enroll up to 21 efficacy evaluable patients at approximately 3 centers in the US. If a patient discontinues the study before post baseline radiographic assessment, he/she will be replaced.

A cycle will consist of 21 days. Patients will receive *nab*-sirolimus by IV infusion over 30 minutes (+10 minutes window allowed, ie, 30- to 40-minute infusion) on Days 1 and 8 of every 21-day cycle. *nab*-Sirolimus will be administered at 100 mg/m^2. Patients will be monitored for at least 2 hours following completion of the first infusion, and as clinically indicated for each subsequent infusion. Three sequential dose reductions for the management of AEs are allowed: 75, 56, and 45 mg/m2.

Patients will be assessed for response using computed tomography (CT) or magnetic resonance imaging (MRI) scan with contrast using RECIST v1.1.

Patients will continue treatment until PD, or unacceptable toxicity, or until in the opinion of the Investigator the patient is no longer benefiting from therapy, or at patient discretion.

The study will be conducted in compliance with the International Council for Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

3.2. Study Duration

The study will enroll patients at approximately 3 sites in the US and is expected to take approximately 12 to 18 months from first patient enrolled to last patient follow-up, including approximately 6 months of enrollment period (from first to last patient in), allowing a minimum of 6 months of treatment for all enrolled patients, a 28-day screening, and a 28-day (4 week) safety follow-up after the last dose.

3.3. End of Study, End of Treatment, End of Treatment Visit, Follow-up Period

- End of Treatment (EOT) for a patient is defined as the date of the last dose of *nab*-sirolimus.

  The End of Treatment Visit (EOT Visit) for a patient is a safety follow-up visit; safety assessments and procedures are performed 28 to 35 days after the last dose of *nab*-sirolimus.

- End of Study (EOS) for a patient is defined as the date of last follow-up.

  The EOS for NET-202 is defined as either the date of the last visit of the last patient to complete the study, or the date of receipt of the last data point from the last patient that is required for primary, secondary, and/or exploratory analysis, as pre specified in the protocol.

  The final patient's last visit for the study will be defined as whichever of the following occurs last:

  - When the last patient on study has completed their 28-day Safety follow-up visit, or
  - When the last patient on study has documented toxicities to *nab*-sirolimus and the toxicity has resolved, returned to baseline or is deemed irreversible after the Safety follow-up visit or
  - When the last patient discontinues the follow-up phase.

- The Follow-up period begins after the EOT Visit. All patients that discontinue the study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase for survival and initiation of new therapy, including surgery or anticancer therapy. If, after *nab*-sirolimus treatment, a patient is able to undergo surgical resection of his/her primary tumor with curative intent, documentation on outcome and disease-free or stable disease status should be followed and documented. Follow-up will continue approximately every 12 weeks (±3 weeks), until death, withdrawal of consent, or the study closes, whichever is the earliest. This evaluation may be made by record review and/or telephone contact.

4. Dose Delay / Adjustments/ Modifications

Doses will be reduced for hematologic and non-hematologic toxicities, as clinically indicated. Up to 3 sequential dose reductions are permitted (75, 56, 45 mg/m^2). Dose modifications/discontinuations (refer to general guidelines in the protocol) are to be made according to the highest-grade toxicity, or when the toxicity grades are the same, follow the guideline that is most conservative. Toxicities will be graded using the NCI CTCAE Version 5.0.

Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in section 6.2.1 of the protocol.

Details on dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation are also provided in section 6.2.1 of the protocol.

5. General Considerations

The primary analysis to address all study objectives will be conducted when all patients have had the opportunity to be treated for at least 6 months or withdrawal within 6 months from the start of study treatment due to any reasons. The timing of the primary analysis will also consider whether the majority (at least 80% patients) of the patients with a response have been followed for at least 6 months from the onset of response (ie, when response was first recorded).

All primary, secondary, and safety analyses will be conducted at the time of the primary analysis, except for the biomarkers in exploratory analyses which may be analyzed at a later date.

Patients who are still active at the time of the primary analysis may continue on study until disease progression or medication intolerance is observed.

Safety data will be using the data collected up to the time of data lock for each primary analysis.

