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

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| **Study Medication:** | *nab*-sirolimus (sirolimus protein-bound particles for injectable suspension [albumin-bound]; ABI009) |
| **Protocol Number:** | NET-202 |
| **Study Phase:** | 2 |
| **Sponsor Name / Address:** | Aadi Bioscience, Inc (Aadi)<br>17383 Sunset Blvd., Suite A250<br>Pacific Palisades, CA 90272 |

| Protocol Version | Date |
|---|---|
| **Version 1.0:** | 04 May 2023 |
| **Version 2.0:** | 07 July 2023 |

***CONFIDENTIAL***

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# MEDICAL MONITOR/EMERGENCY CONTACT INFORMATION

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# PROTOCOL APPROVAL

**Protocol:** NET-202

**Issue Date:** 07 July 2023; Version 2.0

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

[See Appended Signature Page]

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| Loretta M. Itri, MD, FACP<br>Chief Medical Officer<br>Aadi Bioscience, Inc. | Date |

# SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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| **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)/Independent Ethics Committee (IEC) procedures, instructions from Aadi Bioscience, Inc. representatives, the Declaration of Helsinki, International Council for Harmonization (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

## PROTOCOL SYNOPSIS

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| **Study Medication** | *nab*-sirolimus (sirolimus protein-bound particles for injectable suspension [albumin-bound]; ABI009) |
| **Title** | A Phase 2 multi-center, open-label, single arm study of *nab*-sirolimus in patients with well-differentiated neuroendocrine tumors (NETs) of the gastrointestinal tract, lung, or pancreas who have not received prior treatment with mTOR inhibitors |
| **Protocol Number** | NET-202 |
| **Phase** | 2 |

| **Objectives** | **Endpoints** |
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| **Primary** | |
| • To evaluate the efficacy of *nab*-sirolimus in patients with well-differentiated, and locally advanced unresectable or metastatic NETs of the gastrointestinal (GI) tract, lung, or pancreas who have measurable disease per Response Evaluation Criteria in Solid Tumors Version v1.1 (RECIST v1.1). | • Objective Response Rate (ORR), defined as the proportion of patients with best overall response (BOR) of confirmed partial response (PR) or complete response (CR) from the time of study treatment initiation until progression of disease (PD) as determined by the Investigator using RECIST v1.1. |
| **Secondary** | |
| • To evaluate clinical benefit as defined by the duration of response (DOR), disease control rate (DCR), time to response (TTR), and progression-free survival (PFS) via Investigator assessment, and overall survival (OS) of *nab*-sirolimus. | • DOR: Determined for patients with BOR of confirmed CR or PR defined as time from scan first showing response by RECIST v1.1 to PD or death.<br>• DCR: BOR of confirmed CR or PR (either of any duration) or stable disease (SD) ≥12 weeks by RECIST v1.1 following study treatment initiation.<br>• TTR: Time from first dose of study medication to initial measurement of CR or PR, where CR or PR is subsequently confirmed by RECIST v1.1.<br>• PFS: Number of months from study treatment initiation to the date of disease progression or death due to any cause.<br>• OS: Number of months from study treatment initiation to the date of death due to any cause. |
| **Objectives** | **Endpoints** |
| • 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** | |

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| • To measure Chromogranin A levels and evaluate correlation with response to treatment and disease progression | • Chromogranin A (CgA) levels |
| • To evaluate baseline molecular biomarkers and genomics and the association between genomic alterations and clinical outcome, as well as genomic changes during and/or after treatment | • Tumor Sequencing for mutations: From baseline tumor tissue (archival or fresh biopsy, if available) and blood (peripheral blood mononuclear cells, [PBMCs]):<br>o To understand the concomitant alterations and allele frequency at baseline via a standardized method (secondary confirmation) (using next generation sequencing [NGS]).<br>o To evaluate the association between mutational profile and clinical outcome.<br>• To evaluate the expression of pS6 and other relevant markers via immunohistochemistry. |

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| **STUDY DESIGN AND TREATMENT** | This is a prospective Phase 2 single arm, open-label, multi-institutional study to determine the efficacy and safety profile of *nab*-sirolimus administered by intravenous (IV) infusion in patients with functional or non-functional, well-differentiated, locally advanced unresectable or metastatic NETs of the GI tract, lung, or pancreas.<br>The study will enroll up to 21 efficacy evaluable patients at approximately 3 centers in the United States (US). If a patient discontinues the study before post baseline radiographic assessment, he/she will be replaced.<br>A cycle will consist of 21 days. Patients will receive *nab*-sirolimus by IV infusion over 30 minutes (+10 minutes window allowed, ie, 30- to 40-minute infusion) on Days 1 and 8 of every 21-day cycle. *nab*-Sirolimus will be administered at 100 mg/m$^2$. Patients will be monitored for at least 2 hours following completion of the first infusion, and as clinically indicated for each subsequent infusion. Three sequential dose reductions for the management of AEs are allowed: 75, 56, and 45 mg/m$^2$.<br>Patients will be assessed for response using computed tomography (CT) or magnetic resonance imaging (MRI) scan with contrast using RECIST v1.1.<br>Patients will continue treatment until PD, or unacceptable toxicity, or until in the opinion of the Investigator the patient is no longer benefiting from therapy, or at patient discretion.<br>The study will be conducted in compliance with the International Council for Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements. |
| **SAMPLE SIZE ESTIMATE** | Simon's 2-stage design will be used for this study. In the first stage, 12 efficacy evaluable patients will be accrued. If there are 0 responses in these 12 patients, the study may be terminated. Otherwise, 9 additional efficacy evaluable patients will be accrued for a total of 21 patients. If a patient discontinues the study before post baseline radiographic assessment, he/she will be replaced. The null hypothesis of 4% ORR will be rejected if 3 or more responses are observed in 21 efficacy evaluable patients. This sample size yields a type I error rate of 5% and power of 80% when true ORR is 20% for this study |

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| **INCLUSION CRITERIA** | A patient will be eligible for inclusion in this study only if all of the following criteria are met at screening:<br>1. Patients with functional or non-functional, well-differentiated, locally advanced unresectable or metastatic NETs of the GI tract, lung, or pancreas who have received ≤2 prior lines of therapy excluding somatostatin analogs (SSTa).<br>2. Patients with functional NETs may enroll if:<br>a. the patient has been on a stable dose of an SSTa for ≥12 weeks and<br>b. the patient has experienced disease progression while on stable SSTa dose<br>3. Patients must have 1 or more measurable target lesions by RECIST v1.1.<br>4. Age: 18 years or older.<br>5. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 or Karnofsky Performance Status (KPS) ≥80.<br>6. Adequate liver function:<br>a. Total bilirubin ≤1.5 × upper limit of normal (ULN) (unless due to Gilbert's syndrome or attributable to liver metastases, then ≤3 × ULN).<br>b. Aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤2.5 × ULN (≤5 × ULN if attributable to liver metastases).<br>7. Adequate renal function: creatinine clearance ≥30 mL/min, Cockcroft-Gault creatinine clearance = ((140-age) × weight[kg]) / (72 × serum creatinine [mL/min]) × 0.85, if female.<br>8. Adequate hematologic parameters:<br>a. Absolute neutrophil count (ANC) ≥1.0 × $10^9$/L (growth factor support allowed).<br>b. Platelet count ≥100,000/$mm^3$ (100 × $10^9$/L) (transfusion and/or growth factor support allowed).<br>c. Hemoglobin ≥8.0 g/dL (transfusion and/or growth factor support allowed).<br>9. Fasting serum triglyceride must be ≤300 mg/dL; fasting serum cholesterol must be ≤350 mg/dL.<br>10. Minimum of 4 weeks since any major surgery, completion of radiation, and adequately recovered from the acute toxicities of any prior therapy, including neuropathy, to Grade ≤1.<br>11. Male or non-pregnant and non-breastfeeding female:<br>a. Females of childbearing potential must agree to use effective contraception or abstinence without interruption from 28 days prior to starting study medication throughout 3 months after last dose of study medication and have a negative serum pregnancy test (beta human chorionic gonadotropin [β-hCG]) result at screening and agree to ongoing pregnancy testing during the course of the study, and after the end of study (EOS) treatment. A second form of birth control is required even if she has had a tubal ligation.<br>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 |

