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

Investigational Product:	**sirolimus protein-bound particles for injectable suspension (albumin-bound) (ABI-009, *nab*-sirolimus)**
Protocol Number:	**TSC-007**
Study Phase:	**2**
Sponsor Name / Address:	**Aadi Bioscience, Inc (Aadi)** 17383 Sunset Blvd., Suite A250 Pacific Palisades, CA 90272

Protocol Versions	Date
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PROTOCOL APPROVAL

Protocol: TSC-007

Issue Date: V5.0, South Korea V2.0, Aug 01, 2023

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

{See appended electronic signature page}

Loretta M. Itri, MD, FACP Chief Medical Officer Aadi Bioscience, Inc.	Date

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**

Printed Name of Site Principal Investigator

Institution Name:_____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Aadi representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

PROTOCOL SYNOPSIS

INVESTIGATIONAL PRODUCT	sirolimus protein-bound particles for injectable suspension (albumin-bound), (ABI-009, *nab*-sirolimus)
TITLE	A Phase 2 multi-center open-label basket trial of *nab*-sirolimus for adult patients with malignant solid tumors harboring pathogenic inactivating alterations in *TSC1* or *TSC2* genes
PROTOCOL NUMBER	TSC-007
PHASE	Phase 2

Objectives	**Endpoints**
Primary	
• 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	• ORR based on 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 disease progression as determined by IRR using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary	
• To evaluate the duration of response (DOR), disease control rate (DCR), time to response (TTR), and progression-free survival (PFS) via IRR, and overall survival (OS) of *nab*-sirolimus	• 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

Objectives	Endpoints
• To evaluate changes in Quality-of-Life	• Changes from baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire v3.0 (EORTC-QOQ-C30) scores
• To describe the safety and tolerability of *nab*-sirolimus	• 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
Exploratory	
• To evaluate efficacy via investigator-assessed responses and PFS	• Investigator-assessed ORR, DOR, DCR, TTR, and PFS
• To evaluate the time on treatment	• Time on treatment (including patients treated beyond progression)
• To evaluate the rate of surgical resection for patients with inoperable locally advanced disease after treatment with *nab*-sirolimus	• Rate of surgical resection with curative intent for patients with inoperable locally advanced disease at baseline
• To evaluate baseline genomics and the association between genomic alterations and clinical outcome, as well as genomic changes during treatment	• From baseline tumor tissue (archival or fresh biopsy) and blood (peripheral blood mononuclear cells, PBMCs): o To characterize *TSC1* and *TSC2* alterations as germline versus somatic (PBMCs, using next generation sequencing [NGS]) o To understand the concomitant alterations and allele frequency via a standardized method (secondary confirmation) (tissue, using NGS) o To evaluate the association between mutational profile and clinical outcome o 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

STUDY DESIGN AND TREATMENT	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 malignant solid tumors with pathogenic inactivating *TSC1* (Arm A) or *TSC2* (Arm B) alterations, each Arm studied independently.

	It is highly unlikely that pathogenic inactivating *TSC1* and *TSC2* alterations co-exist, but if such case occurs, that patient must be assigned to Arm B, if eligible. To avoid over-enrolling in any one tumor type, as defined by organ and histology, enrollment will be capped at 15 patients for each organ-histology 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). *nab*-Sirolimus will be administered at 100 mg/m^2. Four sequential dose reductions are allowed: 75, 56, 45, and 35 mg/m^2. 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 for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.
PREVALENCE	The prevalence of pathogenic inactivating *TSC1* and *TSC2* alterations is relatively low but they are detected in a wide variety of malignancies. For *TSC1* alterations, bladder cancer, melanoma, renal cancer, and endometrial cancer are the most frequent tumor types. Solid tumors where *TSC2* alterations are most frequent include hepatocellular carcinoma, melanoma, renal cell carcinoma, gynecologic cancers, and sarcoma.
SAMPLE SIZE ESTIMATE	Sample size estimation is based on the primary endpoint of ORR (proportion of patients that achieved a confirmed objective response) evaluated separately for each Arm. The planned sample size for each Arm is approximately 60 patients (total N = 120 in the study). If the observed ORR is ≥32% in either Arm, then an N = 60 will exclude a lower bound of the 95% confidence interval (CI) of 20%. In order to provide a greater chance to detect a true drug effect, a futility analysis, based on 11 patients' data and an interim analysis for efficacy, based on 40 patients' data will be performed. The sample size may be adjusted at interim analysis for efficacy to ensure the predictive probability of the success is ≥90% for the primary analysis.
INCLUSION CRITERIA	A patient will be eligible for inclusion in this study only if all of the following criteria are met at screening: 1. Patients must have a malignant solid tumor with a pathogenic inactivating *TSC1* or *TSC2* alteration. Genetic alterations should be identified using NGS in tumor tissue or liquid biopsy).

	• Patients will be enrolled after the central evaluation of NGS report confirms eligibility. 2. Patients must have solid tumors that are metastatic or locally advanced where surgical resection is not an option or likely to result in severe morbidity. 3. Patients must have received all standard therapies appropriate for their tumor type and stage of disease or, in the opinion of the Investigator, the patient would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy, or the patient has no satisfactory alternative treatments. 4. Patients must have 1 or more measurable target lesions by computed tomography (CT) scan or magnetic resonance imaging (MRI) (RECIST v1.1). 5. Age: 19 years or older. 6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 or Karnofsky Performance Status (KPS) ≥80 or Lansky play-performance scale for pediatric patients ≥80. 7. Adequate liver function: a. Total bilirubin ≤1.5 × upper limit of normal (ULN) (unless due to Gilbert's syndrome, then ≤3 × ULN) b. Aspartate aminotransferase (AST) ≤2.5 × ULN (≤5 × ULN if attributable to liver metastases) 8. Adequate renal function: creatinine clearance ≥30 mL/min, Cockcroft-Gault CCr = ((140-age) × weight[kg]) / (72 × SCr[mL/min]) × 0.85, if female 9. Adequate hematologic parameters: a. Absolute neutrophil count (ANC) ≥1.0 × 10^9/L (growth factor support allowed) b. Platelet count ≥100,000/mm^3 (100 × 10^9/L) (transfusion and/or growth factor support allowed) c. Hemoglobin ≥8.0 g/dL (transfusion and/or growth factor support allowed) 10. Fasting serum triglyceride must be ≤300 mg/dL; fasting serum cholesterol must be ≤350 mg/dL. 11. Minimum of 4 weeks since any major surgery, completion of radiation, or completion of prior systemic anticancer therapy, or at least 5 half-lives if the prior therapy is a single agent small-molecule therapeutic, and adequately recovered from the acute toxicities of any prior therapy, including neuropathy, to Grade ≤1.

	12. Male or non-pregnant and non-breastfeeding female: a. Females of childbearing potential must agree to use effective contraception or abstinence without interruption from 28 days prior to starting investigational product (IP) throughout 3 months after last dose of IP and have a negative serum pregnancy test (beta human chorionic gonadotropin, β-hCG) result at screening and agree to ongoing urine pregnancy testing at every cycle during the course of the study, and after the end of study treatment. A second form of birth control is required even if she has had a tubal ligation. b. Male patients must agree not to donate sperm and must practice abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study and throughout 3 months after last dose of IP. A second form of birth control is required even if he has undergone a successful vasectomy. 13. The patient or the patient's parent(s) or legal guardian(s) understand(s) and sign(s) the informed consent. 14. Willingness and ability to comply with scheduled visits, laboratory tests, and other study procedures.
EXCLUSION CRITERIA	A patient will not be eligible for inclusion in this study if any of the following criteria apply: 1. Prior treatment with an mTOR inhibitor, including *nab*-sirolimus. 2. Severe (Grade ≥3) ongoing infection requiring parenteral or oral anti-infective treatment, either ongoing or completed ≤7 days prior to enrollment. 3. Patients with primary brain tumors or PEComa. 4. Patients who have any severe and/or uncontrolled medical or psychiatric conditions or other conditions that could affect their participation including: a. Patients with meningeal carcinomatosis, leptomeningeal carcinomatosis, spinal cord compression, untreated brain metastases or symptomatic or unstable brain metastases. Note: Patients with stable brain metastases (defined as asymptomatic or no requirement for high dose [defined as dexamethasone 10 mg daily or higher] or increasing dose of systemic corticosteroids) and without imminent need of radiation therapy are eligible. If applicable, patients must have completed brain radiation therapy and recovered adequately from any associated toxicity and/or complications prior to eligibility assessment. For patients

	who have received prior radiation therapy, post-treatment MRI scan should show no increase in brain lesion size/volume. b. Unstable angina pectoris, symptomatic congestive heart failure (New York Heart Association, NYHA class III or IV), myocardial infarction ≤6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease. c. Pre-existing severely impaired lung function. If a patient has a pre-existing pulmonary condition, eligible patients should have a spirometry and diffusing capacity for carbon monoxide (DLCO) that is >50% of the normal predicted value and/or O_2 saturation that is >88% at rest on room air (Note: spirometry and pulmonary function tests [PFTs] not required to be performed unless clinically indicated). d. Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with the study therapy. e. A history of malignancies other than the one under treatment unless the patient is disease-free for more than 5 years from diagnosis. Note, controlled non-melanoma skin cancers, carcinoma in situ of the cervix, resected incidental prostate cancer, certain low grade hematologic malignancies (eg, CLL, follicular lymphoma, etc), or other adequately treated carcinoma-in-situ may be eligible, after discussion with the medical monitor. f. Uncontrolled hypertension (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg). g. Patients with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension. h. Individuals with known human immunodeficiency virus (HIV) infection are excluded from this study as combination antiretroviral therapy could potentially result in significant pharmacokinetic interactions. In addition, these individuals are at increased risk of serious infections due to the immunosuppressive effects of mTOR inhibition. i. Active Hepatitis B or Hepatitis C, with detectable viral load.

	5. Regarding concomitant medications with significant CYP3A4 interactions, discontinuation of strong inhibitors (eg, ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin, telithromycin, and others), strong inducers (eg, rifampin, rifabutin), and known CYP3A4 substrates with a narrow therapeutic window (eg, fentanyl, alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, or terfenadine) is required at least 5 half-lives prior to receiving the first dose of *nab*-sirolimus. 6. Persons with a history of hypersensitivity to sirolimus, rapamycin analogues, or albumin.
DEFINITION of *TSC1* and *TSC2* PATHOGENIC INACTIVATING ALTERATIONS	*TSC1* and *TSC2* alterations must be identified using NGS in tumor tissue or liquid biopsy from a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. The NGS reports for each patient will be evaluated centrally prior to enrollment to confirm eligibility. Alterations in *TSC1* and *TSC2* genes considered to be pathogenic and inactivating if they are truncating mutations or deletions: Truncating mutations within relevant region, defined as • Nonsense mutations (premature stop codon) • out-of-frame insertion and deletion mutations (frameshift) • mutations affecting canonical splice sites (splice) • Intragenic loss/deletion of one or more exons Deletions, defined as • 2-copy deletion (also called deep deletion or homozygous deletion)
DURATION OF TREATMENT AND STUDY PARTICIPATION	The study will enroll patients at approximately 35 sites in the US and globally 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 patients, a 28-day screening and a 28-day (4 week) safety follow-up after the last dose. **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 28–35 days after the last dose of *nab*-sirolimus is administered. **End of Study** (EOS) for a patient is defined as the date of last follow-up. 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 **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.
KEY EFFICACY ASSESSMENTS	Efficacy will be assessed by investigators and independent radiologic review using CT or MRI scans using RECIST v1.1. Patients will be evaluated for CR, PR, SD, or progressive disease (PD) by CT imaging or MRI. The same modality of imaging should be used throughout the study. Baseline scan results can be accepted from outside institutions but must be done within 4 weeks of starting therapy and must include (as clinically indicated), chest, abdominal, and pelvic CT or MRI. The first response assessment by CT or MRI scans documenting target lesions will be done 6 weeks (±7 days) after first treatment and should be repeated every 6 weeks (±7 days) for the first year, then every 12 weeks (±7 days) thereafter until disease progression. If an initial observation of objective response (CR or PR) is made, a confirmation scan should be done 6 weeks (±1 week) after the initial observation. Scans should continue on schedule regardless of delays in *nab*-sirolimus dosing. The BOR and DCR will be reported along with exact 95% CIs computed by the Clopper-Pearson method. Definitions: • DOR is defined as the number of months from the start of CR or PR (whichever response is recorded first) and subsequently confirmed to the first date of documented PD or death. • DCR is defined as BOR of confirmed CR or PR (either of any duration) or SD ≥12 weeks following study treatment initiation. • TTR is defined as the time from first dose of study drug to initial measurement of CR or PR, where CR or PR is subsequently confirmed. • Time on treatment is defined as the time from the first dose to last dose. • PFS is defined as the time from the first dose to the first observation of a disease progression or death due to any cause. • OS is defined as the time of first dose to the date of death due to any cause.

	For PFS, OS, and DOR, the Kaplan-Meier (KM) estimates and corresponding two-sided 95% CIs for the median and quartiles will be provided. The KM plot also may be provided. All patients will be analyzed together across tumor types within each Arm. Tumor types within Arms may also be analyzed separately.
KEY SAFETY ASSESSMENTS	Safety and tolerability will be monitored through continuous reporting of treatment-emergent and treatment-related AEs, AEs of special interest, laboratory abnormalities, and incidence of patients experiencing dose modifications, dose delay/missed, dose interruptions, and/or premature discontinuation of IP due to an AE. All AEs will be recorded by the investigator from the time the patient signs informed consent until 28 days after the last dose of IP. Adverse events will be graded by NCI CTCAE v5.0. Physical examination, vital signs, laboratory assessments (eg, serum chemistry, hematology), and performance status will be monitored. All serious AEs (regardless of relationship to IP) will be followed until resolution. Local laboratory analysis will be performed as per study schedule.
PRIMARY ANALYSIS	The primary analysis to address all study objectives in each Arm will be conducted when patients have had the opportunity to be treated for at least 6 months within an Arm. Analysis will be done in each Arm independently, and the primary analysis for each Arm may occur at different times, should one of the Arms complete enrollment earlier. 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 primary, secondary, and exploratory efficacy and safety analyses will be conducted at the time of the primary analysis for each Arm, with the exception of the biomarkers 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.