The following reporting conventions will apply to the analysis and presentation of summaries:

- A clinical study report (CSR) will be generated when the primary analysis has been completed. The CSR will be updated once the last data point is collected from the last patient that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol.
- Continuous variables will be summarized by the non-missing sample size (n), mean, standard deviation, median, first and third quartiles, minimum and maximum. Minimum and maximum will be presented to the same precision as the raw data. Mean and median will be presented with one more decimal place and standard deviation to 2 more decimal places than the original collected value.
- Categorical variables will be summarized by the n and percent in each category and percentage will be presented to 1 decimal place.
- Point estimates for efficacy endpoint incidences will be accompanied by a 2-sided 95% exact binomial CI and presented to 1 decimal place.
- Statistical summaries described in this plan will be produced using SAS® software version 9.4 or higher.
- Time-to-event endpoints will be summarized descriptively using the Kaplan-Meier (KM) method. KM quartiles (when estimable) along with the 95% 2-sided CIs (**Error! Reference source not found.**) with estimates presented to 1 decimal place. The number of patients censored and the number of events will also be provided. KM estimates will also be presented graphically.
- The day of the first dose of any study drug will be defined as Day 1.

- Unless noted otherwise, baseline value will be defined as the last non-missing value prior to or on the start of study treatment on Day 1 of Cycle 1.
- Any summarization by visit, will be conducted using the scheduled visit unless otherwise noted.
- The start date of each treatment cycle will be calculated based on study drug exposure records for each patient. The start date of the first cycle will be the earliest date the patient receives any study drug. Once the start dates, (eg, S_1, S_2, S_3…) are calculated, the end date of each cycle is calculated as the day before the start date of the following cycle, ie, $E_i = S_{i+1} - 1$. The cycle number for each date of interest, eg, adverse event (AE) will be calculated based on event start date and the cycle window start and end dates. If an event date is on or after S_i and before S_{i+1}, the corresponding cycle number will be i.
- No adjustments for multiplicity are planned for the analysis of the efficacy endpoints.
- No imputation is required if a date is completely missing.

5.1. Incomplete Dates

Where dates are used to classify medications (eg, prior versus concomitant medications) or events (eg, treatment emergent adverse events), the following conventions will be used:

When the start date and the stop date are both incomplete, impute the start date first.

Incomplete start date: If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed as the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of study drug, then the day and month of the date of the first dose of study drug will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of study drug, then 01 Januarywill be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of study drug, then 01 January will be assigned to the missing fields.

Missing month only

The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of study drug, then the day of the date of the first dose of study drug will be assigned to the missing day
- If either the year is before the year of the date of the first dose of study drug or if both years are the same but the month is before the month of the date of the first dose of study drug, then the first day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of study drug or if both years are the same but the month is after the month of the date of the first dose of study drug, then the first day of the month will be assigned to the missing day.

Incomplete stop date: if only the day of the stop date is missing, impute last day of the month; if both day and month are missing, impute December 31 of the year. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date. If the imputed stop date is after the last known date on study then imputed stop date will be equal to last known date. If medication is classified as “PRIOR CANCER SYSTEMIC MEDICATION” and imputed stop date is after first dose date then imputed stop date will be equal to first dose date.

5.2. Sample Size

Sample size calculation based on Simon's 2-stage design will be used for this study. In the first stage, 12 efficacy evaluable patients will be accrued. If there are 0 responses in these 12 patients, the study may be terminated. Otherwise, 9 additional efficacy evaluable patients will be accrued for a total of 21 patients. The null hypothesis of 4% ORR will be rejected if 3 or more responses are observed in 21 efficacy evaluable patients. This sample size yields a type I error rate of 5% and power of 80% when true ORR is 20% for this study.

If a patient discontinues the study before post baseline radiographic assessment, he/she will be replaced.

5.3. Randomization, Stratification, and Blinding

Not Applicable.

5.4. Analysis Set

5.4.1. All Enrolled

The All Enrolled set includes all patients who signed an inform consent form and meet eligibility criteria. Disposition will be summarized based on All Enrolled population.

5.4.2. Full Analysis Set

The Full Analysis Set includes all enrolled patients who receive at least 1 dose of *nab*-sirolimus. The Analyses of safety endpoints will be performed on the Full Analysis Set.