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| | participating in the study and throughout 3 months after last dose of study medication. A second form of birth control is required even if he has undergone a successful vasectomy.<br>c. Sexual abstinence is considered a highly effective contraceptive method only if defined as refraining from heterosexual intercourse from 28 days prior to starting study medication throughout 3 months after last dose of study medication. The reliability of sexual abstinence should be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.<br>12. The patient or the patient's legal guardian(s) understand(s) and sign(s) the informed consent.<br>13. Willingness and ability to comply with scheduled visits, laboratory tests, and other study procedures.<br>14. Patients with a known history of human immunodeficiency virus (HIV) infection are eligible if:<br>a. There has been no acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection in 12 months prior to enrollment.<br>b. The patient has been receiving an antiretroviral therapy regimen for ≥4 weeks and the HIV viral load is <400 copies/mL prior to enrollment.<br>c. Antiretroviral therapy regimen does not include strong cytochrome (CYP)3A4 inhibitors or inducers (see Section 8.2). |
| **EXCLUSION CRITERIA** | A patient will not be eligible for inclusion in this study if any of the following criteria apply:<br>1. Prior treatment with mTOR inhibitors including *nab*-sirolimus. **Note:** Patients who have previously received locoregional or liver-directed therapies (radiofrequency or microwave ablation, transarterial chemoembolization, etc.) are eligible to enroll in the study.<br>2. Patients with functional NETs who are experiencing uncontrolled symptoms attributed to hormones and other vasoactive substances secreted by the tumor.<br>3. Patients with known inactivating tuberous sclerosis complex (TSC)1 or TSC2 alterations (based on tissue or liquid NGS).<br>4. Severe (Grade ≥3) ongoing infection requiring parenteral or oral anti-infective treatment, either ongoing or completed ≤7 days prior to enrollment.<br>5. Patients who have any severe and/or uncontrolled medical or psychiatric conditions or other conditions that could affect their participation including:<br>a. Known or suspected brain metastases<br>b. Severe heart disease defined as unstable angina pectoris, NYHA Class III or IV congestive heart failure, myocardial infarction ≤6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease.<br>c. Severe lung disease defined as a diffusing capacity for carbon monoxide that is ≤50% of normal predicted value and/or an $O_2$ saturation ≤88% at rest on room air (Note: spirometry and |

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| | pulmonary function tests are not required to be performed unless clinically indicated).<br>d. Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with the study therapy.<br>e. A history of malignancies other than the one under treatment unless the patient is disease-free for more than 5 years from diagnosis. Controlled non-melanoma skin cancers, carcinoma in situ of the cervix, resected incidental prostate cancer, certain low-grade hematologic malignancies (eg, chronic lymphocytic leukemia, follicular lymphoma, etc), or other adequately treated carcinoma in situ may be eligible, after discussion with the medical monitor.<br>f. Uncontrolled hypertension (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg).<br>g. Patients with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension.<br>h. Active Hepatitis B and/or Hepatitis C infection and detectable viral load despite antiviral therapy (see Section 8.2).<br>6. Required use of concomitant medications with strong CYP3A4 interactions (induction or inhibition) should be discontinued (strong inhibitors include ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin, telithromycin; strong inducers include rifampin and rifabutin). These agents must be discontinued prior to first dose of *nab*-sirolimus. |
| **DURATION OF TREATMENT AND STUDY PARTICIPATION** | The study will enroll 21 efficacy evaluable patients at approximately 3 sites in the US and is expected to take approximately 12 to 18 months from first patient enrolled to last patient follow-up, including approximately 6 months of enrollment period (from first to last patient in), allowing a minimum of 6 months of treatment for all enrolled patients, a 28-day screening and a 28-day (4 week) safety follow-up after the last dose.<br>**End of Treatment (EOT)** for a patient is defined as the date of the last dose of *nab*-sirolimus. The **EOT Visit** for a patient is a safety follow-up visit; safety assessments and procedures are performed 28 to 35 days after the last dose of *nab*-sirolimus is administered.<br>**End of Study** (EOS) for a patient is defined as the date of last follow-up.<br>The **EOS** 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.<br>The **Follow-up Period** begins after the EOT Visit. All patients who discontinue the study medication and have not withdrawn full consent to participate in the study will continue in the Follow-up Phase for survival and initiation of new therapy, including surgery or anticancer therapy. If, after *nab*-sirolimus treatment, a patient is able to undergo surgical resection of his/her primary tumor with curative intent, documentation on outcome and disease-free or SD status should be followed and documented. Follow-up will continue approximately every 12 weeks (±3 weeks), until death, |

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| | 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 using CT or MRI scan with contrast following RECIST v1.1.<br>Patients will be evaluated by radiographic imaging every 6 weeks for the first 12 weeks (3 months) and every 12 weeks thereafter. 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. The first response assessment by scans documenting target lesions will be performed 6 and 12 weeks (±7 days) after the first treatment and should be repeated every 12 weeks (±7 days) thereafter until PD. If an initial observation of ORR is made (CR or PR), 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.<br>The BOR and DCR will be reported along with exact 95% confidence intervals (CIs) computed by the Clopper-Pearson method.<br>**Definitions:**<br>• DOR (by RECIST v1.1) is defined as the date from the start of CR or PR per Investigator assessment (whichever response is recorded first) and subsequently confirmed to the first date of documented PD or death. Patients without any of these events will be censored at their last evaluable tumor assessment.<br>• DCR (by RECIST v1.1) is defined as BOR of confirmed CR or PR (either of any duration) or SD ≥12 weeks following study treatment initiation.<br>• TTR (by RECIST v1.1) is defined as time from first dose of study medication to initial measurement of CR or PR, where CR or PR is subsequently confirmed.<br>• PFS is defined as the time from the first dose to the first observation of a disease progression or death due to any cause. Patients without any disease progression will be censored at their last evaluable tumor assessment.<br>• OS is defined as the time of first dose to the date of death due to any cause. Patients without death will be censored at their last on-study follow-up visit.<br>For DOR, PFS and OS the Kaplan-Meier estimates and corresponding two-sided 95% CIs for the median and quartiles will be provided. The Kaplan-Meier plot may also be provided. |
| **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 study medication due to an AE. All AEs will be recorded by the Investigator from the time the patient provides informed consent until 28 days after the last dose of study medication. Adverse events will be graded by NCI CTCAE v5.0. |

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| | Physical examination, vital signs, laboratory assessments (eg, serum chemistry, hematology), and performance status will be monitored. All serious adverse events (SAEs) (regardless of relationship to study medication) will be followed until resolution. Local laboratory analysis will be performed as per study schedule. |
| **PRIMARY ANALYSIS** | **Statistical Methods:**<br>All endpoints will be reported by descriptive statistics.<br>**Analysis Population Definitions:**<br>**Full Analysis Set:**<br>The Full Analysis Set includes all enrolled patients who receive at least 1 dose of *nab*-sirolimus. Analyses of safety endpoints will be performed on the Full Analysis Set.<br>**Efficacy Evaluable Set:**<br>The Efficacy Evaluable Set includes all enrolled patients who receive at least one dose of *nab*-sirolimus and have at least one post baseline radiographic assessment for tumor evaluation.<br>**Per-protocol Analysis Set:**<br>Per-protocol Analysis Set (PP) includes all enrolled patients with a measurable tumor per RECIST v1.1, have at least one post-treatment scan, and do not have any prospectively defined major protocol deviations.<br>The primary endpoint of the study is ORR from the Investigator by RECIST v 1.1.<br>The secondary endpoints include:<br>• DOR by RECIST v1.1<br>• DCR by RECIST v1.1<br>• TTR by RECIST v1.1<br>• PFS<br>• OS<br>Exploratory endpoints are:<br>• Chromogrannin (CgA) Levels<br>• Tumor Sequencing for Mutations<br>Descriptive statistics and graphical displays will be used to summarize data collected in the electronic case report form (eCRF). Continuous variables will be summarized using the mean, standard deviation, median, inter-quartile range, minimum and maximum. Categorical variables will be summarized using frequency and percentage. Time to event variables will be summarized using Kaplan-Meier estimates. Two-tailed 95% CIs will be provided whenever appropriate to demonstrate the strength of the findings. |

# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
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| Ab | antibody |
| AE | adverse event |
| AIDS | acquired immunodeficiency syndrome |
| Akt | protein kinase B |
| ALT | alanine transaminase (SGPT) |
| ANC | absolute neutrophil count |
| AST | aspartate transaminase (SGOT) |
| AUC | area under the time-concentration curve |
| β-hCG | beta human chorionic gonadotropin |
| BOR | best overall response |
| BSA | body surface area |
| cAb | core antibody |
| CgA | Chromogranin A |
| $C_{max}$ | maximum plasma drug concentration |
| CBC | complete blood count |
| CI | confidence interval |
| CNS | central nervous system |
| CR | complete response |
| CRO | Contract Research Organization |
| CT | computed tomography |
| CYP | cytochrome |
| DCR | disease control rate |
| DOR | duration of response |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EOS | end of study |
| EOT | end of treatment |
| FDA | Food and Drug Administration |

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| FIH | first-in-human |
| GCP | Good Clinical Practice |
| GEPNET | gastroenteropancreatic neuroendocrine tumors |
| GI | gastrointestinal |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HER2 | human epidermal growth factor receptor 2 |
| HDL | high-density lipoprotein |
| HIV | human immunodeficiency virus |
| ICH | International Council on Harmonization |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| IV | intravenous(ly) |
| KPS | Karnofsky Performance Status |
| LDL | low-density lipoprotein |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| mTOR | mammalian target of rapamycin |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NET | neuroendocrine tumor |
| NGS | next generation sequencing |
| NOAEL | no-observed-adverse-effect level |
| ORR | objective response rate |
| OS | overall survival |
| PI3K | phosphatidylinositol 3-kinase |
| PBMC | peripheral blood mononuclear cell |
| PD | progression of disease |
| PFS | progression-free survival |

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| PK | pharmacokinetic |
| pNET | neuroendocrine tumor of pancreatic origin |
| PP | Per-protocol |
| PR | partial response |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | serious adverse event |
| sAg | surface antigen |
| SD | stable disease |
| SGOT | serum glutamic oxaloacetic transaminase (AST) |
| SGPT | serum glutamic pyruvic transaminase (ALT) |
| SSTa | somatostatin analog |
| TGI | tumor growth inhibition |
| $T_{max}$ | time to maximum plasma drug concentration |
| TRAE | treatment-related AE |
| TSC | tuberous sclerosis complex |
| TSH | thyroid-stimulating hormone |
| TTR | time to response |
| ULN | upper limit of normal |
| US | United States (of America) |
| WBC | White blood cell |

| **Abbreviation or Term** | **Definition/Explanation** |
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| 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.<br>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 prespecified in the protocol. |
| End of Treatment | The date of the last dose of *nab*-sirolimus for an individual patient. |

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| End of Treatment Visit | Safety assessments and procedures are performed after the patient's last treatment; the visit must occur at least 28 to 35 days after the last dose of *nab*-sirolimus. |
| Follow-up Period | The on-study time period after the End of Treatment Visit. All patients who discontinue the study medication and have not withdrawn full consent to participate in the study will continue in the Follow-up Period for survival and initiation of new therapy, including surgery or anticancer therapy. If, after *nab*-sirolimus treatment, a patient is able to undergo surgical resection of his/her primary tumor with curative intent, documentation on outcome and disease-free or SD status should be followed and documented. Follow-up assessments 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. |
| *Data Sets and Primary Analysis* | |
| Full Analysis Set | The Full Analysis Set includes all enrolled patients who receive at least 1 dose of *nab*-sirolimus. Analyses of safety endpoints will be performed on the Full Analysis Set. |
| Efficacy Evaluable Set | Includes all enrolled patients who receive at least 1 dose of *nab*-sirolimus and have at least one post baseline radiographic assessment for tumor evaluation. Primary analyses of efficacy endpoints will be performed on the Efficacy Evaluable Set. |
| Per-protocol (PP) Analysis Set | Includes all enrolled patients with a measurable tumor per RECIST v1.1, have at least one post-treatment scan, and do not have any prospectively defined major protocol deviations. A sensitivity analysis of the primary and secondary efficacy endpoints may be performed on the PP Set. |
| *Efficacy Endpoints* | |
| Best Overall Response (BOR) | 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 v1.1, to be assigned a status of CR or PR, changes in tumor measurements must be confirmed by a repeat assessment. |

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| Disease Control Rate (DCR) | DCR (by RECIST v1.1) is defined as BOR of confirmed CR or PR (either of any duration) or stable disease (SD) ≥12 weeks following study treatment initiation. |
| Duration of Response (DOR) | DOR (by RECIST v1.1) is defined as the date from the start of CR or PR per Investigator assessment (whichever response is recorded first) and subsequently confirmed to the first date of documented PD or death. Patients without any of these events will be censored at their last evaluable tumor assessment. |
| Objective Response Rate (ORR) | The proportion of patients with BOR of confirmed PR or CR from the time of study treatment initiation until PD as determined by the Investigator using RECIST v1.1. |
| Overall Survival (OS) | OS is defined as the time of first dose to the date of death due to any cause. Patients without death will be censored at their last on-study follow-up visit. |
| Progression-free Survival (PFS) | PFS is defined as the time from the first dose to the first observation of a disease progression or death due to any cause. Patients without any disease progression will be censored at their last evaluable tumor assessment. |
| Time to Response (TTR) | TTR (by RECIST v1.1) is defined as time from first dose of study medication to initial measurement of CR or PR, where CR or PR is subsequently confirmed. |

# 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 Visit [d] | Follow-up Period [e] |
|---|---|---|---|---|---|
| | | Day 1 [c] | Day 8 | | |
| **General Assessments** | | | | | |
| Informed Consent | X | | | | |
| Demographics | X | | | | |
| Medical History | X | | | | |
| Physical Examination | X | X | | X | |
| Height and Weight [f] | X [f] | X | | X | |
| Vital Signs | X | X | X | X | |
| BSA Calculation [g] | | X [g] | | | |
| Prior/Concomitant Medication / Procedures Evaluation [h] | X | X | X | Until 28 days after the last dose of study medication | |
| Performance Status (ECOG or KPS) | X | X | | X | |
| Pregnancy Test [i] | X | | | X | |
| Biomarker: Pre-treatment tissues (archival, or fresh) [j] | | X | | X [j] | |
| Biomarker: blood sample [k] | | X | | X | |
| Survival status | | | | | X |
| Adverse Events | Continuously, starting from signing of Informed Consent until 28 days after last dose of study medication[l] | | | | |
| ***nab*-Sirolimus Dosing** [m] | | X | X | | |
| **Local Laboratory Assessments** | | | | | |
| Clinical Chemistry Panel | X | X | | X | |
| CBC, Differential, Platelet Count | X | X | X | X | |
| Thyroid function [n] | X | X | | | |
| HIV Ab, HBV sAg, HBV cAb, HCV Ab | X | | | | |
| Fasting Lipids [o] | X | X [o] | | | |
| **Imaging and Efficacy Assessments** | | | | | |
| CT/MRI scan with contrast [p] | X | Every 6 weeks (±7 days) for first 12 weeks (3 months) after C1D1, and then every 12 weeks (±7 days) thereafter | | X | |

