Statistical Analysis Plan (SAP)

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Protocol TSC-007

A Phase 2 multi-center open-label basket trial of *nab*-sirolimus for adult and adolescent patients with malignant solid tumors harboring pathogenic inactivating alterations in *TSC1* or *TSC2* genes

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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
DMC	data monitoring committee
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
NGS	next generation sequencing
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PE	Physical Examination
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
RAS	Rat sarcoma
RBC	Red blood cell

RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SI	International System of Units
SOC	system organ class
T3	triiodothyronine
T4	thyroxine
TMB	tumor mutation burden
TSC	tuberous sclerosis complex
TSH	thyroid stimulating hormone
TTR	time to response
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

TSC1 and *TSC2* are the tumor-suppressor genes in the mechanistic target of rapamycin (mTOR) pathway located upstream of mTOR.

Inactivating alterations of *TSC1* and *TSC2* genes are found at low frequencyin various cancer types and have been shown to lead to mTORC1 activation.

Solid tumors where *TSC2* mutations are most frequent include hepatocellular carcinoma, melanoma, renal cell carcinoma, gynecologic cancers, and sarcoma. For *TSC1* mutations, bladder cancer, melanoma, renal cancer, and endometrial cancer are the most frequent tumor types.

There are no drugs approved for tumors harboring *TSC1* or *TSC2* inactivating alterations. Tumors with *TSC1* or *TSC2* inactivating alterations are treated according to their respective standards of care without regard to these mutations. There is substantial unmet medical need for these patients with advanced cancer as standard of care approaches eventually fail in essentially all patients. Data from the PEC-001 study demonstrates activity of *nab*-sirolimus in patients with malignant PEComa expressing *TSC1* and *TSC2* pathogenic inactivating alterations (Wagner et al, 2021). Additionally, observations of radiographic responses across several tumor types in the PEX-002 expanded access program provide additional evidence that *nab*-sirolimus should be investigated in patients harboring *TSC1* and *TSC2* inactivating alterations.

This Phase 2 tumor agnostic basket trial will evaluate the efficacy and safety of *nab*-sirolimus in patients with solid tumors harboring pathogenic inactivating *TSC1* or *TSC2* alterations.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objectives

- To determine clinical benefit as described by the overall response rate (ORR) of *nab*-sirolimus via independent radiographic review (IRR) in patients with malignant solid tumors with pathogenic inactivating alterations in *TSC1* or *TSC2* genes

Secondary Objectives

- To evaluate the duration of response (DOR), disease control rate (DCR), time to response (TTR), progression-free survival (PFS) via IRR, and overall survival (OS) of *nab*-sirolimus
- To evaluate changes in Quality-of-Life
- To describe the safety and tolerability of *nab*-sirolimus

Exploratory Objectives

- To evaluate efficacy via investigator-assessed responses and PFS
- To evaluate the time on treatment
- To evaluate the rate of surgical resection for patients with inoperable locally advanced disease
- To evaluate baseline genomics and the association between genomic alterations and clinical outcome, as well as genomic changes during treatment

2.2 Endpoints

Primary Endpoint

- ORR based on the proportion of patients with best overall response (BOR) of confirmed partial response (PR) or complete response (CR) as determined by IRR using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Secondary Endpoints

- DOR: Determined for patients with BOR of confirmed CR or PR (by IRR)
- DCR: BOR of confirmed CR or PR (either of any duration) or stable disease (SD) ≥12 weeks following study treatment initiation (by IRR)
- TTR: Time from first dose of study drug to initial measurement of CR or PR, where CR or PR is subsequently confirmed

- 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
- Changes from baseline in the European Organization for Research and Treatment of Cancer QOL Questionnaire v3.0 (EORTC-QOL-C30) scores, evaluated for each Arm separately and both Arms together
- 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, evaluated for each Arm separately and both Arms together

Exploratory Endpoints

- Investigator assessed ORR, DOR, DCR, TTR and PFS
- Time on treatment (including patients treated beyond progression)
- Rate of surgical resection with curative intent for patients with inoperable locally advanced disease at baseline
- From Baseline tumor tissue (archival or fresh biopsy) and blood (peripheral blood mononuclear cells, PBMCs):
    - To characterize *TSC1* and *TSC2* alterations as germline vs somatic (PBMCs, using next generation sequencing [NGS])
    - To understand the concomitant alterations and allele frequency via a standardized method (secondary confirmation) (tissue, using NGS)
    - To evaluate the association between genomic mutational profile and clinical outcome
    - To evaluate the expression of pS6 and other relevant markers via immunohistochemistry
- Identify dynamic clonal changes from blood samples collected at baseline and during treatment

