Cover Page

Protocol including Statistical Analysis Plan

Last Approved Version & Date: Amendment 2, 11-Dec-2015

Protocol Title:
A phase 2 multi-center investigation of efficacy of ABI-009 (*nab*-rapamycin) in patients with advanced malignant perivascular epithelioid cell tumors (PEComa)

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INVESTIGATIONAL PRODUCT (IP):	**ABI-009**
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PROTOCOL SYNOPSIS

Study Title

A phase 2 multi-center investigation of efficacy of ABI-009 (*nab*-rapamycin) in patients with advanced malignant perivascular epithelioid cell tumor (PEComa)

Study Number: PEC-001

Study Phase: 2

Name of Investigational Product (IP)

ABI-009, rapamycin protein-bound nanoparticles for injectable suspension (albumin bound), *nab*-rapamycin, nanoparticle albumin-bound rapamycin

Indication

Patients with advanced (metastatic or locally advanced) malignant PEComa, who have not been previously treated with an mTOR inhibitor.

Objectives

Primary Objective

The primary objective of this study is to investigate the efficacy of the mTOR inhibitor ABI-009 in advanced malignant PEComa.

Secondary Objectives

The secondary objectives are to further investigate the efficacy and safety of intravenous (IV) ABI-009 100 mg/m^2 given weekly for 2 of 3 weeks in patients with advanced malignant PEComa.

Exploratory Objectives

- To evaluate investigator assessed ORR
- To evaluate pharmacokinetic/pharmacodynamic relationships for safety and/or efficacy endpoints
- To evaluate tumor biomarkers

Endpoints

Primary Endpoint

The primary endpoint is objective overall response rate (ORR), as determined by independent radiologic assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Secondary endpoints

The secondary endpoints are duration of response (DOR), progression-free survival (PFS) rate at 6 months, PFS, overall survival (OS), safety/tolerability.

- DOR, PFS at 6 months, median PFS, and median OS will be assessed separately in subgroups of patients with metastatic disease and locally advanced disease.
- Safety will be analyzed in all treated patients.

Exploratory Endpoints

- Investigator assessed ORR
- Pharmacokinetic/pharmacodynamic relationships for safety and/or efficacy endpoints
- To evaluate tumor biomarkers:
  - **Blood samples** will be obtained for cell-free plasma DNA collection (pretreatment, Cycle 4/Day 1, and post-treatment) for all patients.
    - Molecular analysis of cell-free plasma DNA assay using next-generation sequencing to assess the prevalence of mutations identified in the primary tumor sample over time as a measure of response to therapy.
  - **Tumor biopsy mutation analysis to assess resistance mechanisms.** Pre-treatment tumors (archival or fresh tissue biopsies) are required for all patients on this study to confirm diagnosis. This sample will also be used for baseline mutational analysis. In addition, an optional tumor biopsy will be collected for patients who provide additional consent at the end of treatment and/or if a patient experiences progression while on study.

Study Design

This study is a prospective phase 2, single arm, open-label, multi-institutional study to determine the efficacy and safety profile of ABI-009 administered by IV infusion in patients with advanced malignant PEComa.

The study will be conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs).

Sample Size

At least 30 evaluable patients will be enrolled.

Study Population

Malignant PEComa histology may be assessed locally in each institution for enrollment but will be retrospectively confirmed by a centralized review for every patient after enrollment to meet prespecified criteria for malignant PEComa. If a patient does not meet retrospectively these criteria, a replacement will be considered.

Patient Eligibility

Inclusion Criteria

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

1. Patients must have a histologically confirmed diagnosis of malignant PEComa that is either metastatic or locally advanced and for which surgery is not a recommended option.
2. Patients must have available tumor block along with the corresponding pathology report (or approximately 30 unstained slides, with a minimum of 16 slides), and/or fresh biopsy to allow retrospective centralized confirmation of malignant PEComa and for mTOR pathway analysis and biomarker analysis.
3. Patients must have one or more measurable target lesions by CT scan or MRI. Measurable disease by RECIST v1.1.
4. Patients must not have been previously treated with an mTOR inhibitor.
5. Prior treatment (investigational or other), chemotherapy, radiotherapy, surgery, or other therapeutic agents (except mTOR inhibitors) is allowed, if completed after 5 half-lives or ≥28 days prior to enrollment, whichever is shorter.
6. Eligible patients, 18 years or older, with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
7. Patients must have the following blood chemistry levels at screening (obtained ≤14 days prior to enrollment (local laboratory):
    a. total bilirubin ≤1.5 x upper limit of normal (ULN) mg/dl
    b. AST ≤2.5 x ULN (≤5 x ULN if attributable to liver metastases)
    c. serum creatinine ≤1.5 x ULN
8. Adequate biological parameters as demonstrated by the following blood counts at screening (obtained ≤14 days prior to enrollment, local laboratory):
    a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L;
    b. Platelet count ≥100,000/mm3 (100 × 10^9/L);
    c. Hemoglobin ≥9 g/dL.
9. Serum triglyceride <300 mg/dL; serum cholesterol < 350 mg/dL.