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

a. Unless otherwise specified, visits must occur within ±3 days of the planned visit date.
b. Screening evaluations to be obtained ≤28 days prior to Cycle 1 Day 1 unless specified otherwise.
c. Day 1 evaluations can be omitted if screening evaluations are performed within 3 days of Cycle 1 Day 1.
d. End of Treatment Visit must occur at least 4 weeks (+7 days) after the last dose of *nab*-sirolimus.
e. Follow-up for survival and initiation of anticancer therapy can be performed by telephone contact after the EOT Visit every 12 weeks (±3 weeks) or more frequently if needed, from EOT Visit. All patients who discontinue study medication and have not withdrawn full consent to participate in the study will continue in the Follow-up Phase for survival and anticancer therapy. This evaluation may be made by record review and/or telephone contact.
f. Height only at Screening Visit.
g. BSA calculated according to institutional standard methods. Calculated ONLY on Cycle 1 Day 1; to be recalculated only if the weight changes by >10% in subsequent cycles. Cap BSA at 2 $m^2$, ie, at 200 mg actual dose.
h. Prior: record all medications taken and procedures done ≤28 days prior to screening; Concomitant: any medications or procedures after the signing of informed consent.
i. For females of childbearing potential only. A serum β-hCG pregnancy test must be performed to assess patient eligibility at screening prior to first study medication administration (negative results required for study medication administration). Urine pregnancy test will be performed at EOT Visit (can be done locally) and as clinically indicated as per institutional guidelines.
j. Baseline tissue should be collected from all enrolled patients for exploratory biomarker analysis (up to 20 slides). If archival tissue is not available, fresh biopsy should be collected, if possible. For patients with tissue samples >2 years from screening, fresh biopsies are recommended. While collection of tissue is recommended, patients without tissue will be allowed on study. At the time of disease progression, if a biopsy is performed, a tumor sample will be submitted, if available. The surgical pathology report is to be submitted with the tumor tissue sample.
k. Biomarker (Chromogrannin [CgA] levels): Blood samples will be collected prior to Cycle 1 Day 1, at Week 6, Week 12 and with every 12-week scan (±1 week), and at EOT or disease progression.
l. AEs will be assessed continuously, starting from signing of Informed Consent until 28 days after last dose of study medication; see Section 10.1.2.
m. Maximum dose is 200 mg and dosing is performed after all predose assessments completed. Monitor patients for at least 2 hours following completion of the first infusion, and as clinically indicated for each subsequent infusion.
n. TSH (T3 and T4 if clinically indicated)
o. Fasting lipids are taken on Day 1 of every even numbered cycle starting with Cycle 2, eg, C2, C4, C6 etc.
p. Scans should continue on schedule regardless of delays in *nab*-sirolimus dosing on Week 6, Week 12, Week 24, Week 36, Week 48, etc. The same modality (CT or MRI scan with contrast should be used throughout the study. If an initial observation of ORR is made (CR or PR), a confirmation scan should be done 6 weeks (±1 week) after initial observation. EOT Visit scan should be performed only for those patients who discontinue treatment for a reason other than disease progression.

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# 1. INTRODUCTION

## 1.1. Disease Background

Neuroendocrine tumors (NETs) are a group of rare and heterogeneous malignancies that originate in neuroendocrine cells. They can affect almost any part of the body but most commonly arise from the gastrointestinal (GI) tract (particularly pancreas and small intestine) followed by lung, liver, and thymus (Yao, 2008a). While most NETs are more indolent than other epithelial malignancies, NETs can become aggressive and resistant to therapy. While a patient with low-grade tumor can survive many years, the high-grade counterpart is extremely aggressive and has a dismal outcome (Chauhan, 2020).

Surveillance, Epidemiology and End Result (SEER) is the premier cancer registry and regularly updates cancer statistics in the United States (US). The incidence of common cancers like breast, colon, and lung cancer have plateaued over past few decades but the incidence of NETs has increased almost 7 times in the same period, attributable in part to better diagnostics with increased endoscopies and radiographic imaging as well as greater clinician and patient awareness. It is estimated that the incidence of NETs had risen from 1 in 100,000 (the 1970s) to 6.98 in 100,000 (2012) and there are over 170,000 NET patients in the US alone (Dasari, 2017). The 10-year survival rate for any grade NETs is approximately 46% (Hallet, 2015).

## 1.2. Rationale for the Use of *nab*-Sirolimus in Patients with NETs

Due to rarity and heterogeneity, nonspecific clinical symptoms and unique indolent biology, the management of NETs is still very challenging, and effective and safe therapeutic options are needed for the treatment of these tumors. As with most rare cancers, NETs receive limited focused attention. Although NETs are indolent, they ultimately may prove to be lethal.

There have been few Food and Drug Administration (FDA)-approved therapies for progressive metastatic NETs in the last decade. Sunitinib and everolimus were approved by the FDA for pancreatic NETs in 2011 (Yao, 2011; Blumenthal, 2012), followed by lanreotide's approval as a front-line agent in 2014 for gastroenteropancreatic neuroendocrine tumors (GEPNETs) (Caplin, 2014), and most recently lutetium 177 dotatate was FDA approved in 2018 for progressive GEPNETs (Strosberg, 2017). It is important to highlight that most of the above-mentioned FDA approvals are limited to GEPNETs; however, 30% of NETs are non-GEPNETs. Thus, the treatment options are not only limited but also cater to a subset of NETs. Moreover, most FDA-approved agents have not shown overall survival (OS) benefit yet.

## 1.3. mTOR inhibition in NETs: RADIANT STUDIES

The phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway plays a central role in the regulation of cell proliferation, apoptosis, cell cycle, metabolism, and angiogenesis (Manfredi, 2015). Of note, a number of studies have suggested that the PI3K/AKT/mTOR signaling pathway is strongly implicated in the pathogenesis and progression of NETs (von Wichert, 2000; Moreno, 2008; O'Donnell, 2008; Yao, 2008b; Missiaglia, 2010).

In accordance with nonclinical evidence, everolimus which is an oral mTOR kinase inhibitor, has demonstrated activity in the treatment of NETs of different origins; its efficacy and safety

were explored in the RADIANT studies. Overall, the evidence collected from these studies showed promise to change clinical practice in the treatment of NETs (Pusceddu, 2016).

**Pancreatic Neuroendocrine Tumors (pNET)**

**RADIANT 1** was an open-label Phase 2 study that evaluated the safety and efficacy of everolimus in patients with metastatic pNET who had progressed on chemotherapy. Patients were stratified by prior octreotide therapy (stratum 1: everolimus 10 mg/day, n = 115; stratum 2: everolimus 10 mg/day plus octreotide long-acting release, n = 45). Per independent, central analysis, 11 PRs (9.6%) and 78 SDs (67.8%) were reported in stratum 1; median progression-free-survival (PFS) was 9.7 months. In stratum 2, there were 2 PRs (4.4%), while 36 patients (80%) achieved SD; progression of disease (PD) was never observed. In this group, median PFS was 16.7 months. Daily everolimus, either with or without concomitant octreotide long-acting release, showed promising antitumor activity and was well tolerated in patients with advanced pNETs after failure of prior systemic chemotherapy (Yao, 2010).

**RADIANT 3** was a subsequent randomized and placebo-controlled Phase 3 study in which 410 patients with advanced, low or intermediate grade pNET who showed radiologic progression within the previous 12 months before enrolment were randomly assigned to receive everolimus (10 mg/day; n = 207) or placebo (n = 203). Treatment with somatostatin analogs (SSTa) was allowed as part of best supportive care. The primary endpoint was PFS. Median PFS was significantly longer in the everolimus group, compared with controls (11 months vs 4.6 months) with a 65% reduced risk of progression or death (hazard ratio 0.35; 95% confidence interval (CI) 0.27, 0.45; p<0.001) (Yao, 2011).

**Gastrointestinal or Lung Origin NETs**

**RADIANT 4** was a prospective, randomized, double-blind, placebo-controlled, Phase 3 study of patients with well-differentiated (G1 or G2) advanced NET of GI or lung origin who had reported radiologic progression in the last 6 months. In total, 175 patients had GI NET and 90 patients had lung disease. At central review analysis, everolimus-treated patients showed a prolonged median PFS, as compared with those receiving placebo (11.0 versus 3.9 months, hazard ratio 0.48; 95% CI 0.35, 0.67; p<0.00001). This benefit in PFS was consistent at all subgroup analyses: in particular, there was a 50% improvement in PFS for patients with lung tumors and a 44% benefit for those with GI NETs. Tumor shrinkage was observed in 64% of patients assigned to the everolimus group and 26% of those in the placebo group (Yao, 2016).

As a whole, the RADIANT studies showed a key step forward in the therapy of this heterogeneous group of malignancies. Based on these results and favorable safety profile across the RADIANT studies, everolimus has been approved by FDA for the treatment of adult patients with progressive, well-differentiated, and non-functional NETs of GI, pancreas or lung origin with unresectable, locally advanced or metastatic disease (Pusceddu, 2016).

In nonclinical models, *nab*-sirolimus has demonstrated significantly higher antitumor activity, intratumoral drug accumulation, and greater mTOR target suppression as compared with oral inhibitors. *nab*-Sirolimus via IV administration also overcomes the variable absorption and incomplete target suppression seen with oral sirolimus or everolimus (Leung, 2006).

A Phase 2, NET-001 pilot study of *nab*-sirolimus was previously conducted in patients with metastatic, unresectable, low or intermediate grade NETs of the lung or gastroenteropancreatic

system (NCT03670030). A total of 5 patients were enrolled at one clinical site who received IV *nab*-sirolimus on Days 1 and 8 of a 21-day cycle. 4/5 patients showed SD and no new safety signals were reported. The study was terminated early and only 2 patients were eligible for primary outcome of DCR at 6 months per RECIST v1.1. Similarly, in first-in-human (FIH) study of *nab*-sirolimus (Protocol CA401), 1 patient with a NET in left axillary node had SD for 238 days (Gonzalez-Angulo, 2013).