3. OVERALL STUDY DESIGN

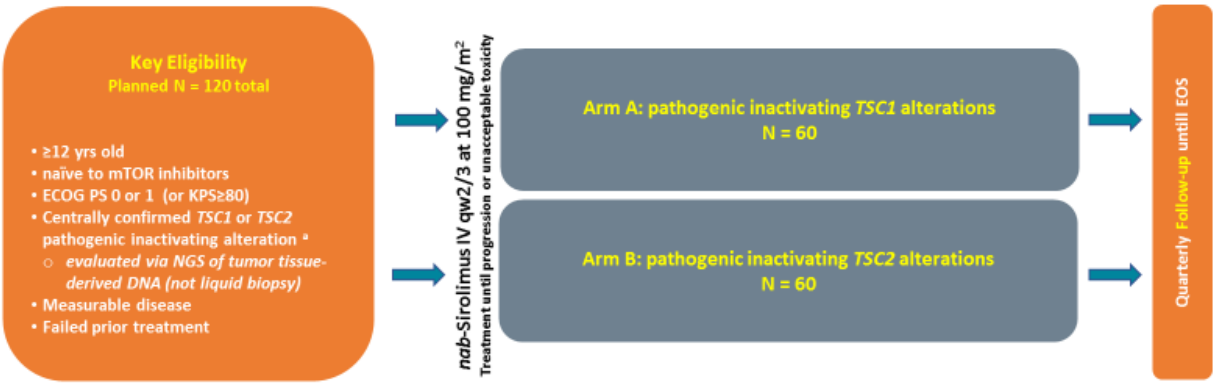
3.1. Study Design

TSC-007 is a prospective phase 2, open-label, multi-institutional basket trial to determine the efficacy and safety profile of *nab*-sirolimus administered by intravenous (IV) infusion to patients with pathogenic inactivating *TSC1(Arm A)* or *TSC2(Arm B)* alterations, studied in 2 independent Arms (Arms A, and B).

It is highly unlikely that pathogenic inactivating *TSC1* and *TSC2* alterations co-exist, but if such case occurs, that patient must be assigned to the Arm B. Patients with any malignant tumor type will be considered for this study if they meet the relevant mutational criteria; however, to avoid over-enrolling in any one type of tumor type, as defined by organ and histology, will be capped at 15 patients in each Arm.

A cycle will consist of 21 days. Patients will receive *nab*-sirolimus by IV infusion over 30 minutes (+10 mins window allowed, ie 30–40 mins infusion) once weekly for 2 weeks followed by a week of rest (qw2/3). The starting dose of *nab*-sirolimus will be 100 mg/m^2. Four sequential dose reductions are allowed: 75, 56, 45, and 35 mg/m^2.

Figure 2: Study Schema



a. Central confirmation of *TSC1* and *TSC2* pathogenic inactivating alterations is via evaluation of NGS Reports. Patients will be enrolled only AFTER central confirmation of eligibility

Note: TSC1 and TSC2 alterations must be determined by analytically validated NGS tests performed in CLIA-certified laboratories.

Patients will continue treatment until disease progression, 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 on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/ GCP and applicable regulatory requirements.

Study Duration

The study will enroll patients in approximately 25-35 sites in the US and additional sites in south Korea and is expected to take approximately 30 months from first patient enrolled to last patient follow-up, including approximately 18-24 months of enrollment period (from first to last patient in), allowing a minimum of 6 months of treatment for all enrolled patient, a 28-day screening and a 28-day (4 week) safety follow-up after the last dose.

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 at least 4 weeks (+7 days) after the last dose of *nab*-sirolimus.

End of Study (EOS) for a patient is defined as the date of last follow-up which is defined as last visit date on or before withdrawal/completion/death.

The **EOS** for TSC-007 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 completes or 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 and response, 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 ADJUSTMENTS / MODIFICATIONS

Doses will be reduced for hematologic and non-hematologic toxicities, as clinically indicated. Up to 4 sequential dose reductions are permitted (75, 56, 45, and 35 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:

- General guidelines for clinically significant toxicities related to study treatment

  and
- Specific guidelines for selected adverse events, that have been observed with higher frequency and/or severity (TSC-007 protocol Table 6).