5.4.3. Efficacy Evaluable Set

The Efficacy Evaluable Set includes all enrolled patients who receive at least one dose of nab-sirolimus and have at least one post baseline radiographic assessment for tumor evaluation. Primary analyses of efficacy endpoints will be performed on the Efficacy Evaluable Set.

5.4.4. Per-protocol Analysis Set

The Per-protocol Analysis Set includes all enrolled patients with measurable tumor per RECIST v1.1 at baseline with at least 1 post treatment scan, and who do not have any prospectively defined major protocol violation. A sensitivity analysis of the primary, secondary efficacy and safety endpoints may be performed on the Per-protocol Analysis Set.

6. Patients Disposition

6.1. Disposition

Patient disposition will be summarized for all patients screened which includes the number and percentage of patients for the following categories: patients signed informed consent and screened , patients enrolled, patients who discontinued study before treatment, patients received study treatment, patients completed study treatment, patients who discontinued study treatment, patients who completed the study, patients discontinued from the study.

The reasons for discontinuation of enrollment before study treatment, study treatment, and study participation, or follow up in each Arm will also be summarized. Patient disposition data will be presented in a listing.

The following events are considered sufficient reasons for discontinuing a patient from the study medication:

- AE(s) (that are intolerable)
- Disease progression
- Physician decision
- Withdrawal of consent from treatment
- Death
- Lost to follow-up
- Protocol violation
- Surgery for locally advanced disease, with curative intent
- Pregnancy
- Other (to be specified on the eCRF)

The following events are considered sufficient reasons for discontinuing a patient from the study:

- Withdrawal of consent from study
- Death
- Lost to follow-up
- Protocol violation
- Begin new anticancer therapy, other than surgical resection
- Other (to be specified on the eCRF)

6.2. Protocol Deviations

Protocol deviations (including violations) will be tracked by the clinical team on an ongoing basis. CSR reportable protocol deviations are defined prior to the start of study enrollment according to clinical assessment as the subset of deviations which are considered to have potential significant impact on patient efficacy or safety outcome.

All protocol deviations will be assessed and reviewed. Any exclusion of enrolled patients from the Per-protocol Analysis Set must be made prior to the database lock.

Patients with CSR reportable protocol deviations will be tabulated. All protocol deviations will be listed.

7. Demographics and Baseline Characteristics

7.1. Demographics and Baseline Characteristics

A summary of demographics and baseline information will be presented. The demographic characteristics consist of age, sex, race, and ethnicity. The baseline characteristics include the following but are not limited to:

- Height (cm)
- Weight (kg)
- Body mass index (BMI, kg/m^2)
- Body surface area (BSA, m^2)
- Eastern Cooperative Oncology Group (ECOG) Performance Status or Lansky play-performance scale
- Number of prior lines of therapies for metastatic disease
- Time from Initial Diagnosis to Informed Consent (months)
- Disease stage at initial diagnosis
- Current disease stage
- Tumor type

Patient demographic and baseline characteristics will also be presented in a listing.

7.2. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with any medical history will be

summarized for each system organ class and preferred term. Percentages will be calculated based on number of patients in the Full Analysis Set.

Patient medical history data including specific details will also be presented in a listing.

7.3. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations noted in the eCRF will be presented for all enrolled patients in a data listing.

8. Treatments and Medications

8.1. Prior and Concomitant Medications and Blood Transfusion

Prior and concomitant medications and blood transfusion are to be collected from the time of enrollment through the EOT Visit.

Medication name including indication, dose, frequency, route, start date and stop date will be recorded on each patient's eCRF(s) for prior and concomitant medication. Blood transfusion type, reason for transfusion and units transfused will be recorded in the eCRF(s).

Prior or concomitant medications (CMs) will be coded using WHO Drug dictionary. The latest version of the WHO Drug will be used during the course of the study.

Prior and Concomitant medications will be summarized. All prior and concomitant medications, blood transfusions will be presented in listing(s).

8.2. Prior and Post-Treatment Cancer Therapy, Radiation Therapy, and Cancer Surgery

Prior treatment (i.e. before first dose of study medication) and post treatment (i.e. after EOT visit) cancer systemic therapy, cancer radiation therapy, and cancer surgery data will be collected on the eCRF(s) for each patient in this study.