Based on preclinical data showing improved target engagement and intratumor dose and prior approval of mTOR inhibitor in NETs, it is hypothesized that *nab*-sirolimus may produce improved antitumor activity in patients with NETs of GI, pancreas or lung origin.

## 1.4. *nab*-Sirolimus Background

### 1.4.1. 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 (also known as 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 nonclinical studies have reported the impact of different biomarkers involved in the mTOR pathway, on the efficacy of mTOR inhibitors, such as:

- *PI3K*, tuberous sclerosis complex *(TSC)1*, *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®; RAPAMUNE Prescribing Information) 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 of advanced renal cell carcinoma, is a prodrug of sirolimus and requires conversion by the cytochrome (CYP)3A enzyme (TORISEL® Prescribing Information). Everolimus is approved for pediatric and adult patients with subependymal giant cell astrocytoma and TSC-associated seizures, for adult patients with advanced hormone receptor-positive human epidermal growth factor receptor 2 (HER2)-negative breast cancer in combination with exemestane, progressive pNETs, advanced renal cell carcinoma

after failure of treatment with sunitinib or sorafenib, and advanced angiomyolipoma and tuberous sclerosis complex (AFINITOR® 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 AEs were hyperglycemia (17%), hypophosphatemia (13%), anemia (9%), and hypertriglyceridemia (6%) (Zhou, 2010). These side effects could lead to the discontinuation of treatment in 60% of patients in some studies.

### 1.4.2. *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).

#### 1.4.2.1. *nab*-Sirolimus Pharmacokinetics

*nab*-Sirolimus produced a fairly dose proportional increase of maximum plasma drug concentration ($C_{max}$) and area under the time-concentration curve (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 hours 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)

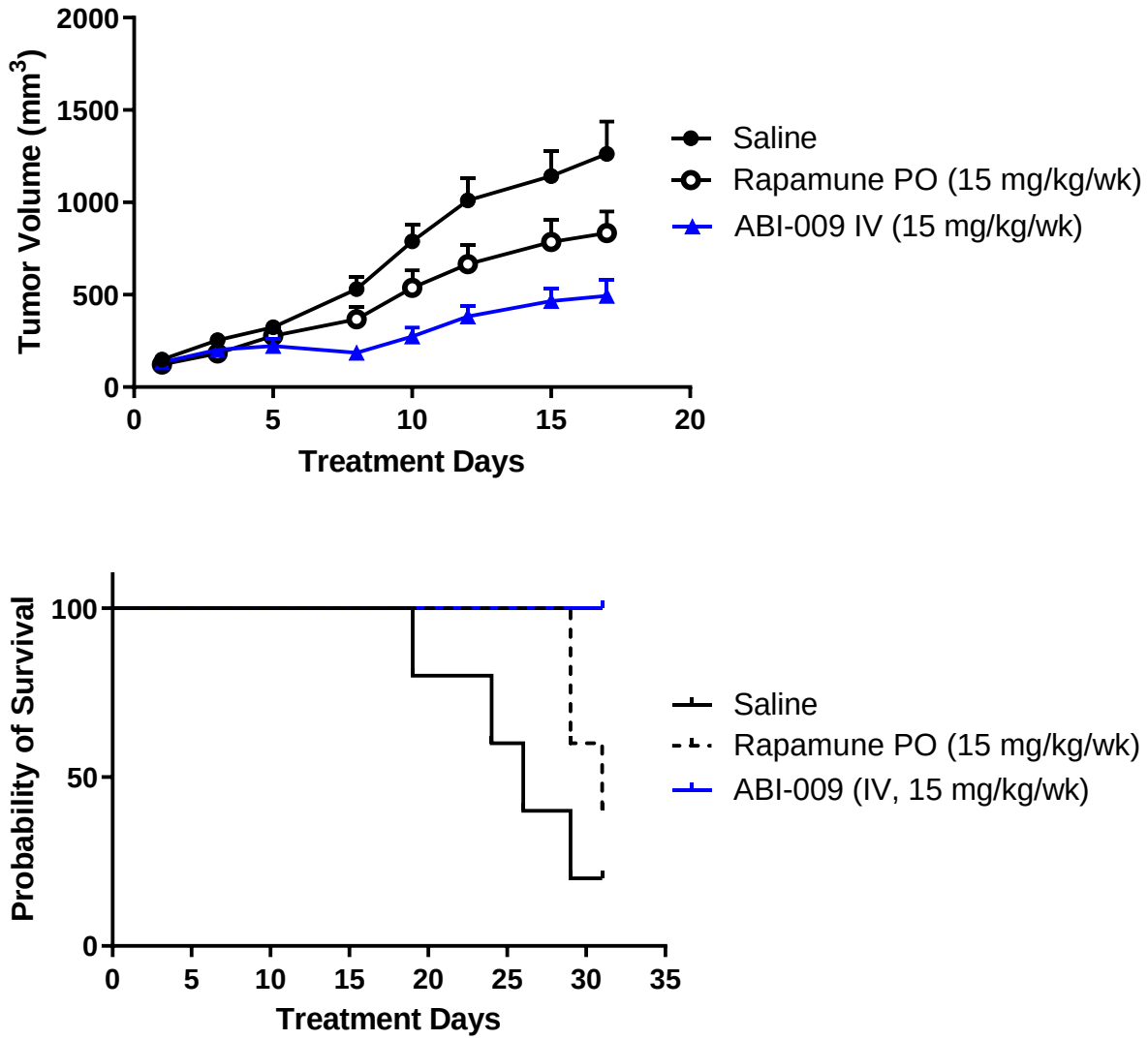
(Danesi, 2013). The administration of *nab*-sirolimus led to a much higher exposure to sirolimus as compared to sirolimus from temsirolimus ($C_{max}$ almost 50 fold higher, AUC almost 12 fold higher for *nab*-sirolimus) or everolimus ($C_{max}$ 50–70 fold higher, AUC 85–200 fold higher for *nab*-sirolimus) (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 an acceptable safety profile could be highly relevant to the treatment of aggressive cancers such as malignant PEComas.

#### 1.4.2.2. 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-programmed death 1 (PD1) antibody, although 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 (TGI) and prolonged animal survival (Figure 1). Compared with an equal weekly dose of oral Rapamune®, *nab*-sirolimus IV treatment resulted in significantly greater antitumor activity (TGI 67.8% versus 36.2%, p=0.04) and longer animal survival (median survival: not reached versus 31 days).

**Figure 1: Antitumor Activity of *nab*-Sirolimus and Oral Sirolimus in *TSC2*-deficient SNU-398 Liver Tumor Xenograft Model**




Abbreviations: IV = intravenous; PO = oral

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

In nonclinical PK studies, PK 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 Good Laboratory Practice PK bridging study, *nab*-sirolimus IV displays a distinct PK profile with early time to $T_{max}$, 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, all of 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 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.

#### 1.4.2.3. Clinical Studies with *nab*-Sirolimus

In a 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 MTD was established at 100 mg/m$^2$.

A Phase 2 registrational study (AMPECT) was conducted in patients with advanced malignant PEComa which has shown that IV *nab*-sirolimus was safe and efficacious with 90% of patients having a best response of PR or SD (Wagner, 2020). Thirty-four patients were treated at 100 mg/m$^2$ *nab*-sirolimus per week for 2 weeks, followed by a week of rest (21-day cycle). The confirmed ORR by independent review was 39%, including 6% complete responses (CRs) (PR, 12/31, 95% CI: 21.8, 57.8), exceeding the prespecified lower-bound ORR of 15% below which the regimen would be considered no more active than standard doxorubicin-based chemotherapy. In AMPECT study, 52% SD (16/31, with 10/16 SD ≥12 weeks), and 10% PD (3/31) was observed, and the disease control rate (DCR, defined as CR + PR + SD ≥12 weeks) was 71%. The median PFS and OS were 10.9 and 53.1 months, respectively (Wagner, 2021; Ganjoo, 2022).

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%), rash (59%), fatigue (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 (Wagner, 2021).