5. GENERAL CONSIDERATIONS

The 2 Arms (Arm A and Arm B) will be analyzed independently. The primary analysis for each Arm may occur at different times, should either of the Arms complete enrollment earlier. The primary analysis to address all study objectives for each Arm will be conducted when all patients have had the opportunity to be treated for at least 6 months within an Arm. 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 exploratory efficacy and safety analyses will be conducted at the time of the primary analysis, except for the biomarkers which may be analyzed at a later date. Once final analyses of study Arms A and B have been completed, the primary endpoint (ORR) and select secondary endpoints (eg. DOR) may be summarized using the combined data in both Arms if there is lack of heterogeneity in response assessment among the Arms.

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 analyzed separately for each Arm and as well as for both Arms combined using the data collected for both Arms, up to the time of data lock for each primary analysis.

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

- An image review charter will outline the procedures for the independent radiology assessment.
- A clinical study report (CSR) will be generated when the primary analysis has been completed for each study Arm. 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, 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. If necessary, the first and third quartiles will also be presented with the same precision as raw data.
- 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 dichotomous efficacy endpoints 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 9.3 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 (Brookmeyer-Crowley) 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 January will 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 the date of the last dose of study drug is missing, then replace it with the last visit date. 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.

5.2. Sample Size

Sample size calculation is based on the primary efficacy endpoint of proportion of patients with a confirmed CR or PR across all tumor types within an Arm.

The planned sample size for this study is approximately 60 treated patients per Arm. The sample size was determined based on the ability to produce a 95% confidence interval which would exclude an ORR of 20% if the observed best ORR is 32%.

The 95% exact CIs for target ORRs ranging from 30% to 55% with sample size of 60 is summarized in Table 1.

Table 1. Observed ORR with Exact 95% CI

Observed ORR	95% Exact CI
30%	[18.8% - 43.2%]
31.7%	[20.3% - 45.0%]
33.3%	[21.7% - 46.7%]
35%	[23.1% - 48.4%]
36.7%	[24.6% – 50.1%]
38.3%	[26.1% – 51.8%]
40%	[27.6% – 53.5%]
45%	[32.1% – 58.4%]
50%	[36.8% – 63.2%]
55%	[41.6% – 67.9%]

CI = confidence interval; ORR = overall response rate

Based on limited knowledge of efficacy in the development of *nab*-sirolimus in patients with various solid tumors and based on efficacy data in patients with malignant PEComa (study PEC-001), there is a potential to observe different ORR rates for patients in Arm A and Arm B after *nab*-sirolimus treatment.

Each Arm is designed as an independent trial in this study. A futility analysis will be conducted once 11 patients have had the opportunity to be treated for at least 3 months and have at least one post baseline response assessment in one of the arm. Enrollment may be stopped if no response is observed; however, the decision with regards to futility will be non-binding. The response rate in the other Arm with fewer than 11 treated patients will also be examined at the time of this futility analysis. The futility analysis with 11 treated patients may not be performed in the Arm with lower enrollment if at least one response is observed during the futility analysis for the first Arm. The sample size of 11 was chosen to be sure that the chance to stop the study for the Arm is <=2% if the true ORR is >=30%. The details are in Section 12.2.

The interim analysis for efficacy will be performed when 40 (67%) of the planned patients in either Arm have had the opportunity to be treated for at least 6 months and have at least one post baseline response assessment.

Two key analyses will be performed at each Arm's interim analysis for efficacy:

(1) The O'Brien-Fleming boundary will be checked, and superiority will be declared if the O'Brien-Fleming boundary is crossed, otherwise

(2) the Bayesian predictive probability of success will be calculated to adjust the sample size for the final analysis. The smallest sample size that provides $\geq$90% predictive probability of success will be chosen for the final analysis.

The details are specified in Section 12.2.

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 primary analysis of all efficacy and safety endpoints will be performed on the Full Analysis Dataset.

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 treatment scan for tumor evaluation. A sensitivity analysis of the primary, secondary efficacy analysis 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, number of screening failures, enrolled, patients received study treatment, patients who discontinued study treatment, patients who discontinued the study.

The reasons for screening failure, study treatment, and study participation, and duration on study in each Arm will also be summarized. Patient disposition data will be presented in a listing.

6.2. Protocol Deviations

Protocol deviations (including violations) will be tracked by the clinical team on an ongoing basis. CSR reportable vs non-CSR reportable protocol deviations are defined prior to the start of study enrollment according to clinical assessment.