Prior cancer systemic therapy, cancer radiation therapy, and cancer surgery will be summarized. Post-treatment data might be summarized if the data warrants a meaningful summary. All collected data will be listed.

8.3. Study Treatments

Treatment cycles are 21 days in duration. Patients will receive *nab*-sirolimus 100 mg/m^2 (IV infusion over 30 minutes (+10 mins window) allowed, ie, 30 to 40 mins infusion]) on Days 1 and 8 of every 21-day cycle. Monitor patients for at least 2 hours following completion of the first infusion, and as clinically indicated for each subsequent infusion. All patients will continue treatment until PD, or unacceptable toxicity, or until in the opinion of the Investigator the patient is no longer benefiting from therapy, or at patient discretion. Three sequential dose reduction levels are allowed: 75, 56, and 45 mg/m^2. Supportive care per the institution's normal standard of care including concomitant medications can be provided at the investigator's discretion.

8.3.1. Extent of Exposure

Duration of exposure is defined as the total number of days a patient is exposed to any study drug and will be presented as the total number of days from the first dose date (Day 1) to the last dose date (date of last dose minus the date of first dose + 1) as recorded on the CRF. If the last dose date is missing, or if a patient is lost to follow-up, but the drug accountability log confirms that the patient has taken study drug, the visit date following the last completed drug accountability log will be used.

Because dose reductions may occur during the study, the exposure to study drug will also be characterized by cumulative dose, which is defined as the cumulative mg/m^2 administered to patients during the study.

Dose intensity during the treatment is defined as the cumulative dose divided by the duration of treatment. Dose intensity will be calculated as [cumulative dose in mg/m^2]/[duration of treatment].

Percentage of protocol dose (%) taken is defined as 100*sum of dose taken in study /sum of planned dose in study.

The duration of exposure, cumulative dose, Number of cycles with nab-sirolimus administered, and dose intensity will be summarized for all patients in the Full Analysis Set and will be presented in a table by summary statistics. The duration of exposure will then be classified by the number of cycles received with the number and percentage of patients in each cycle presented. Percentages will be computed from the number of patients in the Full Analysis Set.

The number and percentage of patients receiving each dose and the number of cycles administered at each dose, number and percentage of patients with at least one interruption, dose reduction, or rate reduction, and number of interrupted infusions will also be provided.

Drug exposure will also be presented in a listing.

9. Efficacy Analysis

Efficacy will be assessed by investigator using RECIST v1.1.

9.1. Timing of analysis at the end of Stage 1, at Primary Efficacy Analysis, and final analysis

This study uses Simon's 2-stage design. In the first stage, 12 efficacy evaluable patients will be accrued. By the end of this study Stage, after all 12 patients are followed up for at least 6 months or discontinue treatment for any reason prior to completing 6 months of treatment, analysis on efficacy will be performed. If there are 0 responses in these 12 patients, the study may be terminated. The study will continue to Stage 2 by enrolling 9 more patients if any responses are observed in Stage 1.

The primary efficacy analysis to address all study objectives will be conducted when all patients have had the opportunity to be treated for at least 6 months. The timing of the

primary analysis will also consider whether the majority (at least 80%) of the patients with a response have been followed for at least 6 months from the onset of response (ie, when response was first recorded). All analyses will be conducted at the time of the primary analysis, with the exception of the biomarkers which may be analyzed at a later date.

Final analysis will be performed at the end of study (EOS), defined in Section 3.1 after final database lock.

9.2. Primary Efficacy Endpoint

The primary endpoint will be ORR as measured by patients' BOR of confirmed objective response of PR or CR during the study from the time of study drug initiation. This is determined by investigator using RECIST v1.1.

ORR is defined as the proportion of patients whose BOR is a confirmed objective PR or CR per RECIST 1.1. If an initial observation of objective response (CR or PR) is made, a confirmation scan should be done at 6 weeks (±7 days) after initial observation.

All patients in the Efficacy Evaluable set will be included in the denominator.

Patients with BOR 'NE' will be summarized by reason for having unknown status.

Tumor assessments will be performed at screening and then every 6 weeks (±7 days) after Cycle 1 Day 1 for the first 12 weeks and then every 12 weeks thereafter (±7 days) with a final assessment at the end of treatment visit.

ORR will be presented along with exact 95% CIs.