*nab*-Sirolimus has been previously studied in NET-001 study which was conducted in patients with metastatic, unresectable, low or intermediate grade NETs of the lung or gastroenteropancreatic system (NCT03670030). The study was terminated early after enrolling 5 patients but only 2 patients were eligible for primary outcome of DCR at 6 months per RECIST v1.1. Interestingly, 4/5 patients showed SD and no new safety signals were reported. Similarly, in FIH study (Protocol CA401), 1 patient with a NET in left axillary node had SD for 238 days (Gonzalez-Angulo, 2013).

Taken together, the clinical data from AMPECT study and the expanded access program, the preclinical data showing improved target engagement and intratumor dose, and prior approval of mTOR inhibitor in NETs, analysis of *nab*-sirolimus in NETs of the gastrointestinal tract, lung, or pancreas is of interest.

# 2. STUDY OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the efficacy of *nab*-sirolimus in patients with well-differentiated, and locally advanced unresectable or metastatic NETs of the GI tract, lung, or pancreas who have measurable disease per Response Evaluation Criteria in Solid Tumors Version v1.1 (RECIST v1.1). | • ORR, defined as the proportion of patients with best overall response (BOR) of confirmed PR or CR from the time of study treatment initiation until PD as determined by the Investigator using RECIST v1.1. |
| **Secondary** | |
| • To evaluate clinical benefit as defined by the DOR, DCR, time to response (TTR), and progression-free survival (PFS) via Investigator assessment, and OS of *nab*-sirolimus. | • DOR: Determined for patients with BOR of confirmed CR or PR defined as time from scan first showing response by RECIST v1.1 to PD or death.<br>• DCR: BOR of confirmed CR or PR (either of any duration) or SD ≥12 weeks by RECIST v1.1 following study treatment initiation.<br>• TTR: Time from first dose of study medication to initial measurement of CR or PR, where CR or PR is subsequently confirmed by RECIST v1.1.<br>• PFS: Number of months from study treatment initiation to the date of disease progression or death due to any cause.<br>• OS: Number of months from study treatment initiation to the date of death due to any cause. |
| • To describe the safety and tolerability of *nab*-sirolimus | • Incidence and severity of treatment-emergent and treatment-related AEs as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. |
| **Exploratory** | |
| • To measure Chromogranin A levels and evaluate correlation with response to treatment and disease progression | • Chromogranin A (CgA) levels |
| • To evaluate baseline molecular biomarkers and genomics and the association between genomic alterations and clinical outcome, as well as genomic changes during and/or after treatment | • Tumor Sequencing for mutations: From baseline tumor tissue (archival or fresh biopsy, if available) and blood (peripheral blood mononuclear cells, [PBMCs]):<br>o To understand the concomitant alterations and allele frequency at baseline via a standardized method (secondary confirmation) (using next generation sequencing [NGS]).<br>o To evaluate the association between mutational profile and clinical outcome.<br>• To evaluate the expression of pS6 and other relevant markers via immunohistochemistry |

# 3. OVERALL STUDY DESIGN

## 3.1. Study Design

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

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

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

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

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

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

## 3.2. Study Duration

The study will enroll 21 efficacy evaluable patients at approximately 3 sites in the US and is expected to take approximately 12 to 18 months from first patient enrolled to last patient follow-up, including approximately 6 months of enrollment period (from first to last patient in), allowing a minimum of 6 months of treatment for all enrolled patients, a 28-day screening, and a 28-day (4 week) safety follow-up after the last dose.

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

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

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

The EOS 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 who discontinue the study medication and have not withdrawn full consent to participate in the study will continue in the

Follow-up Phase for survival and initiation of new therapy, including surgery or anticancer therapy. If, after *nab*-sirolimus treatment, a patient is able to undergo surgical resection of his/her primary tumor with curative intent, documentation on outcome and disease-free or SD 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

In the first stage, 12 efficacy evaluable patients will be accrued. If there are 0 responses in these 12 patients, the study may be terminated. Otherwise, 9 additional efficacy evaluable patients will be accrued for a total of 21 patients.

Sample size considerations are detailed in Section 9.

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 at screening:

1. Patients with functional or non-functional, well-differentiated, locally advanced unresectable or metastatic NETs of the GI tract, lung, or pancreas who have received ≤2 prior lines of therapy excluding SSTa.
2. Patients with functional NETs may enroll if:
    a. the patient has been on a stable dose of an SSTa for ≥12 weeks and
    b. the patient has experienced disease progression while on stable SSTa dose
3. Patients must have 1 or more measurable target lesions by RECIST v1.1.
4. Age: 18 years or older.
5. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 or Karnofsky Performance Status (KPS) ≥80.
6. Adequate liver function:
    a. Total bilirubin ≤1.5 × upper limit of normal (ULN) (unless due to Gilbert's syndrome or attributable to liver metastases, then ≤3 × ULN)
    b. Aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤2.5 × ULN (≤5 × ULN if attributable to liver metastases)
7. Adequate renal function: creatinine clearance ≥30 mL/min, Cockcroft-Gault creatinine clearance = ((140-age) × weight[kg]) / (72 × serum creatinine [mL/min]) × 0.85, if female.
8. Adequate hematologic parameters:
    a. Absolute neutrophil count (ANC) ≥1.0 × $10^9$/L (growth factor support allowed)
    b. Platelet count ≥100,000/mm3 (100 × $10^9$/L) (transfusion and/or growth factor support allowed)
    c. Hemoglobin ≥8.0 g/dL (transfusion and/or growth factor support allowed)

9. Fasting serum triglyceride must be ≤300 mg/dL; fasting serum cholesterol must be ≤350 mg/dL.
10. Minimum of 4 weeks since any major surgery, completion of radiation, and adequately recovered from the acute toxicities of any prior therapy, including neuropathy, to Grade ≤1.
11. 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 study medication throughout 3 months after last dose of study medication and have a negative serum pregnancy test (beta human chorionic gonadotropin [β-hCG]) result at screening and agree to ongoing pregnancy testing during the course of the study, and after the EOS 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 study medication. A second form of birth control is required even if he has undergone a successful vasectomy.
    c. Sexual abstinence is considered a highly effective contraceptive method only if defined as refraining from heterosexual intercourse from 28 days prior to starting study medication throughout 3 months after last dose of study medication. The reliability of sexual abstinence should be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.
12. The patient or the patient's legal guardian(s) understand(s) and sign(s) the informed consent.
13. Willingness and ability to comply with scheduled visits, laboratory tests, and other study procedures.
14. Patients with a known history of human immunodeficiency virus (HIV) infection are eligible if:
    a. There has been no acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection in 12 months prior to enrollment.
    b. The patient has been receiving an antiretroviral therapy regimen for ≥4 weeks and the HIV viral load is <400 copies/mL prior to enrollment.
    c. Antiretroviral therapy regimen does not include strong CYP3A4 inhibitors or inducers (see Section 8.2).

### 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 mTOR inhibitors including *nab*-sirolimus.
   **Note:** Patients who have previously received locoregional or liver-directed therapies (radiofrequency or microwave ablation, transarterial chemoembolization, etc.) are eligible to enroll in the study.

2. Patients with functional NETs who are experiencing uncontrolled symptoms attributed to hormones and other vasoactive substances secreted by the tumor.
3. Patients with inactivating TSC1 or TSC2 alterations (based on tissue or liquid NGS).
4. Severe (Grade ≥3) ongoing infection requiring parenteral or oral anti-infective treatment, either ongoing or completed ≤7 days prior to enrollment.
5. Patients who have any severe and/or uncontrolled medical or psychiatric conditions or other conditions that could affect their participation including:
    a. Known or suspected brain metastases.
    b. Severe heart disease defined as unstable angina pectoris, NYHA Class III or IV congestive heart failure, myocardial infarction ≤6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease.
    c. Severe lung disease defined as a diffusing capacity for carbon monoxide that is ≤50% of normal predicted value and/or an O2 saturation ≤88% at rest on room air (Note: spirometry and pulmonary function tests are 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. Controlled non-melanoma skin cancers, carcinoma in situ of the cervix, resected incidental prostate cancer, certain low-grade hematologic malignancies (eg, chronic lymphocytic leukemia, 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. Active Hepatitis B and/or Hepatitis C infection, and detectable viral load despite antiviral therapy (see Section 8.2).
6. Required use of concomitant medications with strong CYP3A4 interactions (induction or inhibition) should be discontinued (strong inhibitors include ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin, telithromycin; strong inducers include rifampin and rifabutin). These agents must be discontinued prior to first dose of *nab*-sirolimus.

# 5. PROCEDURES

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

## 5.1. Screening Evaluations (Day -29 to -1)

This study will be conducted at approximately 3 sites in the US.