INTERIM DATA MONITORING PLAN AND DATA MONITORING COMMITTEE (DMC)	An external DMC will review safety data and investigator response assessment data for futility as follows: • When the 40th patient has enrolled (considering enrollment across both Arms A and B) and has had 1 post-baseline scan • When the 80th patient has enrolled (considering enrollment across both Arms A and B) and has had 1 post-baseline scan DMC will also review efficacy data as follows: • Futility analysis, which will occur separately in each Arm when 11 patients have had the opportunity to be treated for at least 3 months and have at least one post-baseline response assessment • 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 relevant specialties and 1 statistician.

SCHEDULE OF ASSESSMENTS

Table 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 [k]		X	
Biomarker: Pre-treatment tissues (archival, or fresh) [l]		X		X	
Biomarker: blood sample [l]		X		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				

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		
***nab*-Sirolimus Dosing**		X	X		
Local Laboratory Assessments					
Clinical Chemistry Panel (refer to Table 4)	X	X		X	
CBC, Differential, Platelet Count	X	X	X	X	
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 C1D1 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 Cycle 1 Day 1 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 Cycle 1 Day 1; 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. For all treated patients, ECG is performed at screening, on Cycle 1 Day 1 and Cycle 3 Day 1, thereafter as clinically indicated. In each case, ECG should be performed during infusion around the 30 minute (+10 min) timepoint after the start of the infusion to coincide with the end of the 30-min infusion. For central analysis (US only), for 30 treated patients who sign an optional PK/ECG informed consent, additional 12-lead ECG monitoring will be performed:

- On Cycle 1 Day 1 continuously from 1 hr prior to the start of infusion through 4 hrs (+10 min) after the start of infusion during which time optional PK samples will be collected.

- On Cycle 3 Day 1 continuously from 1 hr prior to the start of infusion through 30 mins (+10 min) after the start of infusion (end of infusion).

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 Day 1 of every cycle and at EOT Visit (can be done locally), and as clinically indicated as per institutional guidelines.

l. 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. Blood samples will be collected at baseline on Cycle 1 Day 1 prior to infusion, at every 12 weeks scan (±1 week) for the first year, and at EOT or disease progression. 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.

m. PK blood samples to be taken from all treated patients 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. Additionally, from 30 patients who sign an optional PK/ECG informed consent, blood will be collected:

- on C1D1 at 15 (±10) and 30 (±10) mins (end of infusion) and at 1 (±10 min), 2 (±10 min), and 4 (±10 min) hrs after the start of infusion, and
- on C3D1 at 30 mins (±10 mins) after the start of infusion (ie, the end of infusion).

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.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
ANC	absolute neutrophil count
AST	aspartate transaminase (SGOT)
AUC	area under the time-concentration curve
BOR	best overall response
BSA	body surface area
C_{max}	maximum plasma drug concentration
CBC	complete blood count
CCr	creatinine clearance
CI	confidence interval
CNS	central nervous system
CR	complete response
CRO	Contract Research Organization
CT	computed tomography
DCR	disease control rate
dL	deciliter
DLCO	diffusing capacity for carbon monoxide
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC-QOQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOS	end of study
EOT	end of treatment

GCP	Good Clinical Practice
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
IRR	Independent Radiographic Review
IV	intravenous(ly)
kg	kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
mTOR	mammalian target of rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ng	nanogram
NGS	next generation sequencing
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCr	serum creatinine
SD	stable disease

SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
T_{max}	time to maximum plasma drug concentration
TMB	tumor mutation burden
TSC	tuberous sclerosis complex
TTR	time to response
ULN	upper limit of normal

Abbreviation or Term	**Definition/Explanation**
Study Day 1	The first day when *nab*-sirolimus is administered to the patient.
End of Study	For a patient: The date of last known follow-up. For the study: 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.
End of Treatment	The date of the last dose of *nab*-sirolimus for an individual patient.
End of Treatment Visit	Safety assessments and procedures are performed after the patient's last treatment; the visit must occur at least 4 weeks (+7 days) after the last dose of *nab*-sirolimus.
Follow-up Period	The on-study time period after the End of Treatment 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. 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), or more frequently as needed, 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.

Data Sets and Primary Analysis	
Full Analysis Set	Includes all enrolled patients who receive at least 1 dose of *nab*-sirolimus. Analyses of all efficacy and safety endpoints will be performed on the Full Analysis Set.
Per-protocol Analysis Set	Includes all enrolled patients with a measurable tumor per RECIST v1.1 with at least 1 post treatment scan, and who do not have any prospectively defined protocol violations.
Primary Analysis	The primary analysis to address all study objectives in each Arm will be conducted when patients have had the opportunity to be treated for at least 6 months within an Arm. Analysis will be done in each Arm independently, and the primary analysis for each Arm may occur at different times, should one of the Arms complete enrollment earlier. 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 primary, secondary, and exploratory efficacy and safety 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. Patients who are still active at the time of the primary analysis may continue on study until disease progression or medication intolerance is observed.
Efficacy Endpoints	
Best Overall Response	The best response recorded for a patient from the start of the treatment until disease progression (assessment for response should be compared to the pre-treatment baseline scan; but assessment for progression at any timepoint should be compared to the preceding scan with the best response). As per RECIST 1.1, to be assigned a status of CR or PR, changes in tumor measurements must be confirmed by a repeat assessment.
Disease Control Rate	The proportion of patients who achieve confirmed CR or PR or SD ≥12 weeks following study treatment initiation.

Duration of Response	The time from the start of CR or PR (whichever response is recorded first and subsequently confirmed) to the first date of documented PD or death.
Objective Response	The response reported at individual timepoints (ie, CR, PR, SD, or PD) at each assessment.
Overall Response Rate	The proportion of patients with confirmed objective response of PR or CR.
Overall Survival	The time from the first dose date to the date of death due to any cause.
Progression-free Survival	The time from the first dose date to the first observation of a disease progression or death due to any cause.
Time on Treatment	The time from the first dose to last dose.
Time to Response	Time from first dose of study drug to initial measurement of CR or PR, where CR or PR is subsequently confirmed.

1. INTRODUCTION

1.1. *TSC1* and *TSC2* Alterations and Disease Background

TSC1 and *TSC2* are the tumor-suppressor genes in the mTOR pathway located upstream of mTOR. It is well recognized that the primary function of the *TSC1–TSC2* complex is as a critical negative regulator of mTORC1 activation (Huang, 2008). The *TSC1–TSC2* complex inhibits aberrant cell growth by regulating the mTOR pathway, specifically mTORC1, thereby preventing excessive activation of S6K. Aberrant mTORC1 signaling is known to be a key driver of cell proliferation and tumor formation triggered by loss of these tumor suppressors (Huang, 2008).

In the rare autosomal dominant genetic disease tuberous sclerosis complex, mutations in *TSC1* or *TSC2* cause multisystem growth of benign tumors in various organs and other hamartomatous lesions. Patients with this genetic disease are not the focus of this study.

Based on the prevalence of *TSC1* or *TSC2* alterations in various tumor types reported in the United States (as per the NIH NCI Genomic Data Commons and SEER database, Table 2), the tumor types expected to be most prevalent in this tissue-agnostic trial are lung, uterine, colon, kidney, melanoma, liver, and esophageal cancers.

Table 2: The Top 10 Tumor Types with Most Prevalent *TSC1* and *TSC2* Mutations

Tumor Types [a]	% of Patients with Definite Impact Mutations [b]	Estimated # of Patients with Definite Impact Mutations in Advanced Diseases [c]
***TSC1* Mutations**		
Lung	0.51%	919
Uterine	2.48%	783
Colon	1.28%	727
Bladder	5.58%	494
Kidney	0.74%	175
Melanoma	0.85%	107
Liver	0.47%	89
Stomach	0.45%	77
Esophageal	0.55%	69
Ovarian	0.16%	28
***TSC2* Mutations**		
Lung	0.94%	1694
Liver	2.57%	486
Uterine	1.24%	391
Colon	0.43%	244
Breast	0.09%	90
Melanoma	0.64%	80
Kidney	0.32%	76
Esophageal	0.55%	69
Cervical	0.98%	66
Prostate	0.20%	59

[a] Tumor types in **bold** overlap in both types of mutation.
[b] The proportion of patients with definite impact mutations was derived from the National Institutes of Health (NIH) National Cancer Institute (NCI) Genomic Data Commons Data Portal (NIH NCI Genomic Data Commons).

[c] Estimated numbers were derived based on the total number of advanced cases of each disease type (Seigel et al. 2019 and SEER database https://seer.cancer.gov/statistics/) and the proportion of patients with definite impact mutations (NIH NCI Genomic Data Commons).

Treatment Options for Patients with *TSC1* and *TSC2* Inactivating Alterations

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 (SOC) without regard to these alterations. There is substantial unmet medical need for these patients with advanced cancer as current SOC approaches eventually fail in essentially all patients.

While drugs targeting the mTOR pathway are approved for various indications (eg, everolimus is approved, among others, for advanced renal cell carcinoma, angiomyolipoma and tuberous sclerosis complex [AFINITOR Prescribing Information], oral sirolimus (rapamycin) for lymphangioleiomyomatosis [RAPAMUNE Prescribing Information]), none of them have been approved for the treatment of solid tumors with pathogenic *TSC1* or *TSC2* alterations.

Targeted therapies and immunotherapies as part of SOC have improved outcomes for a variety of solid tumors over chemotherapeutic approaches. Examples include the immunotherapy combinations of nivolumab plus ipilimumab in metastatic NSCLC that achieved a 35% ORR versus 6% in the control arm, and adding pembrolizumab to chemotherapy resulted in a 45% ORR versus 28% with chemotherapy alone, also in advanced non-small cell lung cancer (NSCLC) (Reck, 2016; Hellmann, 2019). For patients with hepatocellular carcinoma (HCC), sorafenib, the SOC resulted in a 9% overall response rate (ORR), whereas lenvatinib achieved a 24% ORR. Other agents also improved on the ORR of sorafenib in HCC: nivolumab demonstrated a 20% ORR, and pembrolizumab achieved an 18% ORR (El-Khoueiry, 2017; Kudo, 2018; Zhu, 2018); both agents gained Food and Drug Administration (FDA) approval for HCC. As for pan-tumor agents, larotrectinib was approved in 2018 for solid tumors with neurotrophic tropomyosin receptor kinase (NTRK) fusions based on an overall 75% ORR; the ORR varied by tumor type and ranged from 25% for colon to 100% for infantile fibrosarcoma (VITRAKVI Prescribing Information). Similarly, entrectinib produced an overall 57% ORR in patients with NTRK fusion, with a range of 20% for thyroid cancer to 86% for salivary tumors (ROZLYTEK Prescribing information).

Based on review of National Comprehensive Cancer Network (NCCN) guidelines for therapeutic options and outcomes of tumor histologies in which *TSC1* or *TSC2* alterations occur with a known incidence, the ORR is on average 40% (range 11%–73%) for 1st-line therapy and 25% (range 4%–52%) for 2nd-line therapy. Beyond 2nd-line therapy there is limited data available, but it is expected that response rates diminish with each new line of therapy. In tumor agnostic trials, most patients are expected to have over 2 or 3 lines of therapies (KEYTRUDA Prescribing Information [KEYNOTE-158]: 56% of patients had ≥2 lines of therapy; VITRAKVI Prescribing Information: 35% >2 lines; ROZLYTEK Prescribing Information: 17% >2 lines). In the most recent tumor agnostic approval for pembrolizumab in TMB-H, the ORR was 29% and the lower bound of the 95% CI was 21% (KEYNOTE-158). Additionally, since the study requires that patients should have

received all standard therapies appropriate for their tumor type and stage of disease, most of the patients on this study are expected to have 2 or more prior lines of therapy prior to entry. Thus, the current study design for this *TSC1* or *TSC2* tumor agnostic trial proposes an endpoint of a lower bound of the 95% CI to be 20% with a target ORR of approximately 32% for 60 evaluable patients. This would represent meaningful clinical benefit across the various tumor types expected to be treated in this study.

Table 3: Summary of Response Rates in Relevant Diseases in the 1st and 2nd -line Settings

Disease (metastatic, stage IV, or unresectable)	1st-line Therapy	1st-line ORR	2nd-line Therapy	2nd-line ORR
Bladder	pembrolizumab	24%		
	gemcitabine /carboplatin	42%		
	gemcitabine /cisplatin	49%		
			nivolumab	19.6%
			atezolizumab	23%
			erdafitinib	40%
Breast cancer	capecitabine	28%		
	fluvestrant	36%		
	palbociclib / letrozole	42%		
	abemaciclib / letrozole	59%		
	pertuzumab / herceptine / taxane	59%		
	carboplatin / nab-paclitaxel	73%		
			doxorubicin	30–47%
			neratinib / capecitabine	33%
			paclitaxel / bevacizumab	37%
Cervical cancer	cisplatin / paclitaxel / bevacizumab	50%		
	cisplatin / topotecan	27%		
	cisplatin	20–30%		
			various chemo	13.5%
			pembrolizumab	12.2%
Hepatocellular carcinoma	lenvatinib	41%		
	atezolizumab / bevacizumab	34%		
			regorafenib	11%
			cabozatinib	4%
			nivolumab / ipilimumab	14%
			FOLFOX / sorafenib	18%
			pembrolizumab	17%
Melanoma	ipilimumab trials	11-15%		
	pembrolizumab trials	28–36%		
	Nivo / ipi then nivo	58–59%		

Disease (metastatic, stage IV, or unresectable)	1st-line Therapy	1st-line ORR	2nd-line Therapy	2nd-line ORR
	T-VEC / pembrolizumab	62%		
	vemurafenib	36–53%		
	BRAF / MEK inhibitor combos	60–70%		
			nab-paclitaxel	15%
			binimetinib	15%
NSCLC, unresectable	cisplatin / pemetrexed	27%		
	pembrolizumab	27-45%	pembrolizumab	18-19%
	pembrolizumab / carboplatin / pemetrexed	48%		
			pemetrexed	10%
			afatinib / cetuximab	25-32%
Ovarian	topotecan	20%		
	paclitaxel	21%		
	liposomal doxorubicin	26%		
			rucaparib	25%
			pazopanib /paclitaxel	50%
Uterine Cancer, endometrial adenocarcinoma	carboplatin / paclitaxel	40–62%		
	single agent chemo	21-36%	single agent chemo	4-27%
	tamoxifen	20%		
			paclitaxel	27%
			liposomal doxo	9.5%
			pembrolizumab	52%

References: ALIMTA Prescribing Information; LENVIMA Prescribing Information; KEYTRUDA Prescribing Information; NCCN 2001 (Bladder CA v6.2020 pg MS-28-30; NCCN Breast CA v1.2021 pg MS-56-71; NCCN Cervical CA v1.2020 pg MS-16-17; NCCN Hepatobiliary CA v5.2020 pg MS-30-32; NCCN Cutaneous Melanoma v2.2021 pg MS-40-67; NCCN NSC Lung CA, v4.2021 pg MS-84; NCCN Ovarian CA v1.2021 pg MS-85-86; NCCN Uterine CA v1.2021 pg MS-19-21).