9.3. Secondary Endpoints

Secondary efficacy endpoints will be conducted using the Efficacy Evaluable Set and will include DOR, DCR, TTR, PFS, and OS.

9.3.1. Duration of Response

DOR will be determined only for patients with BOR of confirmed CR or PR. DOR is defined as the time from when criteria of response of PR or CR is first met (not confirmation) until the first observation of disease progression per RECIST v1.1 or death due to any cause, whichever comes first. Patients without either of these events will be censored at their last evaluable tumor assessment. Patients who are off treatment and being followed for survival only will be censored at the time of their last scan since their subsequent disease status will be unknown.

The analysis of DOR will be conducted on the Efficacy Evaluable Set and estimated using KM methods. Median DOR and 25% and 75% quartiles will be presented along with 95% CIs. In addition, KM estimates with 95% CIs at 3, 6, 9 and 12 months will be presented for the main analysis. These timepoints will be extended for the final analysis to account for patients with >12 months of follow-up. KM curves will be constructed and presented. Numbers of patients at risk will also be displayed at monthly intervals below the time axis and censored observations will be marked by notches on the curves.

9.3.2. Disease control rate

DCR will be defined for patients with BOR of confirmed CR or PR (either of any duration) or stable disease (SD) ≥12 weeks following study drug initiation.

9.3.3. Time to Response (TTR)

TTR is defined as time from first dose of study drug to initial measurement of CR or PR after first study drug, where CR or PR is subsequently confirmed according to RECIST v1.1.

9.3.4. Progression-free Survival and Overall Survival

PFS will be assessed based on the number of months from initiation of study drug to the date of disease progression or death due to any cause. If a patient has not progressed or died by the data cutoff date, the PFS time will be censored at the time of the last evaluable tumor assessment. Patients who are off treatment and being followed for survival only will be censored at the time of their last scan since their subsequent disease status will be unknown.

OS will be assessed based on the number of months from initiation of study drug to the date of death due to any cause. If a patient is lost to follow-up before the data cutoff date or still alive by the data cutoff date the OS time will be censored at the last contact date.

The analysis for PFS and OS will be conducted on the Efficacy Evaluable Set and use the method specified in reporting convention specified in Section 5.

9.4. Exploratory Endpoints

The following exploratory endpoints will be analyzed:

- Chromogranin A (CgA) level and its correlation with response to treatment and disease progression
- The expression of pS6 and other relevant markers via immunohistochemistry and their correlation with response to treatment and disease progression
- Baseline molecular biomarkers and genomics and the association between genomic alterations and clinical outcome

The analysis of above endpoints including results of biomarker and genomic analyses may be analyzed separately by the assay/tumor biopsy vendor and is outside the scope of this SAP.

Summary statistics and presence/absence of biomarkers may be cross tabulated with patients' tumor response and PFS if appropriate.

9.5. Other Analyses

A sensitivity analysis on primary and secondary efficacy endpoints such as ORR, DOR, etc. may also be conducted using the Per-protocol Set.

- Gender (male and female)
- Age at enrollment (<65 vs ≥65 and <75 vs ≥75 years)
- ECOG Performance Status at baseline (0 vs 1) or Lansky 70–80 vs 90–100

Subgroup analysis on other parameters not listed above may also be performed if data permits and appropriate.

10. Safety Analysis

Safety analyses will be based on the Full Analysis Set. Unless otherwise specified, summary tables will include all safety assessments collected from the first administration of study drug up to 28 days after the last dose of any study drug. All safety data will be listed and those collected later than 28 days after the last dose of study drug will be flagged in the listings.

10.1. Adverse Events

Adverse events will be analyzed in terms of treatment-emergent AEs (TEAEs) which are defined as any AEs that begin or worsen on or after the start of study drug through 28 days after the last study drug, as well as those serious adverse events (SAEs) made known to the investigator at any time thereafter that are suspected of being related to investigational product. All AEs will be coded using the most recent version of Medical Dictionary for Regulatory Affairs® (MedDRA). MedDRA version will be footnoted in the tables and listings. Severity will be graded by the study personnel based on NCI National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Any adverse events recorded on the eCRF with completely missing AE onset and end dates or with completed missing onset date, the end date is on or after the first dose of study drug will also considered as TEAEs.