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 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, as 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
- Prior medications and procedures evaluation: all medications taken ≤28 days prior to Cycle 1 Day 1
- ECOG/KPS performance status assessment
- Serum pregnancy test (women of childbearing potential)
- AE assessment
- Clinical chemistry panel (see Table 2 for analytes to be included)

- Complete blood count (CBC), differential and platelet count
- Thyroid function as defined by thyroid-stimulating hormone (TSH; and T3 and T4, if clinically indicated)
- HIV antibody, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody
- Fasting lipids (triglycerides, total cholesterol, high-density lipoprotein [HDL], and low-density lipoprotein [LDL] cholesterol)
- 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.

From all enrolled patients, every attempt should be made to collect a fresh biopsy tissue sample or provide archival tissue <2 years old. If archival tissue is not available, fresh biopsy should be collected, if possible. For patients with tissue samples >2 years from screening, fresh biopsies are recommended. While collection of tissue is recommended, patients without tissue will be allowed on study. At the time of disease progression, if a biopsy is performed, a tumor sample will be submitted, if available.

### 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 for biomarkers will be collected prior to Cycle 1 Day 1, at Week 6, Week 12 and with every 12-week scan (±1 week), and at EOT or disease progression.

#### 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, respiratory rate, 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)
- Concomitant medication and procedures evaluation
- ECOG/KPS performance status assessment

- 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 the study.
- Blood for biomarkers prior to Cycle 1 Day 1, at Week 6, Week 12, and with every 12-week scan (±1 week), and at EOT or disease progression.
- AE assessment
- Clinical chemistry panel (see Table 2 for analytes to be included)
- CBC, differential and platelet count
- Thyroid function as defined by TSH (and T3 and T4, if clinically indicated)
- Fasting lipids (triglycerides, total cholesterol, HDL, and LDL cholesterol)
- *nab*-Sirolimus dosing

Day 1 evaluations for Cycle 1 may be omitted if screening evaluations are performed within 3 days of Cycle 1 Day 1. Laboratory assessments: chemistry, hematology, pregnancy test (women of childbearing potential, includes tubal ligation) (see Table 2 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, respiratory rate, systolic and diastolic blood pressure, and pulse)
- Concomitant medication and procedures evaluation
- AE assessment
- CBC, differential, and platelet count
- *nab*-Sirolimus dosing

### 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 v1.1. 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, Week 6, Week 12, and every 12 weeks associated with scans (±1 week) for the first year and at the EOT Visit/disease progression.

Patients will be evaluated by radiographic imaging every 6 weeks for the first 12 weeks (3 months) and every 12 weeks thereafter. The first response assessment by scans documenting target lesions will be performed 6 and 12 weeks (±7 days) after the first treatment and should be repeated every 12 weeks (±7 days) thereafter until PD.

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. Determination of disease progression for clinical management of patients on study will be assessed at the local site. **If an initial observation of ORR is made (CR or PR) is made, a confirmation scan should be done 6 weeks (±1 week) after the 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.

The analytes to be included are listed in Table 2.

**Table 2: Analyte Listing**

| Chemistry | Hematology | Other Labs |
|---|---|---|
| Sodium | WBC | Pregnancy test |
| Potassium | RBC | TSH (T3, T4 if clinically indicated) |
| Bicarbonate | Hemoglobin | HIV |
| Chloride | Hematocrit | HBV sAg |
| Total protein | Platelets | HBV cAb |
| Albumin | Differential: | HCV Ab |
| Calcium | -Neutrophils | Total Cholesterol |
| Magnesium | -Lymphocytes | HDL |
| Phosphorus | -Monocytes | LDL |
| Glucose | -Eosinophils | Triglyceride |
| BUN | -Basophils | |
| Creatinine | | |
| Total bilirubin | | |
| Alkaline phosphatase | | |
| AST (SGOT) | | |
| ALT (SGPT) | | |
| Amylase | | |
| Lipase | | |

Abbreviations" 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; 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 clinic visits are complete after the EOT Visit. The EOT Visit is a safety follow-up visit that is to be performed 28 to 35 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 must 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
- Concomitant medication and procedures evaluation (until 28 days after the last dose of study medication)
- ECOG/KPS performance assessment
- Urine pregnancy (women of childbearing potential; can be done locally) and as clinically indicated as per institutional guidelines
- Blood sample for biomarker analysis
- AE assessment
- Clinical chemistry panel (see Table 2 for analytes to be included)
- CBC, differential and platelet count
- Imaging assessment: CT/MRI is to be performed at the EOT Visit only for those patients who discontinue treatment for a reason other than disease progression per RECIST v1.1
- 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.

### 5.4. Follow-up Period for Survival and Initiation of Anticancer Therapy (Telephone Contact)

Post-treatment survival time and any subsequent initiation of anticancer therapy will be collected approximately every 12 weeks (±3 weeks) from the EOT Visit or more frequently as needed by telephone contact, until death, withdrawal of consent, or the study closes, whichever is earliest. If, after *nab*-sirolimus treatment, a patient is able to undergo surgical resection of his/her primary tumor with curative intent, documentation on outcome and disease-free or SD status should be followed and documented. This evaluation may be by record review and/or telephone contact.

### 5.5. 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 provided in Section 2.

# 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 (+10 mins window allowed, ie, 30 to 40 mins infusion]) on Days 1 and 8 of every 21-day cycle. Monitor patients for at least 2 hours following completion of the first infusion, and as clinically indicated for each subsequent infusion. A licensed health care professional (NP, PA, MD/DO, or equivalent) should be available at the time of administration of study medication. Supportive care per the institution's normal standard of care including concomitant medications can be utilized 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 $\geq 1.0 \times 10^9$/L
- Platelet count $\geq 100 \times 10^9$/L
- Hemoglobin $\geq 8.0$ g/dL

If treatment cannot be administered on the planned visit date, *nab*-sirolimus may be administered ±3 days from the scheduled date; however, no dose should be administered ≤4 days from the previous dose. The dose may be delayed for up to 21 days from the expected administration date for the dose, if needed. Approval from the medical monitor is required to restart study treatment after >21 days of interruption (counting from the original planned administration date).

**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**

Up to 3 sequential dose reduction are permitted (75, 56, and 45 mg/m$^2$, Table 3). Doses will be reduced for hematologic and nonhematologic toxicities, as clinically indicated and as shown in Table 4. If the patient is experiencing more than one toxicity simultaneously, then refer to the guidelines below. Dose modifications/discontinuations 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**

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 2 dose level reductions are felt to be the only safe way to resume treatment with the study medication, then the Investigator should discuss with the medical monitor before continuing treatment with the study medication.

If the toxicity does not resolve to Grade 1 or baseline within 21 days, withdrawal from the study medication 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. Dose level reduction guidelines are provided in Table 3.

**Table 3: Dose Level Reduction Guidelines**

| Dose level | *nab*-sirolimus Dose/Schedule |
|---|---|
| 0 (initial dose) | 100 mg/m$^2$ (actual dose capped at 200 mg [body surface area 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$^2$ |

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 for ≥Grade 2 AEs that are considered possibly related to study medication by the Investigator are provided in Table 4.

The dosing schedule is described in the Schedule of Assessments, Table 1.