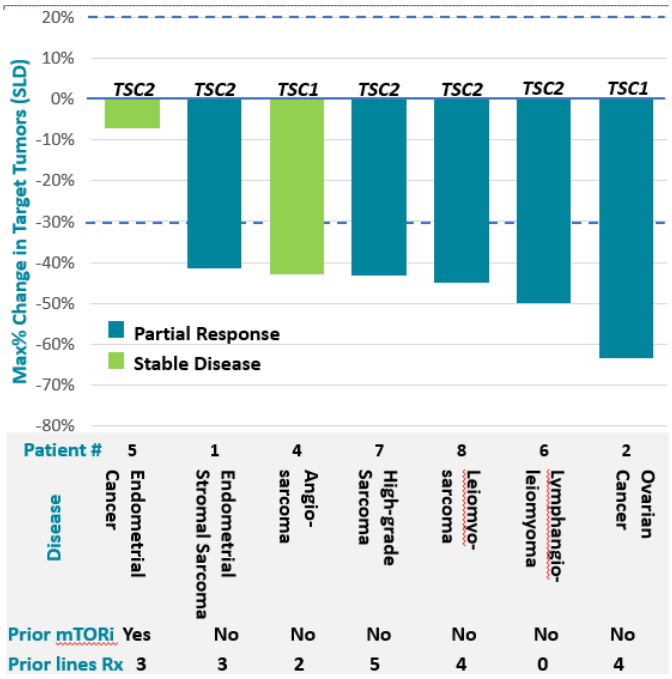
In principle, tumors that exhibit a dependency on the mTOR pathway might be expected to show enhanced sensitivity to mTOR inhibition. As an example, a study of exceptional responders identified 2 activating mTOR alterations in a patient with exquisite sensitivity to everolimus and pazopanib (Wagle, 2014). Given that mTOR pathway activation is often observed in solid tumors with *TSC1* and *TSC2* inactivating alterations, mTOR inhibition is a promising therapeutic target. Although no results are available yet, an NCI-MATCH trial (NCT02465060) enrolled patients with mTOR alterations (Arm L) and *TSC1* or *TSC2* mutation (Arm M) to be treated with sapanisertib, an experimental dual mTOR inhibitor. A recent Phase 2 trial pan-cancer, mutation-selected, basket study investigated the efficacy of everolimus in patients with *TSC1* or *TSC2* inactivating alterations and reported a disappointing ORR (7%) (NCT02201212, Adib, 2021), indicating that everolimus has limited therapeutic benefit in this patient population. The authors discussed a transient nature of tumor shrinkage following everolimus treatment, which may reflect rapid

adoption of bypass or resistance mechanisms, and the need for improved mTOR inhibitors.

On November 22, 2021, *nab*-sirolimus, branded as FYARRO™, was approved by the FDA for the treatment of adult patients with locally advanced unresesectable or metastatic malignant perivascular epithelioid cell tumor based on the results of the registration trial AMPECT (FYARRO Prescribing Information). *nab*-Sirolimus produced an ORR of 39% (Wagner, 2020) in patients with perivascular epithelioid cell tumors (PEComa), for which there are no approved treatments. Exploratory data from the AMPECT trial demonstrated that *TSC2* pathogenic inactivating alterations were associated with response to *nab*-sirolimus in advanced malignant PEComa; 8/9 patients (89%) with *TSC2* pathogenic inactivating alterations had a confirmed partial response and 1/9 (11%) had an unconfirmed PR (SD as best response), with 64% (9/14) responses when the 2 subgroups were combined. Also, in the AMPECT study, 1 of 5 patients (20%) with *TSC1* pathogenic inactivating alterations had a partial response, 2/5 (40%) patients had SD ≥12 weeks, providing preliminary evidence of activity of *nab*-sirolimus in this subset of patients as well.

In a subsequent expanded access program (PEX-002, NCT03817515), encouraging preliminary results were seen in patients with solid tumors treated with *nab*-sirolimus and with *TSC1* and *TSC2* alterations, many of whom had progression on prior therapies, (Dickson, 2021, Figure 1).

Figure 1: Waterfall Plot of Patients with Various Advanced Neoplasms Treated with *nab*-Sirolimus



Note, 1 additional patient with metastatic ovarian cancer with *TSC2* mutation, who received 6 prior lines of therapies including an mTOR inhibitor, progressed clinically after 1 cycle and did not have a post-baseline scan.

1.2. *nab*-Sirolimus Background

1.2.1. Sirolimus and Rapalogs

Sirolimus (also known as rapamycin) is a crystalline powder with the empirical formula $C_{51}H_{79}NO_{13}$ and a molecular weight of 914.2. Sirolimus is a protein kinase inhibitor that is approved for immunosuppression in renal transplant patients and is under investigation as a cancer treatment. Sirolimus inhibits the mammalian target of rapamycin, mTOR, a regulatory protein kinase in cancer that recognizes high stress levels, including depleted nutrient levels and states of hypoxia (Yuan, 2009). mTOR is a serine/threonine-specific protein kinase, downstream of the phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B) pathway, and a key regulator of cell survival, proliferation, stress, and metabolism. Additionally, mTOR is involved in regulating angiogenesis by controlling endothelial and smooth muscle cell proliferation via the hypoxia-inducible factor-1α and vascular endothelial growth factor (Corradetti, 2006). Consistent with its role in cell proliferation, the mTOR pathway is frequently overactivated in a number of human malignancies and is thus considered to be an attractive target for anticancer therapy. Sirolimus and its analogs (rapalogs) function as allosteric inhibitors of mTORC1. Rapalogs are currently used in the treatment of advanced renal cell carcinoma and other tumors (Dowling, 2010).

Numerous preclinical studies have reported the impact of different biomarkers involved in the mTOR pathway, on the efficacy of mTOR inhibitors, such as:

- *PI3K*, *TSC1*, *TSC2*, *AKT*, and *PTEN* gene mutations (Weigelt, 2012)
- Phosphorylated p-AKT, p-S6, p-4EBP1 expression (Li, 2014)
- biomarkers for the proliferation (Ki-67) and apoptosis (PARP) (Dowling, 2010)

Sirolimus (Rapamune) is an oral therapeutic and is an efficacious mTOR inhibitor; however, it has poor solubility, low oral bioavailability, and dose-limiting toxicity (O'Donnell, 2008; Yuan, 2009). Marketed sirolimus analogs are temsirolimus and everolimus. Temsirolimus, approved for the treatment advanced renal cell carcinoma, is a prodrug of sirolimus and requires conversion by the CYP3A enzyme (TORISEL Prescribing Information). Everolimus is approved for pediatric and adult patients with subependymal giant cell astrocytoma (SEGA) and tuberous sclerosis complex-associated seizures, for adult patients with advanced hormone receptor-positive HER2-negative breast cancer in combination with exemestane, progressive neuroendocrine tumors of pancreatic origin (PNETs), advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib, and advanced angiomyolipoma and tuberous sclerosis complex (AFFINITOR Prescribing Information).

Oral sirolimus and currently available rapalogs induce common side effects including hypertension, maculopapular rash (75%), mucositis (50%), asthenia (40%), nausea (43%), thrombocytopenia, metabolic abnormalities, and more rarely pneumonitis (8%, 3% Grade 3) (de Oliveira, 2011; Albiges, 2012; Qi, 2013). The most frequently occurring Grade 3 or 4 adverse events were hyperglycemia (17%), hypophosphatemia (13%),

anemia (9%), and hypertriglyceridemia (6%) (Zhou, 2010). These side effects could lead to the discontinuation of the treatment in 60% of patients in some studies.

1.2.2. *nab*-Sirolimus

The novel nanoparticle albumin-bound sirolimus (ABI-009, *nab*-sirolimus, formerly known as *nab*-rapamycin) is freely dispersible in saline and is suitable for intravenous (IV) administration, and has produced both a favorable safety profile and evidence of efficacy in patients with metastatic solid tumors (Gonzales-Angulo, 2013; FYARRO Prescribing Information).

Nanoparticle albumin-bound (nab) or *nab* technology when applied to hydrophobic molecules, such as paclitaxel (*nab*-paclitaxel; Abraxane®), has led to improved drug delivery, safety, and efficacy in various solid tumors compared with the conventional paclitaxel formulation (Gradishar, 2005). This suggests that the *nab* formulation of sirolimus may also produce similar advantages over the standard sirolimus.

The *nab* technology may enhance tumor penetration and accumulation via the albumin receptor-mediated (gp60) endothelial transcytosis. Albumin is highly soluble, has long plasma half-life, broad binding affinity, and accumulates in tumors, making it an ideal candidate for drug delivery (Kremer, 2002; Kratz, 2008). Albumin circulating in the bloodstream can interact with gp60 to initiate caveolae-mediated transcytosis to reach tumor cells (Schnitzer, 1992; Schnitzer, 1995). Indeed, *nab*-paclitaxel transcytosis across the epithelial monolayer was dependent on caveolae formation (Desai, 2006). In accordance with these observations, at equal doses, *nab*-paclitaxel showed greater selectivity to tumors compared with solvent-based paclitaxel, which is likely attributed to the biologically active ingredient albumin and lack of solvent (Desai, 2006).

1.2.2.1. *nab*-Sirolimus Pharmacokinetics

nab-Sirolimus produced a fairly dose proportional increase of C_{max} and AUC across the dose range tested, and it significantly inhibited mTOR targets S6K and 4EBP1.

nab-Sirolimus has unique characteristics among the available mTOR inhibitors. The pharmacokinetic (PK) profile of sirolimus administered as *nab*-sirolimus is categorically different from those of the other oral or IV administered mTOR inhibitors. Intravenous infusion of *nab*-sirolimus results in high C_{max} of sirolimus upon administration followed by a long half-life of approximately 60 hrs that allows once weekly dosing. Peak levels of sirolimus after *nab*-sirolimus are well above 1000 ng/mL range that may have significant tumor penetration effect. Oral mTOR inhibitors such as sirolimus or everolimus have poor absorption with a high inter- and intra-patient variability and a poor safety profile that requires low basal levels (low ng/mL level) to be maintained over the course of treatment. Temsirolimus on the other hand is a prodrug of sirolimus and as a result, high levels of sirolimus are not achieved (<100 ng/mL) (Danesi, 2013). The administration of *nab*-sirolimus led to a much higher exposure to sirolimus as compared to sirolimus from temsirolimus (C_{max} almost 50 fold higher, AUC almost 12 fold higher for *nab*-sirolimus) or everolimus (C_{max} 50–70 fold higher, AUC 85–200 fold higher for *nab*-sirolimus) (Danesi, 2013; Gonzalez-Angulo, 2013). Unlike with other mTOR inhibitors, micromolar

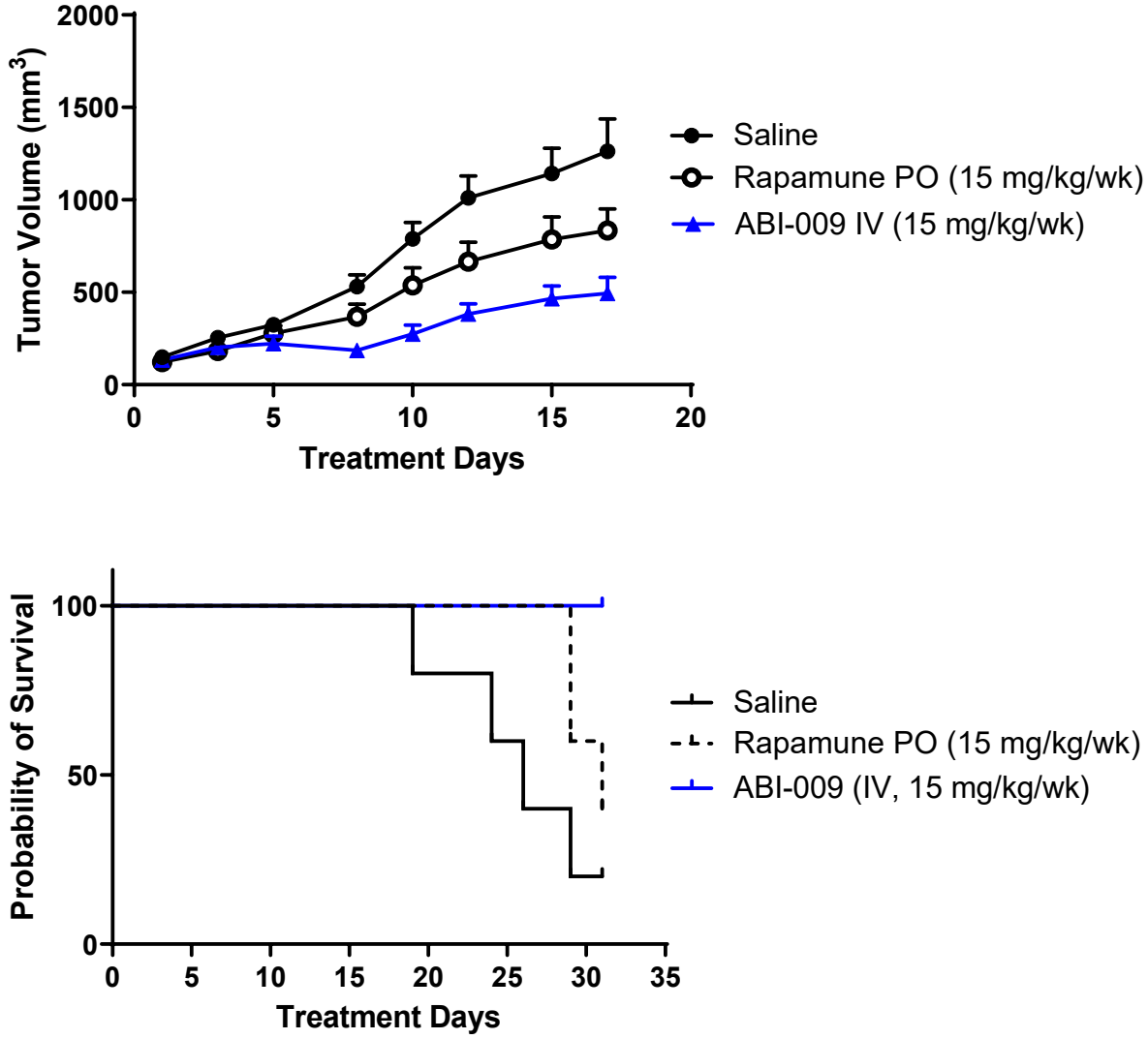
concentrations are reached and maintained for several hours with *nab*-sirolimus which could potentially circumvent acquired resistance to mTOR inhibitors via retroactivation of AKT by TORC2 (Sarbassov, 2006; Lamming, 2012). The high exposure achieved with *nab*-sirolimus with acceptable safety profile could be highly relevant to the treatment of aggressive cancers such as malignant PEComas.