During the conduct of the study the CSR reportable protocol deviations will be reviewed periodically by the sponsor to identify major protocol deviations. The following categories may be considered major protocol deviations:

- Subject that did not meet entry criteria compromised patient safety or study data integrity.
- Study procedure that compromised patient safety or study data integrity

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 major protocol deviations will be tabulated for each Arm. COVID-19 related protocol deviations may be summarized separately. 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)
- Tumor type
- Eastern Cooperative Oncology Group (ECOG) Performance Status or Karnofsky Performance Status (KPS) or Lansky play-performance scale
- Baseline QOL
- Number of prior lines of therapies (≤3, >3)
- Time from Initial Diagnosis to Informed Consent (months)
- Disease stage at initial diagnosis
- Current disease stage

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 overall, for each system organ class and preferred term. Percentages will be calculated based on number of patients in the Analysis population used.

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 patients in a data listing.

8. TREATMENTS AND MEDICATIONS

8.1. Prior and Concomitant Medications and Procedures

Prior medications are to be collected prior to Cycle 1 Day 1. Concomitant medications or procedures are either to be collected after Cycle 1 Day 1 of the study, or when the prior medications are continued after Cycle 1 Day 1. Prior and concomitant medication name along with indication, dose, unit, frequency, route, start and stop date will be recorded on each patient's eCRF(s).

Prior and post treatment radiation location, total dose (cGy), intent of procedure, start and stop date will be recorded on each patient's eCRF(s).

Prior and post treatment surgery will have type of surgery, indication, intent of procedure, and location recorded on each patient's 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 post treatment surgery will be coded using MedDRA dictionary.

Prior and Concomitant medications, prior and post treatment radiations, prior and post treatment surgeries will be summarized by Arm. All prior and concomitant medications, prior and post treatment radiations, prior and post treatment surgeries will also be presented in a listing.

The number of patients who took prohibited medications or underwent prohibited procedures listed in section 8.2 of the protocol will be summarized and listed.

8.2. Prior and Post Systemic Therapy

Prior and post treatment systemic therapy are to be collected in this study. Medication name along with line of therapy setting (neo-adjuvant adjuvant, adjuvant, locally advanced, palliative, metastatic), number of cycles, best overall response, reason to discontinuing, start date and stop date will be recorded on each patient's eCRF(s).

Prior and post treatment systemic therapy will be coded using WHO Drug dictionary. The latest version of the WHO Drug will be used during the course of the study.

Prior systemic therapy will be summarized by Arm. All prior and post treatment systemic therapy will also be presented in a listing.

8.3. Study Treatments

Treatment cycles are 21 days in duration and patients are treated until disease progression or unacceptable toxicities. Patients will receive *nab*-sirolimus100 mg/m^2 (IV infusion over 30 minutes, +10 min) weekly for 2 weeks (on Day 1 and Day 8) followed by a week of rest. Four sequential dose reduction levels are allowed: 75, 56, 45, and 35 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 months from the first dose date (Day 1) to the last dose date (date of last dose minus the date of first dose + X days)/30.4). If the last cycle has only one dose then X=7, if last cycle has two doses then X=14 in the formula. This is based on weekly dose and one week rest after second dose schedule in each cycle. 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 number of weeks between last and first doses accounting for rest week between cycles.

The duration of exposure, time on each infusion (min), cumulative dose in mg, cumulative dose in mg/m^2, 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. Descriptive and categorical summary (>=90%, 80% to <90%,70% to <80%,<70%) on percentage of planned Protocol dose administered , will be tabulated.

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

A summary of each patient’s exposure will be presented in a listing.

9. EFFICACY ANALYSIS

Efficacy will be assessed by independent radiologic review using CT or MRI scans using RECIST v1.1. While the primary and secondary efficacy endpoints are based on the independent radiology review, summary tables will also be produced for investigator assessed response evaluations as exploratory analyses.

9.1. Timing of Primary Efficacy Analysis

The primary efficacy analysis to address all study objectives in each Arm will be conducted when all patients within an Arm have had the opportunity to be treated for at least 6 months. Efficacy analyses of an Arm will be done independently since the primary analysis for each Arm may occur at different times. 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 for each arm, except for the biomarkers which may be analyzed at a later date.

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 independent radiologic assessment using RECIST v1.1. The independent radiologic review will follow a separate imaging charter.