**Table 4: Recommended *nab*-Sirolimus Dosage Modifications for Adverse Reactions**

| Adverse Event | Severity* | Dosage Modifications |
|---|---|---|
| Stomatitis | Grade 2 or 3 | • Withhold *nab*-sirolimus until Grade ≤1.<br>• Restart at the same dose for first occurrence.<br>• If recurs, restart at reduced dose level. |
| | Grade 4 | • Permanently discontinue *nab*-sirolimus. |
| Anemia | Grade 2 | • Withhold *nab*-sirolimus until Hb ≥8 g/dL.<br>• Restart at the same dose level. |
| | Grade ≥3 | • Withhold *nab*-sirolimus until Hb ≥8 g/dL.<br>• Restart at the same dose level.<br>• If recurs, resume at reduced dose level. |
| Thrombocytopenia | Grade 2 | • Withhold *nab*-sirolimus until platelet count >100 × 10$^9$/L.<br>• Restart at the same dose level. |
| | Grade ≥3 | • Withhold *nab*-sirolimus until platelet count >100 × 10$^9$/L.<br>• Restart at reduced dose level. |

| Adverse Event | Severity* | Dosage Modifications |
|---|---|---|
| Neutropenia | Grade 2 or 3 | • Withhold *nab*-sirolimus until absolute neutrophil count ≥$1.5\times10^9$/L.<br>• Restart at the same dose level. |
| | Grade 4 | • Withhold *nab*-sirolimus until absolute neutrophil count ≥$1.5\times10^9$/L.<br>• Restart at reduced dose level. |
| Infections | Grade 3 | • Withhold *nab*-sirolimus until resolved.<br>• Restart at reduced dose level.<br>• If recurs, permanently discontinue *nab*-sirolimus. |
| | Grade 4 | • Withhold *nab*-sirolimus until resolved.<br>• Restart at reduced dose level or permanently discontinue *nab*-sirolimus. |
| Hypokalemia | Grade 2 | • Withhold *nab*-sirolimus until Grade ≤1.<br>• Restart at the same dose level.<br>• If recurs, restart at reduced dose level. |
| | Grade ≥3 | • Withhold *nab*-sirolimus until Grade ≤1.<br>• Restart at reduced dose level.<br>• If recurs, permanently discontinue *nab*-sirolimus. |
| Hyperglycemia | Grade ≥3 | • Withhold *nab*-sirolimus until Grade ≤2.<br>• Restart at reduced dose level. |
| Interstitial Lung Disease / Non-Infectious Pneumonitis | Grade 2 | • Withhold *nab*-sirolimus for up to 3 weeks until Grade ≤1.<br>• Restart at reduced dose level.<br>• If not resolved to Grade ≤1 within 3 weeks, permanently discontinue *nab*-sirolimus.<br>• If recurs, permanently discontinue *nab*-sirolimus. |
| | Grade ≥3 | • Permanently discontinue *nab*-sirolimus. |
| Hemorrhage | Grade 2 or 3 | • Withhold *nab*-sirolimus until Grade ≤1.<br>• Resume at reduced dose.<br>• If recurs, permanently discontinue *nab*-sirolimus. |
| | Grade 4 | • Permanently discontinue *nab*-sirolimus. |
| Other Adverse Reactions | Grade 3 | • Withhold *nab*-sirolimus until Grade ≤1.<br>• Restart at the same dose level.<br>• 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.
For this study, use CTCAE v5.0 to grade AEs.

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

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, and alkaline phosphatase) and/or elevated total bilirubin 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.

### 6.2.2. 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 MEDICATION 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 study medications.

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 medication storage.

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

Only completely unused study medication 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 medication to patients and any remaining study medication after dosing in a study medication accountability record. The study medication record will be made available to Aadi or authorized Aadi-designated monitoring personnel for the purpose of accounting for the study medication supply. Inspections of the study medication 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 study medication 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 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 medication supplies is 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, antiemetics, antidiarrheals, 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 nonirradiated 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 nonprotocol 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 medication 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 medication is held, the Aadi medical monitor can approve such use.

The following medications or nondrug 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 and cannabidiol-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 medication is interrupted. The list may be modified based on emerging data.
- Patients who require antiretroviral or antiviral therapy that are considered strong CYP3A4 inhibitors or inducers should be switched to an alternate effective regimen before study participation or should be excluded from the study if their regimen cannot be altered.
- 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. Analysis Sets and Covariates

### 9.1.1. Analysis Sets

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

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

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

### 9.1.2. Covariates and Subgroups

The following covariates may be (but not limited to) used to examine efficacy and/or safety in subgroups, if sufficient number of patients (≥5) are enrolled in each subgroup:

- Gender (male and female)
- Age at enrollment (<65 versus ≥65 and <75 versus ≥75 years)
- ECOG Performance Status at baseline (0 versus 1) or KPS 70 to 80
- Tumor Type

## 9.2. Sample Size Considerations

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

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

## 9.3. Primary Analysis

The primary analysis to address all study objectives will be conducted when all patients have had the opportunity to be treated for at least 6 months. The primary analysis will include patients who discontinue treatment for any reason prior to 6 months of treatment. 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).

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 Investigator using RECIST v1.1.

## 9.4. Planned Methods of Analysis

### 9.4.1. General Considerations

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 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.

### 9.4.2. Primary Efficacy Endpoints

The primary endpoint, ORR, will be determined by the Investigator using RECIST v1.1.

The primary analysis will evaluate the ORR defined as the proportion of patients of confirmed CR or PR from the time of study treatment initiation until disease progression, as determined by Investigator using RECIST v1.1. The 95% CI for the proportion will also be summarized. The BOR and DCR will be reported along with exact 95% CIs computed by the Clopper-Pearson method.

If an initial observation of ORR is made (CR or PR), a confirmation scan should be done at 6 weeks (±1 week) after initial observation.

The analysis of ORR will be conducted on the Efficacy Evaluable Set. A sensitivity analysis may also be conducted using the PP Analysis Set.

### 9.4.3. Secondary Efficacy Endpoints

The analysis of the DOR will be conducted on the Efficacy Evaluable Set and will be estimated by the Kaplan-Meier method. A sensitivity analysis may also be conducted using the PP Analysis Set.

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% CI.

The analysis of TTR, PFS, and OS will be conducted on the Efficacy Evaluable Set and will be estimated by the Kaplan-Meier method.

Time to response is defined as time from first dose of study medication 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.

### 9.4.4. Safety Endpoints

Safety (incidence and severity of AEs and significant laboratory abnormalities) is a secondary endpoint and will be analyzed using the Full Analysis set.

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

For *nab*-sirolimus exposure, summary statistics will be provided but not limited to 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.

## 10.1. Definition of Adverse Event

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 study medication, whether or not considered related to the study medication [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 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 eCRF, see Section 6.2.2 for the definition of overdose. Any sequela of an accidental or intentional overdose of the study medication should be reported as an AE on the AE eCRF. 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 eCRF but should not be reported as an SAE itself.

An AE does not include the following:

- Medical or surgical procedures (eg, 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 study medication and that does not worsen.
- Situations where an AE 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 AE of special interest (serious or nonserious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize or understand them.

Pneumonitis is considered an AE of special interest and will be monitored. Pneumonitis of any grade should be reported, irrespective of seriousness, in the same expedited manner as an SAE. See Section 10.3.2 for reporting requirements.

### 10.1.2. Adverse Event Reporting Period

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

### 10.2.1. Relationship of Adverse Events to Study Medication

The Investigator must assess and report all AEs and evaluate their relationship to the study medication. The degree of certainty about causality will be graded using the categories in Table 5.

**Table 5: Relationship of Adverse Events to Study Medication**

| Relationship | Attribution | Description |
|---|---|---|
| Unrelated to study medication | Unrelated | The AE ***is clearly NOT related*** to the intervention |
| | Unlikely | The AE ***is doubtfully related*** to the intervention |
| Related to study medication | Possible | The AE ***may be related*** to the intervention. Select this category when the AE is more likely related to the study medication 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: National Cancer Institute Guidelines for Investigators: Adverse event Reporting Requirements for Division of Cancer Treatment and Diagnosis (Cancer Therapy Evaluation Program and the Cancer Imaging Program and Division of Cancer Prevention Investigational New Drug applications and Investigational Device Exemptions). Effective September 16, 2013.

Abbreviations: AE = adverse event

These criteria, in additional 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 study medication, 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.

### 10.2.2. 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 (eg, 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.

## 10.3. 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 judgment, caused the death is the SAE).
- Is life-threatening, defined as an event in which the patient was, in the judgment 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 [eg, 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 AEs of special interest that occurs within the AE reporting periods defined in Section 10.1.2. All SAEs and AEs of special interest (serious and nonserious) 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 and Breastfeeding 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 study medication should discontinue treatment. If a female partner of a male patient taking the study medication becomes pregnant, the male patient should notify the Investigator immediately. The male patient taking the study medication will not need to discontinue from treatment. The Investigator should counsel the patient/patient's female partner regarding the unknown risks of the study medication 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 Study Medication

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

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

The 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 study medication 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 study medication 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 or parent/guardian for patients <18 years after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or the study medication 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 study medication.

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 eCRF 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 study medication 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 sets produced as an outcome of the study is/are as comprehensive as possible.

## 13.4. Sample Storage and Destruction

Any blood, tumor, or biomarker 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, study medication 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.

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| Approval Task<br>Verdict: Approved | Loretta Itri<br>Clinical<br>07-Jul-2023 18:55:02 GMT+0000 |

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