1.2.2.2. Preclinical Studies with *nab*-Sirolimus

nab-Sirolimus demonstrates significant antitumor activity as a single agent against multiple types of tumor models that are driven by mTOR pathway activation, including HT29 (colon), HCT-116 (colon), MX-1 (breast), SK-OV-3 (ovarian), MDA-MB-231 (breast), UMUC3 (bladder), SNU-398 (liver) human tumor xenograft models, and the B16 (melanoma) mouse tumor model. Furthermore, additive and enhanced antitumor activity has been observed for *nab*-sirolimus in combination with other therapeutic agents, including erlotinib, perifosine, doxorubicin, SAHA, *nab*-17AAG, gemcitabine, and anti-PD1 antibody, albeit in some cases with potentially increased toxicity with greater weight loss and mortality. Compared with equal and clinically relevant doses of oral sirolimus and oral everolimus, *nab*-sirolimus demonstrated significantly stronger inhibition of mTOR pathway activity in tumors, greater tumor growth inhibition, and prolonged survival. The improved antitumor activity of *nab*-sirolimus correlated with efficient drug delivery and higher drug accumulation in tumors than oral mTOR inhibitors.

In particular, in a nonclinical study in female athymic mice bearing *TSC2*-deficient SNU-398 human hepatocellular carcinoma xenografts, *nab*-sirolimus administered IV at 15 mg/kg/week dose resulted in significant tumor growth inhibition and prolonged animal survival (Figure 2). Compared with equal weekly dose of oral Rapamune®, *nab*-sirolimus IV treatment resulted in significantly greater antitumor activity (TGI 67.8% vs 36.2%, $P = 0.04$) and longer animal survival (median survival: not reached vs 31 days).

Figure 2: Antitumor Activity of *nab*-Sirolimus and Oral Sirolimus in *TSC2*-deficient SNU-398 Liver Tumor Xenograft Model



IV = intravenous; PO = oral

Safety pharmacology studies showed that *nab*-sirolimus did not result in toxicologically relevant effects on the central nervous system (CNS) and was categorized as a low potency human ether-à-go-go-related (hERG)-channel blocker.

In nonclinical PK studies, pharmacokinetics following *nab*-sirolimus IV administration were characterized by high initial blood sirolimus concentration and rapid tissue distribution, followed by a long elimination phase. *nab*-Sirolimus IV showed a large volume of distribution and a long terminal half- life. C_{max} and AUC increased with higher *nab*-sirolimus dose. In a GLP PK bridging study, *nab*-sirolimus IV displays a distinct PK profile with early time to maximum plasma drug concentration (T_{max}), and greater C_{max} and AUC compared with oral Rapamune. *nab*-Sirolimus IV administration resulted in

significant, rapid, and prolonged tissue sirolimus distribution in different organs including brain. Compared with oral sirolimus and everolimus, *nab*-sirolimus IV resulted in rapid and efficient drug distribution and higher accumulation in the tumor. Furthermore, intratracheal and subcutaneous administration of *nab*-sirolimus resulted in similar blood C_{max}, AUC, and tissue distribution profiles compared with *nab*-sirolimus IV administration.

Of the routes of elimination following *nab*-sirolimus IV administration, the majority of sirolimus was excreted in the form of metabolites in the feces (approximately 90% of total excretion), with urinary excretion being the minor route. Sirolimus excreted in the urine was comprised entirely of sirolimus metabolites. This is consistent with the route of elimination for sirolimus reported in the literature following oral administration of Rapamune in human (Leung, 2006).

In single dose and repeat-dose nonclinical toxicology studies, the no-observed-adverse-effect level (NOAEL) for *nab*-sirolimus administered IV was not established. The maximum tolerated dose (MTD) of *nab*-sirolimus in rats was determined to be 78.9 mg/kg (equivalent to 473.4 mg/m^2 human dose, 4.7 times higher than the 100 mg/m^2 MTD and clinical dose of *nab*-sirolimus). Toxicities observed in these toxicology studies include signs of respiratory toxicity, increases in glucose, cholesterol, and triglycerides, which are consistent with known toxicities of sirolimus. Histopathological analysis revealed that target organs affected by *nab*-sirolimus were the heart, lungs, thymus, and male reproductive organs. In addition, a repeat-dose toxicity study showed that *nab*-sirolimus delivery subcutaneously (SC) was well tolerated with NOAEL at 1.7 mg/kg. Nonclinical toxicology studies of *nab*-sirolimus showed no new or unexpected toxicity compared to what is already known for sirolimus and other mTOR inhibitors, despite higher dose with *nab*-sirolimus and different route of administration.

1.2.2.3. Clinical Studies with *nab*-Sirolimus

In a first-in-human (FIH) Phase 1 dose-finding, safety, and PK study conducted at MD Anderson Cancer Center (Protocol CA401), *nab*-sirolimus was well tolerated with evidence of responses and stable disease (SD) in various solid tumors including renal cell carcinoma and bladder cancer, both of which typically express mTOR (Gonzalez-Angulo, 2013). Twenty-six patients were treated with 45, 56.25, 100, 125, 150 mg/m^2 *nab*-sirolimus IV per week for 3 weeks, followed by a week of rest (28-day cycle). The maximum tolerated dose was established at 100 mg/m^2.

Nineteen patients were evaluable for efficacy. One patient in the 45 mg/m^2 (95 mg actual sirolimus dose) cohort diagnosed with stage IV adenocarcinoma of the kidney and with bone and intrathoracic metastases had a confirmed partial response (PR). The target lesion of this patient was reduced by 35.1% and the duration of response was 183 days. This patient had a Grade 3 AST and Grade 3 hyperglycemia lasting >21 days which would have necessitated treatment discontinuation; however, given the tumor response and benefit, a waiver was instated to allow the patient to continue *nab*-sirolimus at 30 mg/m^2. This patient maintained the PR for 4.5 additional months, indicating that this dose reduction level was efficacious. Two (11%) patients (at doses 45 and 125 mg/m^2, with actual doses of 88 mg and 193 mg *nab*-sirolimus, respectively) had an overall tumor

evaluation of SD (confirmed): 1 patient with mesothelioma had SD for 365 days and 1 patient with a neuroendocrine tumor in the left axillary node had SD for 238 days.

In the Phase 1 study described above, for all cohorts and all grades, 25 of 26 (96%) patients experienced at least 1 adverse event (AE). The most common AEs were mucosal inflammation (10 patients, 38%), fatigue (7 patients, 27%), rash (6 patients, 23%), diarrhea (6 patients, 23%), and nausea (5 patients, 19%). Most of these AEs were Grade 1 or 2 events, with only 3 Grade 3 nonhematologic AEs (2 elevated AST and 1 dyspnea). Specifically, at the maximum-tolerated dose (MTD, 100 mg/m^2), all 7 patients experienced at least 1 AE of any grades, and the most common AEs were mucositis and fatigue (5 patients, 71% each). Four (15%) patients experienced at least 1 treatment-related serious AE, including arrhythmia (Grade 2) and mood alteration (Grade 3) both in the 125 mg/m^2 cohort, vomiting (Grade 3) in the 45 mg/m^2 cohort, and dyspnea (Grade 3) in the 100 mg/m^2 cohort.

The most common hematologic AEs, for all cohorts and grades, were thrombocytopenia (58%), followed by hypokalemia (23%), anemia and hypophosphatemia (19% each), and neutropenia and hypertriglyceridemia (15% each). Most of these events were Grade 1 or 2, and only 1 Grade 4 hematologic event occurred (thrombocytopenia in the 150 mg/m^2 arm). At the MTD, the only hematologic AE was Grade 3 anemia.

In a Phase 2 registration study (AMPECT) in patients with advanced malignant PEComa, *nab*-sirolimus IV was safe and efficacious with 90% of patients having a best response of PR or SD (Wagner, 2020). Thirty-four patients were treated with 100 mg/m^2 *nab*-sirolimus per week for 2 weeks, followed by a week of rest (q2w, 21-day cycle). The confirmed ORR by independent review was 39%, all partial responses (PR, 12/31, 95% CI: 21.8, 57.8), 52% SD (16/31, with 10/16 SD ≥12 weeks), and 10% progressive disease (PD, 3/31); the disease control rate (defined as CR + PR + SD ≥12 weeks) was 71%.

No new safety signals were observed in the Phase 2 study (AMPECT) when compared to the safety observed in the Phase 1 FIH CA401 study or versus oral mTOR inhibitors, despite relatively high doses of *nab*-sirolimus. The most common (>30%) nonhematologic treatment-related AEs (TRAEs) of any grade were mucositis (79%), fatigue (59%), and rash (56%), nausea (47%), diarrhea and weight loss (38% each), hyperglycemia (35%), hypertriglyceridemia, hypercholesterolemia, and decreased appetite (32% each). The most common (>30%) hematologic TRAEs were anemia (47%) and thrombocytopenia (32%). Pneumonitis (18%) was Grade 1 or 2. The most common (>10%) Grade 3 TRAEs were mucositis (18%), anemia (12%); No Grade ≥4 TRAEs were observed.

1.3. Rationale for the Use of *nab*-Sirolimus in Patients with Pathogenic Inactivating *TSC1* and *TSC2* Alterations

Exploratory data from the AMPECT trial in advanced malignant PEComa demonstrated that *TSC2* pathogenic inactivating alterations were associated with response to *nab*-sirolimus; 8/9 patients (89%) with *TSC2* pathogenic inactivating alterations had a CR or PR. Furthermore, in this study, 1 of 5 patients (20%) with *TSC1* pathogenic inactivating alterations had a PR, with 64% (9/14) responses when the 2 subgroups combined, providing preliminary evidence of activity of *nab*-sirolimus in this subset of patients as

well. The manageable safety profile, promising response rates (89%), and clinically meaningful DOR seen in the AMPECT trial in patients with advanced PEComa, and particularly those with *TSC1* or *TSC2* inactivating alterations, indicate that treatment with *nab*-sirolimus may provide significant therapeutic benefit to patients with advanced solid tumors bearing *TSC1* or *TSC2* inactivating alterations.

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

1.3.1. Rationale for the Schedule and Dose of Administration of *nab*-Sirolimus

The same dose and schedule of *nab*-sirolimus (100 mg/m^2 qw2/3 IV) administration has been selected in the present study that was well-tolerated in the PEComa registrational Phase 2 study (AMPECT).

The patient population in this study is expected to be heavily treated. Thus, up to 4 sequential dose reductions are permitted (75, 56, 45, and 35 mg/m^2) based on data from the AMPECT Study, in which the dose reduction levels were 75 and 56 mg/m^2 and the FIH CA401 Study described in Section 1.2.2.3, studying doses as low as 30 mg/m^2, and producing anti-tumor activity. Doses will be reduced for hematologic and other non-hematologic toxicities, as clinically indicated.

Dose reduction of *nab*-sirolimus should be considered as clinically indicated as described by Section 6.1.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• 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	• ORR based on 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 disease progression as determined by IRR using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary	
• To evaluate the duration of response (DOR), disease control rate (DCR), time to response (TTR), and progression-free survival (PFS) via IRR, and overall survival (OS) of *nab*-sirolimus	• 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
• To evaluate changes in Quality-of-Life	• Changes from baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire v3.0 (EORTC-QOQ-C30) scores
• To describe the safety and tolerability of *nab*-sirolimus	• 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
Exploratory	
• To evaluate efficacy via investigator-assessed responses and PFS	• Investigator-assessed ORR, DOR, DCR, TTR, and PFS
• To evaluate the time on treatment	• Time on treatment (including patients treated beyond progression)

Objectives	Endpoints
• To evaluate the rate of surgical resection for patients with inoperable locally advanced disease after treatment with *nab*-sirolimus	• Rate of surgical resection with curative intent for patients with inoperable locally advanced disease at baseline
• To evaluate baseline genomics and the association between genomic alterations and clinical outcome, as well as genomic changes during treatment	• From baseline tumor tissue (archival or fresh biopsy) and blood (peripheral blood mononuclear cells, PBMCs): o To characterize *TSC1* and *TSC2* alterations as germline versus somatic (PBMCs, using next generation sequencing [NGS]) o To understand the concomitant alterations and allele frequency via a standardized method (secondary confirmation) (tissue, using NGS) o To evaluate the association between mutational profile and clinical outcome o 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

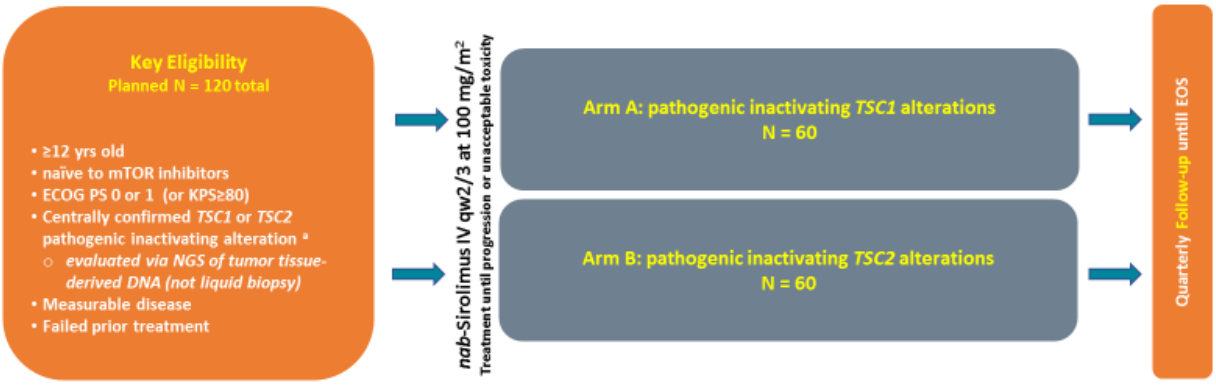
3.1. Study Design

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 malignant solid tumors with pathogenic inactivating *TSC1* (Arm A) or *TSC2* (Arm B) alterations, each Arm studied independently.