If a patient experiences the same AE more than once with different toxicity grades, then the event with the highest grade will be tabulated in “by grade” tables. If a patient experiences multiple AEs under the same preferred term (system organ class), then the patient will be counted only once for that preferred term (system organ class).

Summarizations of TEAEs per person-year of exposure are carried out in exposure-adjusted event rates, which is defined as number of events occurred per treatment exposure year.

The following categories of TEAEs will be summarized by system organ class and preferred term:

- TEAEs
- Treatment-emergent related AEs (TERAEs)

- TEAEs by intensity (severity grade)
- Treatment-emergent serious AEs (TESAE)
- Treatment-emergent related serious AEs (TERSAE)
- Treatment-emergent adverse event of special interest (AESI)
- TEAEs leading to study treatment discontinuation
- TEAEs leading to death

Separate listings will be provided for TEAEs, TESAEs, TE AESI, TEAEs leading to study treatment discontinuation, and TEAEs leading to death.

For safety reporting, any clinically significant findings after first dose of study drug will be evaluated by the investigator and will be recorded in the eCRF as AEs (i.e., PE, MRI, laboratory, etc).

For the purpose of inclusion in TEAE summaries, incomplete AE onset and end dates will be imputed as outlined in section 5.1.

10.1.1. Incidence of Adverse Events

Summaries of the number and percentage of patients with at least one TEAE will be provided. The number of patients will be presented by system organ class (SOC) and PT.

The most common TEAEs (occurring in ≥10% of patients) will also be summarized by SOC and PT. Summaries of TEAEs will be presented in descending order from the SOC with the highest incidence to the SOC with the lowest incidence. If the incidence for any two or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented order of descending occurrence.

10.1.2. Relationship of Adverse Events to Study Drug

According to the NCI guidance, related/unrelated AEs are classified as below:

Table 1. NCI Guidance to Define Related/Unrelated Adverse Events

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly* ***NOT related*** to the intervention
	Unlikely	The AE *is* ***doubtfully related*** to the intervention
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the intervention
	Probable	The AE ***is likely related*** to the intervention

	Definite	The AE ***is clearly related*** to the

A summary of TERAEs will be presented. The investigator will provide an assessment of the relationship of the event to the study drug. In summarization of TERAEs, if a patient reports multiple occurrences of the same TEAE, only the most closely related occurrence will be presented. TEAEs with missing relationship or a relationship other than “Not Related” will be presented in the summary as “Related” but will be presented in the data listing with a missing relationship or the actual relationship respectively. Percentages will be calculated based on the number of patients in the Full Analysis set.

The TERAE data will be categorized and presented by SOC, PT in a manner similar to that described in Section 10.1.1.

10.1.3. Severity of Adverse Event

A summary of TEAEs by severity will be presented. Severity will be graded according to the NCI CTCAE Version 5.0 criteria. The possible severities are “Grade 1 Mild,” “Grade 2 Moderate,” “Grade 3 Severe”, “Grade 4 Life-threating” and “Grade 5 Death”. In the summarization of TEAE severity, if a patient reported multiple occurrences of the same TEAE, only the most severe occurrence will be presented. TEAEs with missing severity will be summarized as “Grade 3 Severe” but will be presented in the data listing with a missing severity.

The TEAE severity data will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 10.1.1.

10.1.4. Serious Adverse Events

The seriousness of an AE will be assessed by the Investigator independently from the severity of the AE. A participant is counted once if a patient reported more than one event.

The TE SAE data will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 10.1.1.

10.1.5. Adverse Events of Special Interest

An AE of special interest (serious or nonserious) is one of scientific and medical concern specific to the Sponsor’s product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize or understand them.

Pneumonitis is considered an AE of special interest and will be monitored. Pneumonitis of any grade should be reported, irrespective of seriousness, in the same expedited manner as an SAE.

The TEAE AESI data will be listed.

10.1.6. Adverse Events Leading to Treatment Discontinuation

TEAEs with a study drug action taken of “Drug Withdrawn” will be summarized as TEAEs leading to treatment discontinuation. A patient is counted once if the patient reported more than one event.

TEAEs leading to treatment discontinuation will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 10.1.1.