ORR is defined as the proportion of patients whose BOR is a confirmed objective PR or CR per RECIST 1.1. Patients without a post-baseline disease assessment will be considered not to have achieved a response. 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.

The analysis of ORR will be conducted separately in each Arm. All patients in the Full analysis 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 year and then every 12 weeks thereafter (±7 days) with a final assessment at the end of treatment visit.

ORR will be presented for each Arm along with exact 95% CIs.

9.3. Secondary Endpoints

Secondary efficacy endpoints will be conducted using the Full Analysis Set and will include DOR, DCR, TTR, PFS via IRR.and OS.

9.3.1. Time to Response (TTR) and Duration of Response (DOR) via IRR

TTR and DOR will be determined only for patients with BOR of confirmed CR or PR via IRR.

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.

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 TTR and DOR will be conducted on the Full Analysis Set and estimated using KM methods. Median 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 on DOR will be presented. 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 for each Arm. Numbers of patients at risk will also be displayed at monthly intervals below the time axis and censored observations will be marked on the curves.

9.3.2. Disease control rate via IRR

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 via IRR. DCR is defined as the time from when criteria of response of PR, CR, or SD 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.

DCR will be presented for each Arm along with exact 95% CIs.

9.3.3. Progression-free Survival via IRR and Overall Survival

PFS will be assessed based on the number of months from initiation of study drug to the date of disease progression via IRR 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 in each Arm will be conducted on the Full Analysis Set and use the method specified in reporting convention specified in Section 5.

In addition, KM estimates with 95% CIs at 3, 6, 9 and 12 months will be presented. These timepoints will be extended for the final analysis to account for patients with >12 months of follow-up.

9.4. Exploratory Endpoints

Investigator assessed ORR, DOR, TTR, DCR, and PFS will be summarized using the same method specified for the ORR, DOR, TTR, DCR, and PFS by IRR in section 9.2 and 9.3 above.

Time on treatment (including patients treated beyond progression) will be reported under Section 8.2.1, extent of exposure, defined as the time from the first dose to last dose. For patients with locally advanced disease at baseline, the rate of surgical resection will be summarized descriptively.

The analysis of other exploratory endpoints including results of biomarker and genomic analyses from exome sequencing (tumor tissue and blood) and immunohistochemistry will be analyzed separately by the assay/tumor biopsy vendor and is outside the scope of this SAP. Patients with somatic vs genomic *TSC1* or *TSC2* mutations will be cross tabulated by response. In addition, presence/absence of genomic biomarkers may also be cross tabulated with patients' tumor response.

9.5. Other analyses

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

In addition, the following covariates will be used to examine efficacy in subgroups within Arms if at least 5 patients are treated in a given subgroup category:

- Gender (male and female)
- Age at enrollment (<65 vs ≥65 and <75 vs ≥75 years)
- ECOG Performance Status at baseline (0 vs 1 vs 2) or KPS 70-80 vs 90-100 or Lansky 70–80 vs 90–100
- Number of prior lines of therapies (≤3 vs >3)
- Tumor Type (for each tumor type or group all tumor types that treated at least 5 patients vs the ones treated <5 patients, all tumor types with less than 5 patients will be pooled together in one group labeled 'Other')
- Somatic vs germline *TSC1* or *TSC2* mutations

Analysis for impact of COVID-19 on efficacy may also be performed if data permits.

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. All safety analyses will be conducted for each Arm separately and for all Arms combined.

10.1. Adverse Events

Adverse events (AE) 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 the study drug. 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 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

Any adverse events recorded on the eCRF with AE onset and end dates completely missing or with only onset date completely missing, 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, TEAESI, TEAEs leading to study treatment discontinuation, and TEAEs leading to death.

For safety reporting, any clinically significant findings after first dose of study drug from physical examinations, laboratory tests, vital signs, or diagnostic procedures will be evaluated by the investigator and will be recorded in the eCRF as AEs..

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 for each Arm and for Arms combined. The number of patients will be presented by system organ class (SOC) and PT.

The most common TEAEs (occurring in ≥10% of patients in a given Arm) will also be summarized by SOC and PT. Summaries of TEAEs will be presented in descending order from the SOC with the highest total incidence (in the combined Arm) to the SOC with the lowest total incidence (in the combined Arm). If the total 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 in order of descending occurrence in the combined Arm.