It is highly unlikely that pathogenic inactivating *TSC1* and *TSC2* alterations co-exist, but if such case occurs, that patient must be assigned to Arm B, if eligible. To avoid over-enrolling in any one tumor type, as defined by organ and histology, enrollment will be capped at 15 patients for each organ-histology 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). *nab*-Sirolimus will be administered at 100 mg/m^2. Four sequential dose reductions are allowed: 75, 56, 45, and 35 mg/m^2.

Figure 3: Study Schema



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

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.

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 for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/GCP and applicable regulatory requirements.

3.2. Study Duration

The study will enroll patients at approximately 35 sites in the US and globally 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 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 at least 4 weeks (+7 days) after the last dose of *nab*-sirolimus is administered.

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

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 (survival follow-up to continue). 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. STUDY POPULATION

4.1. Number of Patients

Sample size estimation is based on the primary endpoint of ORR (proportion of patients who achieve a confirmed objective response) evaluated separately for each Arm.

The expected enrollment is approximately 60 patients in each Arm (total N = 120 in the study). The sample size of 60 for each Arm was determined based on the ability to produce a 95% confidence interval (CI) that would exclude an ORR of 20% if the observed ORR is 32%. One analysis for futility and one interim analysis for efficacy are planned. The sample size may be adjusted at interim for efficacy to ensure the predictive probability of success will be ≥90% in the final analysis.

The rationale for the number of patients is further detailed in Section 9.

Tumor types, as defined by organ and histology, will be capped in each Arm at 15 patients to avoid over-enrolling in any one type of cancer.

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate, date, and outcome of the screening process (eg, enrolled into study, reason for ineligibility, or refusal to participate).

Before any study-specific procedure, the appropriate written informed consent must be obtained (see Section 12.1).

4.2. Inclusion Criteria

A patient will be eligible for inclusion in this study only if all of the following criteria are met:

1. Patients must have a malignant solid tumor with a pathogenic inactivating *TSC1* or *TSC2* alteration. Genetic alterations should be identified using NGS in tumor tissue or liquid biopsy.
    - Patients will be enrolled after the central evaluation of NGS report confirms eligibility.
2. Patients must have solid tumors that are metastatic or locally advanced where surgical resection is not an option or likely to result in severe morbidity.
3. Patients must have received all standard therapies appropriate for their tumor type and stage of disease or, in the opinion of the Investigator, the patient would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy, or the patient has no satisfactory alternative treatments.
4. Patients must have 1 or more measurable target lesions by computed tomography (CT) scan or magnetic resonance imaging (MRI) (RECIST v1.1).
5. Age: 19 years or older.

6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 or Karnofsky Performance Status (KPS) ≥80 or Lansky play-performance scale for pediatric patients ≥80.
7. Adequate liver function:
    a. Total bilirubin ≤1.5 × upper limit of normal (ULN) (unless due to Gilbert's syndrome, then ≤3 × ULN)
    b. Aspartate aminotransferase (AST) ≤2.5 × ULN (≤5 × ULN if attributable to liver metastases)
8. Adequate renal function: creatinine clearance ≥30 mL/min, Cockcroft-Gault CCr = ((140-age) × weight[kg]) / (72 × SCr [mL/min]) × 0.85, if female
9. Adequate hematologic parameters:
    a. Absolute neutrophil count (ANC) ≥1.0 × 10^9/L (growth factor support allowed)
    b. Platelet count ≥100,000/mm^3 (100 × 10^9/L) (transfusion and/or growth factor support allowed)
    c. Hemoglobin ≥8.0 g/dL (transfusion and/or growth factor support allowed)
10. Fasting serum triglyceride must be ≤300 mg/dL; fasting serum cholesterol must be ≤350 mg/dL.
11. Minimum of 4 weeks since any major surgery, completion of radiation, or completion of all prior systemic anticancer therapy, or at least 5 half-lives if the prior therapy is a single agent small-molecule therapeutic, and adequately recovered from the acute toxicities of any prior therapy, including neuropathy to Grade ≤1.
12. Male or non-pregnant and non-breastfeeding female:
    a. Females of childbearing potential must agree to use effective contraception or abstinence without interruption from 28 days prior to starting investigational product (IP) throughout 3 months after last dose of IP and have a negative serum pregnancy test (beta human chorionic gonadotropin, β-hCG) result at screening, and agree to ongoing urine pregnancy testing at every cycle during the course of the study, and after the end of study treatment. A second form of birth control is required even if she has had a tubal ligation.
    b. Male patients must agree not to donate sperm and must practice abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study and throughout 3 months after last dose of IP. A second form of birth control is required even if he has undergone a successful vasectomy.
13. The patient or the patient's parent(s) or legal guardian(s) understand(s) and sign(s) the informed consent.

14. Willingness and ability to comply with scheduled visits, laboratory tests, and other study procedures.

4.3. Exclusion Criteria

A patient will not be eligible for inclusion in this study if any of the following criteria apply:

1. Prior treatment with an mTOR inhibitor, including *nab*-sirolimus.
2. Severe (Grade ≥3) ongoing infection requiring parenteral or oral anti-infective treatment, either ongoing or completed ≤7 days prior to enrollment.
3. Patients with primary brain tumors or PEComa.
4. Patients who have any severe and/or uncontrolled medical or psychiatric conditions or other conditions that could affect their participation including:
    a. Patients with meningeal carcinomatosis, leptomeningeal carcinomatosis, spinal cord compression, untreated brain metastases or symptomatic or unstable brain metastases. Note: Patients with stable brain metastases (defined as asymptomatic or no requirement for high dose [defined as dexamethasone 10 mg daily or higher] or increasing dose of systemic corticosteroids) and without imminent need of radiation therapy are eligible. If applicable, patients must have completed brain radiation therapy and recovered adequately from any associated toxicity and/or complications prior to eligibility assessment. For patients who have received prior radiation therapy, post-treatment MRI scan should show no increase in brain lesion size/volume.
    b. Unstable angina pectoris, symptomatic congestive heart failure (New York Heart Association, NYHA class III or IV), myocardial infarction ≤6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease.
    c. Pre-existing severely impaired lung function. If a patient has a pre-existing pulmonary condition, eligible patients should have a spirometry and diffusing capacity for carbon monoxide (DLCO) that is >50% of the normal predicted value and/or O_2 saturation that is >88% at rest on room air (Note: spirometry and pulmonary function tests [PFTs] not required to be performed unless clinically indicated).
    d. Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with the study therapy.
    e. A history of malignancies other than the one under treatment unless the patient is disease-free for more than 5 years from diagnosis. Note, controlled non-melanoma skin cancers, carcinoma in situ of the cervix, resected incidental prostate cancer, certain low grade hematologic malignancies (eg, CLL, follicular lymphoma, etc), or other adequately treated carcinoma-in-situ may be eligible, after discussion with the medical monitor.

f. Uncontrolled hypertension (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg).

g. Patients with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension.

h. Individuals with known human immunodeficiency virus (HIV) infection are excluded from this study as combination antiretroviral therapy could potentially result in significant pharmacokinetic interactions. In addition, these individuals are at increased risk of serious infections due to the immunosuppressive effects of mTOR inhibition.

i. Active Hepatitis B or Hepatitis C, with detectable viral load.

5. Regarding concomitant medications with significant CYP3A4 interactions, discontinuation of strong inhibitors (eg, ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin, telithromycin, and others), strong inducers (eg, rifampin, rifabutin), and known CYP3A4 substrates with a narrow therapeutic window (eg, fentanyl, alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, or terfenadine) is required at least 5 half-lives prior to receiving the first dose of *nab*-sirolimus.
6. Persons with a history of hypersensitivity to sirolimus, rapamycin analogues, or albumin.

5. PROCEDURES

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

5.1. Screening Evaluations

This study will be conducted at approximately 35 sites in the US. Additional sites may be added globally.

Each patient who enters into the screening period for the study receives a unique patient identification number before any study-related procedures are performed. The patient identification number will be assigned. This number will be used to identify the patient throughout the clinical study and must be used on all study documentation related to that patient.

The patient identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment if a patient changes sites. A new number will be assigned if the patient rescreens.

Before patients may be entered into the study, Aadi requires a copy of the site's written Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval of the protocol, informed consent form, and all other patient information and/or recruitment material, if applicable. A signed and dated IRB/IEC-approved informed consent form (latest approved version) must be obtained from each patient prior to performing any study-specific procedures. All patients or legally acceptable representatives must personally sign and date the consent form before commencement of study-specific procedures. Adverse events (AEs) are to be collected for a patient once they have signed the informed consent. The patients' tumor samples will be tested for biomarker analyses after the collection on Cycle 1 Day 1.

Screening evaluations will be performed for all patients to determine study eligibility. These evaluations must be obtained ≤28 days prior to Cycle 1 Day 1. Any questions regarding patient eligibility should be directed to Aadi or other Aadi-nominated representatives or designees for approval.

The following procedures are to be completed during the screening period, after signed informed consent has been obtained, designated in the Schedule of Assessments, Table 1.

- Demographics (if allowed by local regulations, date of birth, sex, race, and ethnicity)
- Medical History
- Physical examination as per standard of care
- Vital signs (eg, blood pressure, pulse, respiration rate, temperature)
- Height and weight
- ECG

- ECOG/KPS/Lansky performance status assessment
- Prior medications and procedures evaluation: all medications taken ≤28 days prior to Cycle 1 Day 1
- Informed consent signed to collect pre-treatment tumor sample (archived or fresh) and blood sample for biomarker and molecular analysis (banked)
- Adverse event assessment
- Local Laboratory Assessments: complete blood count (CBC), chemistry, differential, platelet count, thyroid function, pregnancy test (women of childbearing potential, includes tubal ligations), HIV antibody, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, fasting lipids
- CT or MRI, must be performed within 4 weeks prior to Cycle 1 Day 1, preferably as close to the Cycle 1 Day 1 as possible

A patient is considered eligible and enrolled when the investigator decides that the patient has met all eligibility criteria. The investigator is to document this decision and date, in the patient's medical record and in/on the electronic case report form (eCRF).

All screening tests and procedures must be performed within 28 days of study Day 1, unless specified otherwise in the study procedures listed in the Schedule of Assessments, Table 1. Once eligibility is confirmed, a site representative will complete and send an eligibility/NGS review form to an Aadi representative. The Aadi representative will acknowledge receipt of the paperwork and confirm enrollment for that individual patient.

From all enrolled patients, every attempt should be taken to collect a fresh biopsy tissue sample or provide archival tissue <2 years old (if sample <2 years is not available, samples >2 years may be submitted). While tissue sample submission is recommended, if no tissue is available, patients may still be enrolled in the study.

5.2. Treatment Period

nab-Sirolimus is to be administered after all other protocol-specified pre-dose assessments have been performed during each visit that it is required. 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. Note: blood samples (banked) for biomarker analysis will be collected at baseline, associated with every 12 weeks scan (±1 week) for the first year, and at EOT or disease progression.

5.2.1. Day 1 Assessment

The following assessments will be performed on Day 1 of each cycle prior to *nab*-sirolimus administration, unless otherwise specified:

- Physical examination as per standard of care
- Vital signs (temperature, systolic and diastolic blood pressure, and pulse)

- Weight assessment
- Body surface area (BSA) calculation based on actual weight (calculated ONLY on Cycle 1/Day 1 per institutional standard methods; to be recalculated only if the weight changes by >10% in subsequent cycles)
- ECOG/KPS/Lansky performance status assessment
- Concomitant medication and procedures evaluation
- EORTC-QOQ-C30 v3.0 on D1 of every cycle up to Cycle 24
- Clinical chemistry panel (see Table 4 for analytes to be included)
- CBC, differential and platelet count
- Thyroid function as defined by TSH (and T3 and T4, if available)
- Fasting lipids (triglycerides, total cholesterol, HDL, and LDL cholesterol) on even numbered Cycles, starting with Cycle 2
- Urine pregnancy test (for females of childbearing potential only)
- Baseline blood for biomarkers prior to infusion on Cycle 1 Day 1, then every 12 weeks thereafter corresponding to the CT scans, for up to 1 year.
- Baseline tissue biomarker collection (Cycle 1 only)
- Adverse event assessment
- For all treated patients, sirolimus concentrations (PK), trough levels assessment on Day 1 of Cycles 1, 2, 3, and 4 prior to treatment with *nab*-sirolimus (central lab)
    - Patients who sign a separate optional consent (US only) will have additional sirolimus concentration (PK) collection;
        - on Cycle 1 Day 1 at 15 (±10 min), and 30 (±10 min) minutes (end of infusion) and at 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
- For all treated patients, ECG (on Cycle 1 Day 1 and Cycle 3 Day 1) at 30 mins (+10 mins) after the start of infusion to coincide with the end of infusion (local analysis)
    - Patients who sign a separate optional consent (US only) will have additional 12-lead ECG monitoring (central analysis):
        - on Cycle 1 Day 1 continuous monitoring from 1 hour prior to the start of infusion through 4 hrs (+10 mins) after the start of infusion, and
        - on Cycle 3 Day 1 continuous monitoring from 1 hour prior to the start of infusion through 30 mins (+10 mins) after the start of infusion

Day 1 evaluations for Cycle 1 may be omitted if screening evaluations are performed within 72 hours of Cycle 1 Day 1. Laboratory assessments: chemistry, hematology, pregnancy test (women of childbearing potential, includes tubal ligation) (see Table 4 for analyte listing).