10. Male or non-pregnant and non-breast feeding female:
    - Females of child-bearing potential must agree to use effective contraception without interruption from 28 days prior to starting IP and while on study medication and have a negative serum pregnancy test (β -hCG) result at screening and agree to ongoing pregnancy testing during the course of the study, and after the end of study treatment. A second form of birth control is required even if she has had a tubal ligation.
    - Male patients 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. A second form of birth control is required even if he has undergone a successful vasectomy.
11. Life expectancy of >3 months, as determined by the investigator.
12. Ability to understand and sign informed consent.
13. Willingness and ability to comply with scheduled visits, laboratory tests, and other study procedures.

Exclusion Criteria

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

1. Patients with lymphangioleiomyomatosis (LAM) are excluded.
2. Known active uncontrolled or symptomatic central nervous system (CNS) metastases. A patient with controlled and asymptomatic CNS metastases may participate in this study. As such, the patient must have completed any prior treatment for CNS metastases ≥28 days (including radiotherapy and/or surgery) prior to start of treatment in this study and should not be receiving chronic corticosteroid therapy for the CNS metastases.
3. Active gastrointestinal bleeding.
4. Pre-existing thyroid abnormality is allowed provided thyroid function can be controlled with medication.
5. Uncontrolled serious medical or psychiatric illness. Patients with a “currently active” second malignancy other than non-melanoma skin cancers, carcinoma in situ of the cervix, resected incidental prostate cancer (staged pT2 with Gleason Score ≤ 6 and postoperative PSA <0.5 ng/mL), or other adequately treated carcinoma-in-situ are ineligible. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are free of disease for ≥1 year).
6. Liver-directed therapy within 2 months of enrollment. Prior treatment with radiotherapy (including radio-labeled spheres and/or cyberknife, hepatic arterial embolization (with or without chemotherapy) or cyrotherapy/ablation) is allowed if these therapies did not affect the areas of measurable disease being used for this protocol.

7. Recent infection requiring systemic anti-infective treatment that was completed ≤14 days prior to enrollment (with the exception of uncomplicated urinary tract infection or upper respiratory tract infection).
8. Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy.
9. Unstable coronary artery disease or myocardial infarction during preceding 6 months.
10. Receiving any concomitant antitumor therapy.
11. Patients with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension.
12. Use of strong inhibitors and inducers of CYP3A4 within the 14 days prior to receiving the first dose of ABI-009. Additionally, use of any known CYP3A4 substrates with narrow therapeutic window (such as fentanyl, alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, terfanide) within the 14 days prior to receiving the first dose of ABI-009.
13. Known Human Immunodeficiency Virus (HIV).
14. Active Hepatitis B or Hepatitis C.

Length of Study

The study is expected to take approximately 32 months from first patient enrolled to last patient follow-up, including approximately 24 months of enrollment period, an estimated 6 months of treatment (or until treatment is no longer tolerated) and an end of treatment visit at 4 weeks (+/- 7 days) after last treatment.

The End of Study (EOS) 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.

End of Treatment (EOT) for a patient is defined as the date of the last dose of ABI-009. End of Treatment Visit for a patient is when safety assessments and procedures are performed after the last treatment, which must occur at least 4 weeks (± 7 days) after the last dose of ABI-009.

Follow-up period is the on-study time period after the EOT Visit. All patients that discontinue study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase for survival and initiation anticancer therapy. 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.

Study Treatments

Patients will receive ABI-009 100 mg/m^2 for 2 of every 3 weeks by IV infusion over 30 minutes. Two dose reduction levels will be allowed: 75 mg/m^2 and 56 mg/m^2. Patients will continue to therapy until disease progression, unacceptable toxicity, until in the opinion of the investigator the patient is no longer benefiting from therapy, or at the patients discretion.