10.1.2. Relationship of Adverse Events to Study Drug

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

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to investigational agent/intervention[1]	Unrelated	The AE *is clearly* ***NOT*** *related* to the intervention.
	Unlikely	The AE *is* ***doubtfully related*** to the intervention.
Related to investigational agent/intervention[1]	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 intervention.

[1]Adapted from: NCI Guidelines for Investigators: Adverse event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs. Effective September 16, 2013.

A summary of TEAEs by relationship (i.e. “Related” and “Not Related”) to study drug will be presented. The investigator will provide an assessment of the relationship of the event to the study drug. In summarization of TEAEs, 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 TEAE data will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 10.1.1.

10.1.3. 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 *nab*-sirolimus, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation to characterize or understand them.

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

The TE 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 for on treatment (defined as deaths from first dose of study medication to ≤28 days of last dose of study medication) and during follow up (defined as deaths on study but after 28 days from last study medication) along with the primary reasons will be presented for each Arm as well as for Arms combined. 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 in each Arm at each scheduled visit. The above-mentioned analyses will also be provided for the Arms combined.

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 laboratory 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 for each Arm as well as for Arms combined

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.

10.5. Electrocardiogram

ECG will be monitored at screening, Cycle 1 Day 1 and Cycle 3 Day 1, and thereafter as clinically indicated. In each case ECG is to be monitored during infusion around the 30 min time point after start of infusion to coincide with the end of infusion period which lasts 30 minutes.

ECG results (rhythm, heart rate, PR interval, QRS duration, QT Interval, derived QTcF, and overall ECG results) will be summarized. QTcF, Fridericia's Correction formula, is defined as QT divided by Cube Root RR(seconds).

Summaries of actual values and changes from baseline over time for each ECG parameter will be presented. For QTcF, values greater than 450 msec or change from baseline of over 30 msec, on the first day of each cycle and at end of study will also be presented.

The overall ECG interpretation will be summarized by presenting the number and percentage of patients with 'Normal', 'Abnormal, not clinically significant' and 'Abnormal, clinically significant'. Shift from baseline to worst during the treatment period in the overall ECG interpretation will be displayed in crosstabulations.

Descriptive summaries of actual values and changes from baseline for the ECG parameters, in addition to QTcF, will also be presented type of disease.

11. PHARMACOKINETICS

Whole blood samples for sirolimus trough (pre-treatment) levels will be analyzed centrally for all patients from Cycle 1 Day 1 through Cycle 4 Day 8:

- on Cycles 1, 2, 3, and 4 on Days 1 and 8 (C1D1, C1D8, C2D1, C2D8, C3D1, C3D8, C4D1, and C4D8) anytime predose (before infusion).

Additionally, from 30 patients who sign an optional PK/ECG informed consent, post-infusion blood samples will be collected

• on Cycle 1 Day 1 at 15 minutes (±10 min), 30 minutes (±10 min, end of infusion), 1 hr (±10 min), 2 hrs (±10 min), and 4 hrs (±10 min) after the start of infusion, and

• on Cycle 3 Day 1 at 30 mins (±10 min) after the start of infusion.).

Sirolimus concentration data will be summarized for each patient along with date, study day, nominal and actual time of blood sampling for sirolimus.

The analysis of PK parameters will be prepared by a PK analysis vendor and is outside of this statistical analysis plan.

12. INTERIM ANALYSIS

12.1. Interim Data Monitoring Plan

An external DMC will review study data as follows:

For Safety

- When the 40th patient has been treated in study (considering treatment across Arms A and B) and has had 1 post-baseline scan
- When the 80th patient has been treated in study (considering enrollment across Arms A and B) and has had 1 post-baseline scan

For Efficacy

- Futility analysis, which will occur when 11 patients have had the opportunity to be treated for at least 3 months and have at least one post baseline response assessment in either Arm
- Interim analysis for efficacy which will also occur separately in each arm when approximately 40 patients have had the opportunity to be treated for at least 6 months and have at least one post baseline response assessment

Ad hoc DMC meetings, including in the event of a death (any reason) that may be at least possibly attributed to *nab*-sirolimus, will be held.

The DMC will consist of at least 2 clinicians with experience in relevant specialties and 1 statistician.