5.2.2. Day 8 Assessment

The following assessments will be performed on Day 8 of each cycle prior to *nab*-sirolimus administration, unless otherwise specified:

- Vital signs (temperature, systolic and diastolic blood pressure, and pulse)
- Concomitant medication and procedures evaluation
- CBC, differential, and platelet count
- Adverse event assessment
- Sirolimus concentrations, trough levels assessment on Day 8 of Cycles 1, 2, 3, and 4 prior to treatment with *nab*-sirolimus (central lab)

5.2.3. Response Assessment

Tumor response will be assessed by CT or MRI scan of the chest, abdomen, and pelvis; image preparation and evaluation will follow the specifications provided in the RECIST version 1.1. The same modality (CT or MRI) should be used at screening and throughout the study. Blood samples for biomarker analysis should be collected at baseline, every 12 weeks associated with scans (±1 week) for the first year and at the EOT visit/disease progression.

CT/MRI scans to be performed at the following frequency:

- ≤28 days prior to C1D1 (screening)
- followed by every 6 weeks after C1D1 for the first 1 year (±7 days)
- followed by every 12 weeks (±7 days) thereafter until disease progression. End of Treatment Visit CT/MRI should be performed only for those patients that discontinue treatment for a reason other than disease progression.

An unscheduled scan for suspected disease progression may be performed at any time. However, adherence to the planned imaging schedule is critical regardless of dose delays or unscheduled or missed assessments. Scans will be submitted to an independent central imaging laboratory for assessment by RECIST 1.1 and for determination of measurable disease. Determination of disease progression for clinical management of patients on study will be assessed at the local site. **If an initial observation of objective response (CR or PR) is made, a confirmation scan should be done 6 weeks (±1 week) after initial observation.**

At the time of disease progression, if a biopsy is performed, a tumor sample should be collected, if available. The surgical pathology report is to be submitted with the tumor

tissue sample. Refer to the Laboratory Manual for tissue handling instructions for processing and shipping details.

Table 4: Analyte Listing

Chemistry	Hematology	Other Labs
Sodium	WBC	Pregnancy test
Potassium	RBC	Sirolimus PK (central lab)
Bicarbonate	Hemoglobin	TSH (and T3, T4 if available)
Chloride	Hematocrit	HIV
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		

Ab = antibody; ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; cAb = core antibody; HDL = high-density lipoprotein; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDL = low-density lipoprotein; PK = pharmacokinetic(s); RBC = red blood cell; sAg = surface antigen; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TSH = thyroid stimulating hormone; WBC = white blood cell.

5.3. End of Treatment Visit Assessment

Patient visits are complete after the EOT Visit. The EOT Visit is a safety follow-up visit that is to be performed at least 4 weeks (+7 days) after the last dose of *nab*-sirolimus. All efforts should be made to conduct this visit. If it is not possible to conduct the EOT Visit, documentation of efforts to complete the visit should be provided.

The following procedures will be completed at the EOT Visit as designated in the Schedule of Assessments, Table 1:

- Physical examination
- Vital signs (eg, blood pressure, pulse, respiration rate, temperature)

- Weight
- ECOG/KPS/Lansky performance assessment
- Laboratory assessments: chemistry, CBC, differential, platelet count, pregnancy test (women of childbearing potential)
- Blood sample for biomarker analysis (banked)
- Imaging assessment: CT/MRI is to be performed at the end of study visit only for those patients that discontinue treatment for a reason other than disease progression per RECIST v1.1
- Concomitant medication and procedures evaluation
- Adverse event assessment

5.4. Follow-up Period for Survival and Initiation of Anticancer Therapy

Post-treatment survival time and any subsequent initiation of anticancer therapy will be collected approximately every 12 weeks (±3 weeks) from EOT Visit or more frequently as needed, until death, withdrawal of consent, or the study closes, whichever is earliest. 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. This evaluation may be by record review and/or telephone contact.

5.5. Pharmacokinetic Study

Whole blood samples for sirolimus trough (pre-treatment) levels will be analyzed centrally for all treated 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 pre-dose (before infusion).

Additionally, from 30 patients who sign an optional PK/ECG informed consent (US only), 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.

5.6. ECG Study

Electrocardiogram measurements will be collected and analyzed locally for all treated patients at screening, on Cycle 1 Day 1 and Cycle 3 Day 1 at 30 minutes (±10 min) after the start of infusion (to coincide with the end of infusion), thereafter as clinically indicated.

Additionally, for 30 treated patients who sign an optional PK/ECG informed consent form (US only), 12-lead ECG continuous monitoring using Sponsor-provided Holter monitors will be performed

- on Cycle 1 Day 1 from 1 hour prior to the start of infusion through 4 hrs (+10 min) after the start of infusion, and
- on Cycle 3 Day 1 from 1 hour prior to the start of infusion through 30 mins (+10 min) after the start of infusion.

The ECG data from these 30 patients will be analyzed centrally (refer to the Holter Acquisition Guide for detailed instructions for Holter ECG and collection of optional PK samples during Holter monitoring).

5.7. Biomarker Analysis

Baseline tissue (archival or fresh biopsy) of up to 20 slides, if available, and blood samples will be required from all patients.

The key objectives of the baseline tissue profiling for the exploratory biomarker analysis and baseline blood biomarker analysis (PBMCs) are:

a. To characterize *TSC1* and *TSC2* alterations as germline versus somatic (PBMCs, using next generation sequencing, NGS)

b. To understand the concomitant alterations and allele frequency via a standardized method (secondary confirmation on tissue, using NGS)

c. To evaluate the association between genomic alterations (including but not limited to nonsense, in-frame deletion, missense, allele frequency) and clinical outcome

d. pS6 via immunohistochemistry

The key objective of the longitudinal blood biomarker analysis during treatment is to evaluate genomic changes to treatment. Blood samples will be collected at baseline on Cycle 1 Day 1 (prior to infusion), at every 12 weeks (±1 week) scan for the first year, and at the EOT visit or disease progression.

6. DESCRIPTION OF STUDY TREATMENTS

6.1. *nab*-Sirolimus Dosage, Administration, and Schedule

Treatment cycles are 21 days in duration. Patients will receive *nab*-sirolimus 100 mg/m^2 (IV infusion over 30 minutes [-0 to +10 min]) on Days 1 and 8 of every 21-day cycle (2/3 weekly schedule). A licensed health care professional (NP, PA, MD/DO, or equivalent) should be available at the time of administration of IP. Supportive care per the institution's normal standard of care including concomitant medications can be provided at the investigator's discretion.

6.2. Dose Modification (Delays, Reductions) and Treatment Discontinuation

6.2.1. Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Prior to *nab*-sirolimus administration on Days 1 and 8, patients must meet the following hematological requirements prior to dosing:

- ANC ≥1.0 × 10^9/L
- Platelet count ≥100 × 10^9/L
- Hemoglobin ≥8.0 g/dL

If treatment cannot be administered on the planned visit date, *nab*-sirolimus may be administered ±3 days from the scheduled date, no dose should be administered ≤4 days from the previous dose. The dose may be held for up to 21 days until the patient has fulfilled these criteria. Approval from the Medical Monitor is required to restart study treatment after >21 days of interruption (counting from the last dose).

Day 1 Dose Delayed

If the dose is not administered on the planned Day 1 ±3 days, the cycle starts when the first dose of the cycle is actually administered.

Day 8 Dose Is Missed or Delayed

If the Day 8 dose is not administered on the planned day ±3 days, then that week becomes a week of rest. The next dose (if counts and chemistries permit) becomes Day 1 of a new cycle (ie, if Day 8 cannot be administered by Day 11 of any cycle, then the Day 8 dose of the cycle is skipped, and Day 1 of the next cycle should be planned to start 14 days after the previous dose).

Dose Reductions

Doses will be reduced for hematologic and non-hematologic toxicities, as clinically indicated and as shown in Table 6. Up to 4 sequential dose reduction are permitted (75, 56, 45, and 35 mg/m^2, Table 5). If the patient is experiencing more than one toxicity simultaneously, then refer to the guidelines below. Dose modifications/discontinuations (refer to general guidelines and Table 6 below) 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/AEs 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 this section:

- 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 (Table 6).

General guidelines: In the event of any clinically significant AE(s), treatment may be withheld, and supportive therapy administered as clinically indicated. If the toxicity or event is not Grade 3 or 4 and resolves to baseline or Grade 1 within 21 days of withholding therapy, then treatment may be restarted.

Dose reduction of *nab*-sirolimus may be implemented for any toxicities considered intolerable of any grade, at the discretion of the Investigator. If two dose level reductions are felt to be the only safe way to resume treatment with the IP, then the Investigator should discuss with the Medical Monitor before continuing treatment with the IP.

If the toxicity does not resolve to Grade 1 or baseline within 21 days, withdrawal from treatment with the IP is recommended. However, if the investigator, patient, and Aadi Medical Monitor agree that further treatment would benefit the patient, treatment can continue with a dose level reduction.

Table 5: Dose Level Reduction Guidelines

Dose level	*nab*-sirolimus Dose/Schedule
0 (initial dose)	100 mg/m^2 (actual dose capped at 200 mg [BSA 2 m^2])
-1 (first dose reduction)	75 mg/m^2: 25% reduction of initial dose of 100 mg/m^2
-2 (second dose reduction)	56 mg/m^2: 25% reduction from 75 mg/m^2
-3 (third dose reduction)	45 mg/m^2: 20% reduction from 56 mg/m^2
-4 (fourth dose reduction)	35 mg/m^2: 25% reduction from 45 mg/m^2

If an AE resolves to Grade 1 or baseline at the reduced dose level, and no additional toxicities are seen during the following cycle of study treatment at the reduced dose, the dose may be increased to the previous dose level at the Investigator's discretion.

nab-Sirolimus dose modification guidelines are outlined in Table 5 and Table 6 for clinically significant toxicities that are deemed related by the Investigator. The dosing schedule is described in the Schedule of Assessments, Table 1.

Table 6: Dose Modification Algorithms for Adverse Events Possibly Related to *nab*-Sirolimus

Adverse Reaction	Severity*	Dosage Modifications
Stomatitis**	Grade 2 or 3	• Withhold *nab*-sirolimus until Grade ≤1. • Restart at the same dose for first occurrence. • If recurs, restart at reduced dose level.
	Grade 4	• Permanently discontinue *nab*-sirolimus.
Anemia	Grade 2	• Withhold *nab*-sirolimus until Hb ≥8 g/dL. • Restart at the same dose level.
	Grade ≥3	• Withhold *nab*-sirolimus until Hb ≥8 g/dL. • Restart at the same dose level. • If recurs, resume at reduced dose level.
Thrombocytopenia	Grade 2	• Withhold *nab*-sirolimus until platelet count >100 × 10^9/L. • Restart at the same dose level.
	Grade ≥3	• Withhold *nab*-sirolimus until platelet count >100 × 10^9/L. • Restart at reduced dose level.
Neutropenia	Grade 2 or 3	• Withhold *nab*-sirolimus until absolute neutrophil count ≥1.5×10^9/L. • Restart at the same dose level.
	Grade 4	• Withhold *nab*-sirolimus until absolute neutrophil count ≥1.5×10^9/L. • Restart at reduced dose level.
Infections	Grade 3	• Withhold *nab*-sirolimus until resolved. • Restart at reduced dose level. • If recurs, permanently discontinue *nab*-sirolimus.
	Grade 4	• Withhold *nab*-sirolimus until resolved. • Restart at reduced dose level or permanently discontinue *nab*-sirolimus.
Hypokalemia	Grade 2	• Withhold *nab*-sirolimus until Grade ≤1. • Restart at the same dose level. • If recurs, restart at reduced dose level.
	Grade ≥3	• Withhold *nab*-sirolimus until Grade ≤1. • Restart at reduced dose level. • If recurs, permanently discontinue *nab*-sirolimus.
Hyperglycemia	Grade ≥3	• Withhold *nab*-sirolimus until Grade ≤2. • Restart at reduced dose level.

Adverse Reaction	Severity*	Dosage Modifications
Interstitial Lung Disease / Non-Infectious Pneumonitis	Grade 2	• Withhold *nab*-sirolimus for up to 3 weeks until Grade ≤1. • Restart at reduced dose level. • If not resolved to Grade ≤1 within 3 weeks, permanently discontinue *nab*-sirolimus. • If recurs, permanently discontinue *nab*-sirolimus.
	Grade ≥3	• Permanently discontinue *nab*-sirolimus.
Hemorrhage	Grade 2 or 3	• Withhold *nab*-sirolimus until Grade ≤1. • Resume at reduced dose. • If recurs, permanently discontinue *nab*-sirolimus.
	Grade 4	• Permanently discontinue *nab*-sirolimus.
Hypersensitivity/Infusion-Related Reactions	Grade ≥3	• Permanently discontinue *nab*-sirolimus.
Other Adverse Reactions	Grade 3	• Withhold *nab*-sirolimus until Grade ≤1. • Restart at the same dose level. • If recurs, restart at reduced dose level.
	Grade 4	• Permanently discontinue *nab*-sirolimus.

* Severity based on Common Terminology Criteria for Adverse Events Version 4.03.

** Includes Gastritis and Mucositis

For this study, use CTCAE v5.0 to grade adverse events.

6.2.2. Hepatotoxicity Stopping Rules

Patients with abnormal hepatic laboratory values (ie, ALT, AST, total bilirubin) and/or clinical signs/symptoms of hepatitis may meet the criteria for permanent discontinuation of *nab*-sirolimus as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. Any patient meeting the criteria for severe drug-induced liver injury (ie, Hy's Law) should permanently discontinue *nab*-sirolimus.