10.1.7. Adverse Events Leading to Death

A summary of AEs in the database where the answer to “Outcome” is “Fatal” or “Death” is marked as “Yes” will be summarized. Percentages will be calculated out of the number of patients in the Full Analysis set.

TEAEs leading to death will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 10.1.1.

10.1.8. Overall Death

A summary of patient deaths along with the primary reasons will be presented. A patient listing on death will also be provided.

10.2. Clinical Laboratory Evaluations

Observed values and changes from baseline will be summarized for protocol defined clinical laboratory parameters at each scheduled visit using International System of Units (SI) for each laboratory parameter. Changes from baseline to each scheduled post-baseline visit will also be presented using box plots separately for each parameter at each scheduled visit.

All relevant clinical laboratory tests will be graded according to the NCI CTCAE 5.0 criteria. Grade shifts will be presented by comparing the results from baseline to worst post-baseline grade for each laboratory parameter. The number and percentage of patients with grade 3 or higher laboratory toxicities will be summarized.

A plot of median plus quartile values over time will be provided for each laboratory parameter.

Both SI units and the local units provided by the central or local laboratories will be presented in the listings.

Blood and urine samples that will be collected for clinical safety laboratory parameters (chemistry, coagulation [if applicable], hematology, urinalysis, serology, and pregnancy testing) are listed in the table below.

Table 2. Analyte Listing

Chemistry	Hematology	Other Labs
Sodium	WBC	Pregnancy test
Potassium	RBC	Sirolimus PK (central lab)
Bicarbonate	Hemoglobin	TSH
Chloride	Hematocrit	HIV Ab
Total protein	Platelets	HBV sAg
Albumin	Differential:	HBV cAb
Calcium	-Neutrophils	HCV Ab
Magnesium	-Lymphocytes	Total Cholesterol
Phosphorus	-Monocytes	HDL
Glucose	-Eosinophils	LDL
BUN	-Basophils	Triglyceride
Creatinine		
Total bilirubin		
Alkaline phosphatase		
AST (SGOT)		
ALT (SGPT)		
Amylase		
Lipase		

Summarization will take place separately for Hematology, Chemistry, and “Other Labs” parameters.

Listings of all clinical laboratory data from central laboratory with abnormal flags will be provided by patients and parameters. Listings will also be provided for collected local laboratory data.

10.3. Vital Sign Measurements

Evaluation of vital signs includes height (only at screening), weight, temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, and respiratory rate at scheduled visits.

Vital sign measurements will be listed by scheduled visit for each patient. Descriptive statistics for vital signs (except height), both observed values and changes from baseline, will be summarized over time.

10.4. Physical Examination

Abnormal physical exam results will be recorded as adverse events. Abnormal results will be included in AE listings and will be listed by body system, and preferred terms for each patient.

11. Pharmacokinetics

Not applicable.

12. References

Brookmeyer R. and Crowley J (1982). "A confidence interval for the median survival time." Biometrics 38: 29-41.

Wagner AJ, et al. (2021) nab-Sirolimus for Patients with Malignant Perivascular Epithelioid Cell Tumors. J Clin Oncol 39:3660-3670.

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Appendix 1. Schedule of Assessments

Assessment [a]	Screening [b] (Day -28 to -1)	Cycle 1 through Last Cycle (Treatment Period)		End of Treatment (EOT) Visit [d]	Follow-up Period [e]
		Day 1 [c]	Day 8		
General Assessments					
Informed Consent	X				
Demographics	X				
Medical History	X				
Physical Examination	X	X		X	
Height and Weight [f]	X [f]	X		X	
Vital Signs	X	X	X	X	
BSA Calculation [g]		X [g]			
Prior/Concomitant Medication / Procedures Evaluation [h]	X	X	X	Until 28 days after the last dose of study medication	
Performance Status (ECOG or KPS)	X	X		X	
Pregnancy Test [i]	X			X	
Biomarker: Pre-treatment tissues (archival, or fresh) [j]		X		X [j]	
Biomarker: blood sample [k]		X		X	
Survival status					X
Adverse Events	Continuous starting from signing of Informed Consent until 28 days after last dose of study medication [l]				
***nab*-sirolimus Dosing [m]**		X	X		
Local Laboratory Assessments					
Clinical Chemistry Panel	X	X		X	
CBC, Differential, Platelet Count	X	X	X	X	