If the first 7 patients treated within a tumor type (within an Arm) have no responses after at least 1 post-baseline scan of the 7th patient (0/7 rule, monitored by the CRO), then further experience in enrollment for that tumor type within an Arm will be halted until the DMC recommends further action. The probabilities of seeing 0 responder are below:

Table 1. Probability of Observing 0 Responders Out of N Patients

N	observed K	True Rate	Prob of Observing k/N
5	0	0.15	44%
5	0	0.20	33%
5	0	0.25	24%
5	0	0.30	17%
5	0	0.35	12%
5	0	0.40	8%
5	0	0.45	5%
5	0	0.50	3%
5	0	0.55	2%
6	0	0.15	38%
6	0	0.20	26%
6	0	0.25	18%
6	0	0.30	12%
6	0	0.35	8%
6	0	0.40	5%
6	0	0.45	3%
6	0	0.50	2%
6	0	0.55	<1%
7	0	0.15	32%
7	0	0.20	21%
7	0	0.25	13%
7	0	0.30	8%
7	0	0.35	5%
7	0	0.40	3%
7	0	0.45	2%
7	0	0.50	<1%
7	0	0.55	<1%

Details regarding the responsibilities of the DMC will be outlined in the DMC charter.

12.2. Futility Analysis and Interim Analysis for Efficacy

Each interim analysis will occur independently for Arm A and Arm B.

12.2.1. Futility Analysis

The futility analysis with 11 patients who have had the opportunity to be treated for at least 3 months and have at least one post baseline response assessment in any Arm

will be performed. The enrollment may be stopped if we observe no response among 11 patients but the stopping for futility is non-binding.

The response rate in the other Arm with fewer than 11 treated patients will also be examined at the time of this futility analysis. If there is at least one response at this time, then the futility analysis with 11 treated patients need not be performed in the Arm with lower enrollment. The sample size of 11 is chosen to make sure that the chance of stopping the study is <=2% if final observed ORR is >=30% according to the table below.

Table 3. Probability to claim futility based on various observed response rate

Observe	ORR 0.20	ORR 0.30	ORR 0.31	ORR 0.32	ORR 0.33	ORR 0.34	ORR 0.35
Futility	0.086	0.020	0.017	0.014	0.012	0.010	0.009

No alpha spending occurs at these interims as no early success stopping is possible.

12.2.2. Interim Analysis for Efficacy

The interim analysis for efficacy and sample size re-calculation will be performed when approximately 40 patients have had the opportunity to be treated for at least 6 months and have at least one post baseline response assessment in any Arm. If the criterion for early stopping is met in the first Arm (the first to reach 40 patients with IRR response data), the ORR by IRR will be reported descriptively at that time in the 2nd Arm and for the pooled Arms

At the interim, ORR and the exact binomial confidence interval will be calculated.

The efficacy based on ORR by IRR will be declared at the interim analysis for efficacy with approximately 67% information proportion of the planned sample size of 60 based on O'Brien-Fleming boundary and if the O'Brien-Fleming boundary is crossed. This is analogous to produces a 1-sided boundary of 0.0071 at the 40-patient interim analysis. Observing 16 responses among 40 patients, 40% and double the 20% goal, would achieve this early stopping rule.

Bayesian predictive probability of success will be calculated to adjust the sample size for the final analysis if the O'Brien-Fleming boundary is not crossed. The smallest sample size that provides ≥90% predictive probability of success will be chosen for the final primary analysis.

If at the interim, X_o responses are observed in N_o (N=40) patients, then the predictive probability is calculated as follows:

Let p = ORR and use a uniform prior,

$$p \sim Beta(1,1).$$

Then the current posterior probability for the ORR is

$$p|X_o,N_o \sim Beta(1+X_o, 1+N_o-X_o)$$

And the probability of the 'new' sample being responses given Nn additional study subjects is

$$X_n \sim Binomial(N_n, p)$$

Where N_n ("N new") may range from 20 to 50 thus creating a final sample size of 60 to 90 study participants. There would be a maximum of 90 patients per arm.

This distribution may also be written as a beta-binomial

$$X_n|N_n,X_o,N_o \sim Beta\text{-}Binomial(N_n, 1+X_o, 1+N_o-X_o)$$

Then the predictive probability for any given final sample size, Nf, is the sum of the probabilities for which the final p-value is < 0.025.

$$PredProb(N_f) = \sum_{x=0}^{N_n} \Pr(X_n|N_n, X_o, N_o)\, I(\text{Exact } 95\% \text{ CI} > 20\%)$$

Here the indicator function is 1 if the entire exact 95% confidence interval is > 20% and 0 otherwise. This is calculated for every value from i = 0 to Nn out of the Nn remaining subjects. Therefore, the sum only sums the probabilities of X_n that provide cases where the confidence interval entirely exceeds the performance goal at the final analysis.