Hy's Law is defined as: AST and/or ALT values of ≥3 × upper limit of normal (ULN) ***and*** a serum total bilirubin (TBL) level of >2 × ULN and/or an INR >1.5 ULN without signs of cholestasis (eg, alkaline phosphatase <2x ULN) and with no other clear alternative reason to explain the observed liver-related laboratory abnormalities.

6.2.2.1. Criteria for Permanent Discontinuation of *nab*-Sirolimus Due to Potential Hepatotoxicity

nab-Sirolimus should be discontinued permanently, and the patient should be followed for possible drug-induced liver injury (DILI), if **ALL** of the criteria below are met:

- AND AST and/or ALT ≥3 × ULN (or 2× from baseline value if elevated prior to *nab*-sirolimus exposure);

- AND increased ≥3 × ULN AST or ALT from the relevant baseline value as specified below:
- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:
  - Hepatobiliary tract disease
  - Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, Cytomegalovirus, Herpes Simplex Virus, Varicella, Toxoplasmosis, and Parvovirus)
  - Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
  - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - Alpha-1 antitrypsin deficiency
  - Alcoholic hepatitis
  - Autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
  - Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

6.2.2.2. Criteria for Conditional Withholding of *nab*-Sirolimus Due to Potential Hepatotoxicity

For patients who do not meet the criteria for permanent discontinuation of *nab*-sirolimus due to severe drug-induced liver injury but who develop liver transaminase abnormalities, refer to the following rules below for withholding of *nab*-sirolimus:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	>8 × ULN at any time
Any	>5 × ULN but <8 × ULN for ≥2 weeks
Any	>5 × ULN but <8 × ULN and unable to adhere to enhanced monitoring schedule
Any	≥3 × ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice).

- OR: TBL >3 × ULN at any time
- OR: ALP >8 × ULN at any time

nab-Sirolimus should be withheld pending investigation into alternative causes of drug-induced liver injury (DILI).

6.2.2.3. Criteria for Rechallenge with *nab*-Sirolimus After Potential Hepatotoxicity

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, and ALP) and/or elevated TBL is discovered and the laboratory abnormalities resolve to normal or baseline. The decision to rechallenge the patient after *nab*-sirolimus has been held for potential hepatotoxicity should be discussed and agreed upon unanimously by the patient, investigator, and Aadi medical monitor.

If signs or symptoms recur with rechallenge, then *nab*-sirolimus should be permanently discontinued. Patients who clearly meet the criteria for permanent discontinuation (as described in Section 6.2.1) should never be rechallenged.

6.2.3. Overdose

On a per dose basis, an overdose is defined as 10% over the protocol-specified dose of *nab*-sirolimus assigned to a given patient, regardless of any associated AEs or sequelae.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate of 30 minutes for each infusion.

7. STUDY DRUG MANAGEMENT

7.1. Description of *nab*-Sirolimus

7.1.1. *nab*-Sirolimus Packaging, Labeling, and Storage

nab-Sirolimus will be supplied by Aadi in single-use vials as lyophilized cake. Each single-use 50-mL vial will contain 100 mg sirolimus and approximately 850 mg of human albumin. Each vial will be labeled according to country-specific regulatory requirements for labeling of IPs.

Reconstituted *nab*-sirolimus in the vial should be used immediately but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 6 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from light. Discard any unused portion.

The suspension for infusion when prepared as recommended in an infusion bag should be used immediately but may be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from light for a maximum of 9 hours.

The total combined refrigerated storage time of reconstituted *nab*-sirolimus in the vial and in the infusion bag is 15 hours. This may be followed by storage in the infusion bag at ambient temperature (approximately 25°C) and lighting conditions for a maximum of 4 hours. Discard any unused portion.

The reconstituted suspension for infusion in a syringe should be used immediately but may be stored in the syringe at ambient temperature (approximately 25°C) and lighting conditions for a maximum of 4 hours. Discard any unused portion.

Temperature records for *nab*-sirolimus must be made available to Aadi or Aadi-nominated Contract Research Organization (CRO) monitoring teams for verification of proper study drug storage.

7.2. *nab*-Sirolimus Accountability, Disposal, and Compliance

Only completely unused study drug vials should be retained by the site until a representative from Aadi or Aadi-nominated CRO has completed an inventory. Partially used and completely used vials should be destroyed according to the site's guidelines, and their disposition should be recorded on the Investigational Drug Accountability Record Form.

The Investigator, or designee, shall record the dispensing of study drug to patients and any remaining study drug after dosing in a study drug accountability record. The study drug record will be made available to Aadi or authorized Aadi-designated monitoring personnel for the purpose of accounting for the study drug supply. Inspections of the study drug supply for inventory purposes and assurance of proper storage will be conducted as necessary. Any significant discrepancy will be recorded and reported to Aadi or their designee and a plan for resolution will be documented.

Accurate recording of all *nab*-sirolimus administration will be made in the appropriate section of the patient's eCRF and source documents. The investigator or designee is responsible for accounting for all study-specific IP either administered or in their custody during the course of the study.

7.3. *nab*-Sirolimus Reconstitution and Dosing

NOTE: It is not a requirement to use filter needles in the preparation, or in-line filters during the administration of *nab*-sirolimus. In any event, filters of pore size <15 microns (<15 µm) must not be used.

nab-Sirolimus will be reconstituted by designated study personnel per instructions noted in the Pharmacy Manual and administered to the patient at the study site. The investigator or designee will calculate the BSA of the patient per institutional standard methods in order to determine the total amount of *nab*-sirolimus to be administered. Dosing will be capped at a BSA of 2 m^2. The calculated Dosing Volume of 5 mg/mL (rounded to the nearest mL) reconstituted *nab*-sirolimus suspension will be administered by IV infusion over 30 minutes (+10 minute window).

7.4. Receipt and Return of *nab*-Sirolimus

The process for handling the receipt and return of the study drug supplies are described in the Pharmacy Manual.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

All concomitant treatments, including blood and blood products, must be reported on the eCRF. Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.2.

Prior medications taken and procedures are to be collected ≤28 days prior to screening. Concomitant medications or procedures are to be collected after the signing of informed consent through the EOT Visit. Therapy name including indication, dose, frequency, route, start date, and stop date will be recorded on each patient's eCRF(s).

8.1. Permitted Medications and Procedures

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior cancer therapies will be recorded in the eCRF.

Patients should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. White blood cell (WBC) and platelet growth factors may be administered at the discretion of the investigator, consistent with institutional guidelines.

Palliative radiation therapy or palliative surgery must not be initiated during protocol participation except during the first 8 weeks of treatment, with medical monitor approval, and is allowed only in cases when other non-irradiated lesions are also followed for response beside the irradiated one(s). The need to initiate radiation therapy or palliative surgery beyond 8 weeks would be considered non-protocol therapy and therefore a treatment failure.

Extreme precaution must be taken with contraceptives (either combined or progesterone only), as it is not known if there is the potential of inhibition/induction of enzymes that affect the metabolism of estrogens and/or progestins.

8.2. Prohibited Medications and Procedures

The use of certain medications, and illicit drugs within 5 half-lives or 28 days, whichever is shorter prior to the first dose of study drug and for the duration of the study will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while study drug is held, the Aadi medical monitor can approve such use.

The following medications or non-drug therapies are prohibited:

- Other anticancer therapy while on treatment in this study, except as noted above (Section 8.1).
- Antiretroviral drugs (patients with known HIV are ineligible for study participation).

- Herbal remedies (eg, St. John's wort) unless approval is granted by the medical monitor (tetrahydrocannabinol [THC] and cannabidiol [CBD]-containing products are permitted).
- Use of strong inhibitors and inducers of CYP3A4 within 5 half-lives prior to receiving the first dose of *nab*-sirolimus. Sirolimus is metabolized primarily by CYP3A4. Drugs that are strong inhibitors or inducers of CYP3A4 may only be used under special circumstances (eg, as a single use for a procedure) while treatment with study drug is interrupted. The list may be modified based on emerging data.
- Use of any known CYP3A4 substrates with a narrow therapeutic window (such as fentanyl, alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, or terfenadine) within 5 half-lives prior to receiving the first dose of *nab*-sirolimus. Other medications may be allowed if there is agreement between the Aadi and investigator.

9. STATISTICAL CONSIDERATIONS

9.1. Study Endpoints, Analysis Sets, and Covariates

All patients within each Arm will be analyzed together across tumor types for both efficacy and safety. Efficacy by tumor types within Arms may also be summarized separately.

Safety will also be summarized combined across both Arms.

9.1.1. Study Endpoints

Primary Endpoint

- ORR based on the proportion of patients with BOR of confirmed PR or CR from the time of study treatment initiation until disease progression as determined by IRR using 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 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 EORTC-QOQ-C30 scores
- Incidence and severity of treatment-emergent and treatment-related AEs as assessed by the NCI CTCAE v5.0

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
- Baseline tumor tissue (archival or fresh biopsy), if available, and blood (PBMCs) samples are required from all patients:
    - To characterize *TSC1* and *TSC2* alterations as germline versus somatic (PBMCs, using NGS)
    - To understand the concomitant alterations and allele frequency via a standardized method (secondary confirmation) (tissue, using NGS)
    - To evaluate the association between mutational profile and clinical outcome

- To evaluate the expression of S6 via immunohistochemistry
- Identify dynamic clonal changes from blood samples collected at baseline and during treatment

9.1.2. Analysis Sets

Full Analysis Set (Treated Population)

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

Per-protocol Analysis Set

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

9.1.3. Covariates and Subgroups

The following covariates may be used to examine efficacy and/or safety in subgroups within Arms, if sufficient number of patients (≥5) are enrolled in the subgroups:

- Gender (male and female)
- Age at enrollment (<65 vs ≥65 and <75 vs ≥75 years)
- ECOG Performance Status at baseline (0 vs 1) or KPS or Lansky 70–80 versus 90–100
- Number of prior lines of therapies for metastatic disease
- Tumor Type
- Somatic versus germline *TSC1* or *TSC2* alterations

9.2. Sample Size Considerations

Based on limited efficacy data in patients with various solid tumors and in patients with malignant PEComa (study PEC-001, AMPECT) harboring *TSC1* or *TSC2* inactivating alterations, there is a potential to observe different ORR rate for patients in Arm A and Arm B after *nab*-sirolimus treatment.

Each Arm is designed as an independent trial and will be comprised of 1 futility analysis and 1 interim analysis on efficacy which allows sample size adjustment in each Arm, if necessary. Enrollment will be ongoing during the time of each interim analysis. Details on futility analysis and interim analysis for efficacy will be specified in the statistical analysis plan.

The planned sample size for this study is approximately 60 treated patients per Arm. Sample size estimation (N = 60 for each Arm, analyzed separately) is based on the primary efficacy endpoint of proportion of patients with a confirmed CR or PR across all tumor types.

Tumor types will be capped at 15 patients in each Arm to avoid over-enrolling in any one tumor type, as defined by organ and histology. The sample size was determined based on the ability to produce a 95% CI that would exclude an ORR of 20% if the observed ORR is 32%.

The 95% exact CIs for target ORRs ranging from 30% to 55% with sample size of 60 is summarized in Table 7.

Table 7. Observed ORR with Exact 95% CI (N = 60)

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

9.3. Primary Analysis

The primary analysis to address all study objectives in each Arm will be conducted when all patients have had the opportunity to be treated for at least 6 months within an Arm. Analysis will be done in each Arm independently, and the primary analysis for each Arm may occur at different times, should one of the Arms complete enrollment earlier. 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 primary, secondary, and exploratory efficacy and safety analyses will be conducted at the time of the primary analysis for each arm, with the exception of 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) may be summarized across both Arms if there is lack of heterogeneity in response 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.

The primary endpoint, ORR, will be assessed by independent radiologic assessment. Overall response rate evaluated by investigator assessment will be collected and summarized as an exploratory analysis.

Safety will be summarized by Arm and combined across Arms.

9.4. Interim Data Monitoring Plan and Data Monitoring Committee

An external DMC will review safety, investigator response assessment data for futility and for efficacy as follows:

- When the 40th patient has enrolled (considering enrollment across both Arms A and B) and has had 1 post-baseline scan
- When the 80th patient has enrolled (considering enrollment across both Arms A and B) and has had 1 post-baseline scan

DMC will also review efficacy data as follows:

- Futility analysis, which will occur separately in each Arm when 11 patients have had the opportunity to be treated for at least 3 months and have at least one post-baseline response assessment
- 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 relevant specialties and at least 1 statistician.

9.5. Planned Methods of Analysis

9.5.1. General Considerations

A clinical study report will be generated when the primary analysis has been completed for each study Arm. If one Arm completes enrollment faster than the other Arm a separate report summarizing the efficacy for that one Arm will be generated and will include all safety data for both study Arms collected up to that point. The study report 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.

The analyses of all study objectives will be descriptive and hypothesis generating in nature.

Continuous variables will be summarized by the non-missing sample size (n), mean, standard deviation, first and third quartiles, minimum and maximum. Categorical variables will be summarized by the n and percent in each category.

Point estimates for efficacy endpoint incidences will be accompanied by a 2-sided 95% exact binomial CI.

Time to event endpoints will be summarized descriptively using the Kaplan-Meier (KM) method (Kaplan, 1958). Kaplan-Meier quartiles (when estimable) along with the 95% 2-sided CIs (Brookmeyer, 1982), the number of patients censored and the number of events will be provided. Kaplan Meier estimates may also be presented graphically.

No adjustments for multiplicity are planned for the analysis of the efficacy endpoints.

9.5.2. Primary Efficacy Endpoints

The primary endpoint, ORR, will be determined by independent radiologist(s).

The primary analysis will evaluate the ORR defined as the proportion of patients with independently assessed BOR of confirmed CR or PR from the time of study treatment initiation until disease progression, as determined by independent radiologic assessment using RECIST v1.1. The 95% confidence interval for the proportion will also be summarized.

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 4 weeks after initial observation.

The analysis of ORR will be conducted on the Full Analysis Dataset. A sensitivity analysis also may be conducted using the Per-protocol Analysis Dataset.

9.5.3. Secondary Efficacy Endpoints

The analysis of the DOR will be conducted on the Full Analysis Dataset and will be estimated by the KM method. A sensitivity analysis may also be conducted using the Per-protocol Analysis Dataset.