Assessment [a]	Screening [b] (Day -28 to -1)	Cycle 1 through Last Cycle (Treatment Period)		End of Treatment (EOT) Visit [d]	Follow-up Period [e]
		Day 1 [c]	Day 8		
Thyroid function [n]	X	X			
HIV Ab, HBV sAg, HBV cAb, HCV Ab	X				
Fasting Lipids [o]	X	X [o]			
Imaging and Efficacy Assessments					
CT/MRI scan with contrast [p]	X	Every 6 weeks (±7 days) for first 12 weeks (3 months) after C1D1, and then every 12 weeks (±7 days) thereafter		X	

Abbreviations: Ab = antibody; β-hCG = beta human chorionic gonadotropin; BSA = body surface area; cAb = core antibody; C1D1 = Cycle 1 Day 1; CBC = complete blood count; CR = complete response; CT = computer tomography; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; HBV =hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; KPS = Karnofsky Performance Status; MRI = magnetic resonance imaging; ORR = objective response rate; PR = partial response; sAg = surface antigen; TSH = thyroid-stimulating hormone

a. Unless otherwise specified, visits must occur within ±3 days of the planned visit date.

b. Screening evaluations to be obtained ≤28 days prior to Cycle 1 Day 1 unless specified otherwise.

c. Day 1 evaluations can be omitted if screening evaluations are performed within 3 days of Cycle 1 Day 1.

d. End of Treatment Visit must occur at least 4 weeks (+7 days) after the last dose of nab-sirolimus.

e. Follow-up for survival and initiation of anticancer therapy can be performed by telephone contact after the EOT Visit every 12 weeks (±3 weeks) or more frequently if needed, from EOT Visit. All patients who discontinue study medication and have not withdrawn full consent to participate in the study will continue in the Follow-up Phase for survival and anticancer therapy. This evaluation may be made by record review and/or telephone contact.

f. Height only at Screening Visit.

g. BSA calculated according to institutional standard methods. Calculated ONLY on Cycle 1 Day 1; to be recalculated only if the weight changes by >10% in subsequent cycles. Cap BSA at 2 m2, ie, at 200 mg actual dose.

h. Prior: record all medications taken and procedures done ≤28 days prior to screening; Concomitant: any medications or procedures after the signing of informed consent.

i. For females of childbearing potential only. A serum β-hCG pregnancy test must be performed to assess patient eligibility at screening prior to first study medication administration (negative results required for study medication administration). Urine pregnancy test will be performed at EOT Visit (can be done locally) and as clinically indicated as per institutional guidelines.

j. Baseline tissue should be collected from all enrolled patients for exploratory biomarker analysis (up to 20 slides). If archival tissue is not available, fresh biopsy should be collected, if possible. For patients with tissue samples >2 years from screening, fresh biopsies are recommended. While collection of tissue is recommended, patients without tissue will be allowed on study. At the time of disease progression, if a biopsy is performed, a tumor sample will be submitted, if available. The surgical pathology report is to be submitted with the tumor tissue sample.

k. Biomarker (Chromogrannin [CgA] levels): Blood samples will be collected prior to Cycle 1 Day 1, at Week 6, Week 12 and with every 12-week scan (±1 week), and at EOT or disease progression.

l. AEs will be assessed continuously, starting from signing of Informed Consent until 28 days after last dose of study medication; see Section 10.1.2.

m. Maximum dose is 200 mg and dosing is performed after all predose assessments completed. Monitor patients for at least 2 hours following completion of the first infusion, and as clinically indicated for each subsequent infusion.

n. TSH (T3 and T4 if clinically indicated)

o. Fasting lipids are taken on Day 1 of every even numbered cycle starting with Cycle 2, eg, C2, C4, C6 etc.

p. Scans should continue on schedule regardless of delays in nab-sirolimus dosing on Week 6, Week 12, Week 24, Week 36, Week 48, etc. The same modality (CT or MRI scan with contrast should be used throughout the study. If an initial observation of ORR is made (CR or PR), a confirmation scan should be done 6 weeks (±1 week) after initial observation. EOT Visit scan should be performed only for those patients who discontinue treatment for a reason other than disease progression.