Because of the discreteness of the sampling distribution, there are a finite number of trial paths and the Type 1 error of the design described is 0.0180. This was verified through simulation. Running 100 sets of 100,000 simulations with various seeds, the Type 1 error was shown to be well controlled.

The table below provides the overall study power based on the final sample size and varies by true ORR rate. The design offers >80% power if the true ORR is 34% or greater.

Table 4. Study Power Based on the Final Sample Size and True ORR rate

True ORR	0.20	0.30	0.31	0.32	0.33	0.34	0.35	0.36	0.37	0.38	0.39	0.40
Power	0.018	0.531	0.609	0.682	0.747	0.815	0.849	0.887	0.916	0.939	0.956	0.968

13. REFERENCES

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

TSC-007 Basket Trial Protocol (Precision 1)_V5

1. 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	
Vital Signs, Height and Weight [f]	X	X [f]	X [f]	X [f]	
BSA Calculation [g]		X [g]			
ECG (12-lead) [h]	X	X [h]			
EORTC-QOQ-C30 v3.0 [i]		X [i]			
Prior/Concomitant Medication / Procedures Evaluation [j]	X	X	X	Until 28 days after the last dose of IP	
Performance Status (ECOG or KPS or Lansky)	X	X		X	
Pregnancy Test [k]	X			X	
Biomarker: Pre-treatment tissues (archival, or fresh) [l]	X				
Biomarker: blood sample [l]	X	X [l]		X	
Survival status					X
Blood Sample for Sirolimus (PK) [m]		Pre-treatment [m]	Pre-treatment [m]		
Adverse Events	Continuous starting from signing of Informed Consent until 28 days after last dose of IP				
***nab*-sirolimus Dosing**		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	X	X			
HIV Ab, HBV sAg, HBV cAb, HCV Ab	X				
Fasting Lipids [n]	X	X [n]			
Imaging and Efficacy Assessments					
CT/MR [o]	X	Every 6 weeks (±7 days) after C1 D1 for the first year, then every 12 weeks (±7 days) thereafter		X	

Ab = antibody; BSA = body surface area; cAb = core antibody; ECG, electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QOQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EOT = End of Treatment; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; KPS = Karnofsky Performance Status; PK = pharmacokinetic PT = prothrombin time; PTT = partial thromboplastin time; sAg = surface antigen

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 enrollment unless specified otherwise.

c. Day 1 evaluations can be omitted if screening evaluations are performed within 72 hours 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 that discontinue study drug 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. Vitals and weight only. On Day 8, vitals only.

g. Calculated ONLY on C1/D1; to be recalculated only if the weight changes by >10% in subsequent cycles. Cap BSA at 2 m^2, ie at 200 mg actual dose.

h. ECG is performed at screening, at Cycle 1 Day 1 and on Cycle 3 Day 1, thereafter as clinically indicated. In each case, ECG should be performed during infusion around the 30 minutes timepoint after the start of the infusion to coincide with the end of the 30-min infusion. The ECG data (QTc) will be analyzed by a central laboratory for a subset of patients.

i. EORTC-QOQ-C30 v3.0 should be done prior to treatment on day 1 of each cycle, and up to cycle 24 (approximately 1.5 yrs).

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

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

l. Baseline tissue to be collected from all patients for exploratory biomarker analysis (min 20 slides). If archival tissue is not available, fresh biopsy should be collected. For patients with tissue samples >2 years from screening, fresh biopsies are recommended. Blood samples will be collected at baseline, at every 12-week scan for the first year, and at EOT or disease progression.

m. PK samples to be taken only prior to dosing from Cycle 1 Day 1 through Cycle 4 Day 8 (C1D1, C1D8, C2D1, C2D8, C3D1, C3D8, C4D1, and C4D8) evaluated in a central laboratory.

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

o. Scans should continue on schedule regardless of delays in *nab*-sirolimus dosing on week 6, week 12, week, 18, week 24, etc. The same modality (CT or MRI) should be used throughout the study. If an initial observation of objective response (CR or PR) is made, a confirmation scan should be done 6 weeks after initial observation. EOT visit CT/MRI should be performed only for those patients that discontinue treatment for a reason other than disease progression per RECIST 1.1.