Only patients achieving an ORR will be included in the analysis of DOR. Duration of response is defined as the time from when criteria of response is first met until the first observation of disease progression per RECIST v1.1 or death due to any cause, whichever comes first. Patients without any of these events will be censored at their last evaluable tumor assessment.

The analysis of DCR will be summarized as proportion of patients achieving DCR along with the 95% confidence interval.

The analysis of TTR, PFS, and OS will be conducted on the Full Analysis Dataset and will be estimated by the KM method.

Time to response is defined as time from first dose of study drug to initial measurement of CR or PR, where CR or PR is subsequently confirmed

Progression-free survival is defined as the time from the first dose date to the first observation of a 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.

Overall survival is defined as the time from the first dose date 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.

9.5.4. Safety Endpoints

Safety (incidence and severity of AEs and significant laboratory abnormalities) is a secondary endpoint and will be analyzed using the Full Analysis Dataset. All safety analyses will be performed separately by Arm and combined across both Arms.

Patient incidence of all treatment-emergent AEs will be tabulated by System Organ Class and Preferred Term. Tables of fatal adverse events, serious adverse events, treatment-related AEs, Grade 3 or 4 AEs, adverse events of special interest, and adverse events leading to withdrawal from investigation product will also be provided. The MedDRA will be used to code adverse events and the NCI CTCAE version 5.0 will be used to grade severity of adverse events and laboratory toxicities.

For *nab*-sirolimus exposure, summary statistics will be provided for total number of doses, average dose administered, and duration of treatment.

For select laboratory parameters, changes of laboratory values over time (eg, change from baseline summary statistics), grade shifts in laboratory values from baseline to worst on-study value, and Grade 3 or higher laboratory toxicities will be summarized.

10. MONITORING, RECORDING AND REPORTING OF ADVERSE EVENTS

nab-Sirolimus is a formulation of sirolimus. No unexpected toxicities not already known for sirolimus (Rapamune®) or the sirolimus prodrug, temsirolimus (Torisel®), were identified in the nonclinical toxicity studies, or observed in the Phase 1 and 2 studies for *nab*-sirolimus.

More details on the known precautions, warnings, and AEs of sirolimus and rapalogs are found in the Rapamune®, Torisel® Package Inserts (RAPAMUNE Prescribing Information; TORISEL Prescribing Information), and Fyarro™ (FYARRO Prescribing Information).

10.1. Definition of Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory value), symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product [ICH E6 (R2)]. The investigator should attempt to establish a diagnosis of an event based on signs, symptoms, and test results or other medical information (when obtained). In such cases, the diagnosis should be documented as the AE rather than the individual signs or symptoms (eg, nausea and vomiting are 2 distinct AEs, unless a diagnosis can be made that encompasses both symptoms, in which case only the diagnosis should be reported as the AE).

The definition of an AE includes worsening of a pre-existing condition. Worsening indicates that the pre-existing medical condition has increased in severity and/or frequency.

Note: Disease progression and the term death will not be recorded as an AE. The event that, in the investigator's judgment, caused the death will be reported as a serious adverse event (SAE).

Out of range laboratory values that are assessed as clinically meaningful per investigator's medical judgment must be reported as AEs with severity grading. The investigator is responsible for reviewing all laboratory test results (either collected as per protocol or for any other reason) and determining whether an abnormal value in an individual patient is a clinically meaningful change from the patient's baseline values.

Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the appropriate CRF, see Section 6.2.3 for the definition of overdose. Any sequela of an accidental or intentional overdose of the IP should be reported as an AE on the AE CRF. If the sequela of an overdose meets the definition of an SAE, see Section 10.3.2 for reporting of SAEs. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, dental extraction); the condition that necessitates the procedure should be reported as the AE and the procedure should be captured as treatment for the AE.
- Any pre-existing disease or laboratory abnormality, which is present prior to the start of the IP and that does not worsen.
- Situations where an adverse event has not occurred (ie, hospitalization for elective surgery, social admission).

All patients will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the patient's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

10.1.1. Adverse Events of Special Interest

An adverse event of special interest (serious or non-serious) 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 adverse event of special interest and will be monitored. Report pneumonitis of any grade, irrespective of seriousness, in the same expedited manner as an SAE. See Section 10.3.2 for reporting requirements.

10.1.2. Adverse Event Reporting Period

Report AEs considered related to study procedures from the time of signing of informed consent until the first administration of IP. All AEs, related or not related to IP or study procedures, must be reported from first administration of IP through 28 days after the last dose of IP. After this reporting period, any AEs considered **related** to the IP or study procedures should be reported.

Serious adverse events should be reported as specified above. See Section 10.3.2 for more details on SAE reporting requirements.

The investigator's clinical judgment is used to determine whether a patient is to be removed from treatment due to an AE. The investigator is responsible for ensuring that all AEs are reported using the applicable eCRF.

Investigators are not obligated to actively seek AEs/SAEs after the conclusion of the study participation. However, if the investigator learns of any AE/SAEs, at any time after a patient has withdrawn from the study, or after the study has ended, and he/she considers the event to be reasonably related to the IP, the investigator must promptly notify Aadi.

10.2. Adverse Event Assessment and Follow-up

The investigator is to report all AEs that occur in the patient as specified in Section 10.1.2. The investigator should follow each AE until the event has resolved to baseline grade or better, the AE is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered related to investigational product until a final outcome is reported.

10.2.1. Serious Versus Severe Adverse Events

To avoid confusion between the terms “serious” and “severe”, which may have different implications in the context of a clinical study, the following definitions (based on ICH E2A [1994]) are provided:

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild/Grade 1, moderate/Grade 2, severe/Grade 3, life-threatening/Grade 4, and death/Grade 5). However, the event itself may be of only minor medical significance (eg, a severe headache). This is not the same as “serious”, which is based on a patient/event outcome or action criteria associated with events that threaten a patient’s life or functioning. Seriousness (not severity) serves as a guide to the sponsor to determine regulatory reporting obligations.

The severity of each AE will be determined using the NCI CTCAE v5.0.

Since the criteria for the CTCAE grading scale differs from the criteria for regulatory reporting of SAEs, if AEs correspond to Grade 4 “life threatening” CTCAE grading scale criteria (e.g., laboratory abnormality reported as Grade 4 without manifestation of life-threatening status), it will be left to the investigator’s judgment to report these abnormalities as SAEs. For any SAE that applies to this situation, comprehensive documentation of the event’s severity status must be recorded in the patient’s medical record.

10.2.2. Relationship of Adverse Events to Investigational Product

The Investigator must assess and report all AEs and evaluate their relationship to the investigational product. The degree of certainty about causality will be graded using the categories below.

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. Select this category when the AE is more likely related to the study drug than to other explanations or possible causes.
	Probable	The AE ***is likely related*** to the intervention
	Definite	The AE ***is clearly related*** to the intervention

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

These criteria, in addition to the investigator's clinical judgment, should be used as a guide in determining the causal assessment. If the event is considered not related to IP, then an alternative explanation should be provided, as applicable.

The relationship to required study procedures should also be provided when an AE is suspected to be related to these procedures.

10.3. Serious Adverse Events

10.3.1. Definition of Serious Adverse Events

An SAE is defined as an AE that meets at least 1 of the following serious criteria:

- Results in death (death is a result of an SAE, and not an SAE itself; the event that, in the investigator's judgement, caused the death is the SAE).
- Is life-threatening, defined as an event in which the patient was, in the judgement of the investigator, at immediate risk of death.
- Requires inpatient hospitalization or prolongation of existing hospitalization. (Inpatient hospitalization means the event necessitated an admission to a hospital for medical cause [e.g., overnight stay]).
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Other medically important serious event

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention and do not result in inpatient hospitalization.

10.3.2. Serious Adverse Event Reporting Requirements

Aadi must be notified immediately within 24 hours of the investigator's knowledge of the event of any SAE or AESI that occurs within the AE reporting periods defined in Section 10.1.2. All SAEs and AESIs (serious and non-serious) must be reported to Aadi Drug Safety via email or facsimile using the SAE Report Form, in addition to recording in the AE eCRF. This pertains to initial and any follow-up SAE reports.

The initial report should be sent with as much information as is available at the time and include a concise summary of hospital records and other relevant documents. Supplemental information may be provided using a follow-up report and should not delay the initial report. Aadi Drug Safety, or designee, may contact the study site to solicit additional information or to follow-up on the event. If a patient died and an autopsy has been performed, please provide a copy of the autopsy report and death certificate to Aadi Drug Safety as soon as these become available.

Where required by local legislation, the investigator is responsible for reporting unanticipated problems involving risk to patients or others, including SAEs, to the IRB/EC according to institutional policy, regional, national and local laws or regulations. The investigator must keep copies of all SAE information on file including correspondence with Aadi and the IRB/EC.

10.4. Pregnancy and Breastfeeding Reporting

All pregnancies or breastfeeding in a female patient, or pregnancies in a female partner of a male patient, occurring after the informed consent is signed through 3 months after the last dose of *nab*-sirolimus must be reported to Aadi Drug Safety within 24 hours of the investigator's knowledge of the event using the Pregnancy Report Form. Neither pregnancy, breastfeeding, nor an induced elective abortion to terminate a pregnancy for nonmedical reasons is considered an AE.

A female patient who becomes pregnant during treatment with IP should discontinue treatment. If a female partner of a male patient taking the IP becomes pregnant, the male patient should notify the investigator immediately. The male patient taking the IP will not need to discontinue from treatment. The investigator should counsel the patient/patient's female partner regarding the unknown risks of the IP on the fetus and the need to inform the investigator of the outcome of the pregnancy. The patient/patient's partner must also be encouraged to schedule regular prenatal visits with an appropriately qualified health care provider and inform the investigator of any problems with the pregnancy.

The investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Aadi using the Pregnancy Report Form. If the end of pregnancy occurs after the study has been completed, the outcome should be reported to Aadi.

For breastfeeding in a female patient, the investigator should make every effort to obtain breastfeeding information (eg, initiation and end of breastfeeding).

11. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

11.1. Discontinuation from Treatment with the Investigational Product

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

- 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 reason for treatment discontinuation should be recorded in the eCRF and in the source documents.

11.2. Discontinuation from the Study

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)

The reason for study discontinuation should be recorded in the eCRF and in the source documents.

At the time of withdrawal, it should be determined whether the patient is withdrawing from treatment alone, or from treatment and collection of further data (eg, survival). Every effort should be made to collect survival data after patient withdraws from treatment.

Patients have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

11.3. Investigator or Aadi Decision to Withdraw or Terminate Patient's Participation Prior to Study Completion

The investigator and/or Aadi can decide to withdraw a patient(s) from IP and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Patients may be eligible for continued treatment with IP and/or other protocol required therapies by a separate protocol or as provided for by the local country's regulatory mechanism.

12. REGULATORY OBLIGATIONS

12.1. Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from Aadi to the investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a patient's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or the IP is administered.

The investigator is also responsible for asking the patient if the patient has a primary care physician and if the patient agrees to have his/her primary care physician informed of the patient's participation in the clinical study. If the patient agrees to such notification, the investigator is to inform the patient's primary care physician of the patient's participation in the clinical study. If the patient does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the patient's medical record.

The acquisition of informed consent and the patient's agreement or refusal of his/her notification of the primary care physician is to be documented in the patient's medical records, and the informed consent form to be signed and personally dated by the patient or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the patient or legally acceptable representative.

If a potential patient is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

12.2. Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Aadi before recruitment of patients into the study and shipment of Aadi IP.

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from Aadi, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB approval [IRBs only]/renewal [IRBs and IECs] throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to Aadi.

12.3. Patient Confidentiality

The investigator must ensure that the patient's confidentiality is maintained for documents submitted to Aadi.

- Patients are to be identified by a unique patient identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique patient identification number, include the age at time of enrollment.
- For SAEs reported to Aadi, patients are to be identified by their unique patient identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Aadi (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit such individuals to have access to his/her study-related records, including personal information.

12.4. Protocol Amendments

If Aadi amends the protocol, agreement from the investigator must be obtained. The IRB must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB to Aadi.

12.5. Termination of the Study

Aadi reserves the right to terminate the study at any time. Both Aadi and the investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The investigator is to notify the IRB in writing of the study's completion or early termination and send a copy of the notification to Aadi.

13. DATA HANDLING AND RECORDKEEPING

13.1. Data/Documents

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed, and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; X-ray film and reports; and records kept at the pharmacy; and the laboratories, as well as copies of eCRFs or CD-ROM.

13.2. Data Management

Data will be collected via eCRF and entered into the clinical database. These data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

13.3. Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including patients not receiving protocol-required therapies) as stipulated in the protocol for each patient in the study. For patients who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments Table 1, the investigator can search publicly available records (where permitted) to ascertain survival status.

This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

13.4. Sample Storage and Destruction

Any blood, tumor, biomarker or pharmacokinetic sample collected according to the Schedule of Assessments Table 1 can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study patients. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be no less than single coded prior to being shipped from the site for analysis, or storage. Tracking of samples will be independent of the patient's identification number for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the patient, Aadi can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the cancer, the

dose response and/or prediction of response to *nab*-sirolimus*,* characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the patient directly or to alter the treatment course, the results of biomarker, biomarker development, or other exploratory studies are not placed in the patient's medical record and are not to be made available to the patient, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The patient retains the right to request that the sample material be destroyed by contacting the Investigator. Following the request from the patient, the investigator is to provide Aadi with the required study and patient number so that any remaining blood or tumor samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed.

Aadi is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the patient through the Investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, Aadi owns the commercial product. The patient has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. Study Monitoring

The Aadi representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that patient confidentiality is respected.

The Aadi representative is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. Monitoring will include on-site visits with the investigator and his/her staff as well as any appropriate communications by mail, email, or telephone. During monitoring visits, the facilities, IP storage area, eCRFs, patient's source documents, and all other study documentation will be inspected/reviewed by the Aadi representative in accordance with the Study Monitoring Plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

14.2. Audits and Inspections

In accordance with ICH GCP and Aadi's audit plans, this study may be selected for audit by representatives from Aadi's Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

15. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Authorship decisions will follow the guidelines of the International Committee of Medical Journal Editors (ICMJE).

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