Overview of Key Efficacy Assessments

Patients will be evaluated for complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) by CT imaging. Contrast enhanced MRI can also be used, as long as the same modality is used throughout the study. Baseline scan results can be accepted from outside institutions, but must be done within 4 weeks of starting therapy and must include (as clinically indicated), chest abdominal, and pelvic CT or MRI. The first response assessment by CT or MRI scans documenting target lesions will be done 6 weeks after first treatment and should be repeated every 6 weeks for the first year, then every 12 weeks thereafter until disease progression. If an initial observation of objective response (CR or PR) is made, a confirmation scan should be done at 6 weeks after initial observation. Scans should continue on schedule regardless of delays in ABI-009 dosing. The primary endpoint, ORR, will be determined by independent radiologist(s). The independent radiologic review will follow a separate imaging charter.

After disease progression, patients will be followed for survival every 12 weeks, or more frequently as needed, until death, withdrawal of consent, or the study closes, whichever is the earliest.

Overview of Key Safety Assessments

Safety and tolerability will be monitored through continuous reporting of treatment-emergent and treatment-related adverse events (AEs), AEs of special interest, laboratory abnormalities, and incidence of patients experiencing dose modifications, dose delay/dose not given, dose interruptions, and/or premature discontinuation of IP due to an AE. All AEs will be recorded by the investigator from the time the patient signs informed consent until 28 days after the last dose of IP. Adverse events will be graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Physical examination, vital sign, laboratory assessments (eg, serum chemistry, hematology), and ECOG performance status will be monitored. All SAEs (regardless of relationship to IP) will be followed until resolution. Laboratory analysis will be performed as per study schedule.

Statistical Considerations

Efficacy Analyses:

The primary analysis will address all study objectives and it will be conducted when all patients have had the opportunity to be treated for at least 6 months. All primary, secondary, and exploratory efficacy and safety analyses will be conducted at the time

of the primary analysis, with the exception of the biomarkers which may be analyzed at a later date.

The primary endpoint is ORR by independent radiologic review, and is defined as the proportion of patients who achieve a confirmed PR or CR per RECIST 1.1.

The focus of the study is to estimate the ORR in patients treated with ABI-009. The number and percentage of patients achieving response will be summarized and an exact 95% confidence interval (CI) will be provided. Assuming an observed ORR of 30%, the lower bound of the 95% CI for the estimated ORR will exclude values less than 14.7%. With 30 patients the half-width of the 95% CI for the estimated ORR will be no more than 18.7%.

Analysis of secondary efficacy endpoints DOR, PFS rate at 6 months, PFS, and OS will be done separately for 2 subgroups of patients: 1) those with metastatic disease; and 2) those with locally advanced disease for which surgery is not a recommended option. Some of the patients in the locally advanced subgroup may be clinically indicated to receive surgery if there is sufficient tumor shrinkage, which would introduce a bias to the analysis.

For patients with metastatic disease, DOR, PFS at 6 months, median PFS, and OS will be summarized using Kaplan-Meier (KM) analysis. Quartiles with 95% CIs will be summarized. The number of patients with locally advanced disease for which surgery is not an option is expected to be small; therefore DOR, PFS at 6 months, median PFS, and OS for these patients will be summarized by descriptive statistics.

Safety Analyses:

The treated population (Full Analysis Set) will be the analysis population for all safety analyses. Adverse events will be coded using the Medical Dictionary for Medical Activities (MedDRA) and grouped by their system organ class and preferred term. Summary tables will include the number and percentage of patients with AEs, serious AEs, fatal AEs and other AEs of interest. Safety will be analyzed in both patient groups together (metastatic and locally advanced).

An external Data Monitoring Committee (DMC) will assess safety data approximately when a third of patients enrolled and received at least 2 cycles of therapy. For a full description of statistical analysis methods please refer to Section 10.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
AML	angiomyolipoma
ANC	absolute neutrophil count
AST	aspartate transaminase (SGOT)
AUC	area under the time-concentration curve
BSA	body surface area
C_{max}	maximum plasma drug concentration
C_{min}	minimum plasma drug concentration
CBC	complete blood count
CCST	clear cell sugar tumor
CI	confidence interval
CNS	central nervous system
CR	complete response
CT	computed tomography
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRT	data review team
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry

IND	investigational new drug
IP	investigational product
IRB	Institutional Review Board
IV	intravenously
LAM	lymphangioleiomyomatosis
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
mTOR	mammalian target of rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	progressive disease
PEComa	perivascular epithelioid cell tumors
PFS	Progression-free survival
PK	pharmacokinetics
PR	partial response
PTEN	protein tyrosine phosphatase
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SPARC	secreted protein acid rich in cysteine
TBL	total bilirubin level
TSC	tuberous sclerosis complex
ULN	upper limit of normal

Abbreviation or Term	Definition/Explanation
Advanced malignant PEComa	Histologically confirmed malignant PEComa that is either metastatic or is locally advanced where surgery is not an option
Study Day 1	First day that protocol-specified IP is administered to the patient.
End of Study	Either the date of the last visit of the last patient to complete the study, or the date of receipt of the last data point from the last patient that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol.
End of Treatment	The date of the last dose of ABI-009 for an individual patient.
End of Treatment Visit	For a patient is when safety assessments and procedures are performed after the last treatment, which must occur at least 4 weeks (± 7 days) after the last dose of ABI-009.
Primary Analysis	For this study will occur after all patients have either completed the study or completed 6 months of treatment. Patients who are still active at the time of the primary analysis may continue on study until disease progression or medication intolerance is observed.
Follow-up Period	The on-study time period after the End of Treatment Visit. All patients that discontinue study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase for survival and anticancer therapy. Follow up will continue approximately every 12 weeks (+/- 3 weeks), or more frequently as needed, until death, withdrawal of consent, or the study closes, whichever is the earliest. This evaluation may be made by record review and/or telephone contact.
Efficacy Analysis Dataset	All enrolled patients with measurable tumor per RECIST v1.1 at baseline who receive at least one does of ABI-009 and have a confirmed diagnosis of PEComa.
Full Analysis Set	All enrolled patients who receive at least one dose of ABI-009 (treated population).
Per-protocol Analysis Set	All enrolled patients who do not have any prospectively defined protocol violations.
Progression-free	The time from the first dose date to the first observation of a

survival	disease progression or death due to any cause.
Overall survival	The time from the first dose date to the date of death due to any cause.
Overall response rate	The proportion of patients who achieve a confirmed partial response or complete response per RECIST 1.1. Response rates based on an independent assessment by radiologists not involved in the conduct of the trial, and by the investigators assessment of response will be reported separately.
Duration of response	The time from when criteria of response are first met until the first observation of disease progression per RECIST v1.1 or death due to any cause, whichever comes first.

1. INTRODUCTION

1.1. Malignant PEComa Disease Background

Perivascular epithelioid cell tumors (PEComa) is a rare subset of soft tissue sarcomas recently recognized as a distinct entity by the World Health Organization [1, 2]. PEComas are a family of rare mesenchymal tumors composed of histologically and immunohistochemically distinctive epithelioid cells. PEComas appear to arise most commonly at visceral (especially gastrointestinal and uterine), retroperitoneal, and abdominopelvic sites. PEComas have a strong female predominance and can occur in a wide age range, with a median age of approximately 43 years.

According to the most recent classification, the PEComa family of tumors include angiomyolipoma (AML), clear cell "sugar" tumor of the lung (CCST), lymphangioleiomyomatosis (LAM), and PEComa not otherwise specified (PEComa-NOS), a term referring to less well-characterized PEComas of a variety of other anatomic origins [3, 4].

Most PEComas are benign, but there is a subset of aggressive PEComas, advanced malignant PEComas [5, 6], that may be either metastatic or locally advanced where surgery is not an option, for which there are currently no approved therapies, but a few case reports of clinical experience with unapproved treatments for this disease. The prognosis for patients with this patient subset is poor, with a median survival estimated to be 12-17 months following diagnosis of advanced disease, based on data combined from published retrospective analyses of very few patients and personal communications with clinicians who have treated malignant PEComa [3, 7-9]. These data included a mix of patients treated with chemotherapy, radiotherapy, and mTOR inhibitors. Therefore, a significant unmet need exists for effective therapies to treat this aggressive and life-threatening disease.

Due to the extremely rare nature of malignant PEComa, there is very limited information on its incidence. Only one publication has provided an estimate of the incidence of malignant PEComa as 0.012-0.024/100,000 or 0.12-0.24/1,000,000 [10]. Based on this information, it is estimated that there are approximately 42-84 new patients per year in the USA with malignant PEComa. Based on limited information on survival of patients with malignant PEComa [3, 7-9], our estimate for prevalence of malignant PEComa is 0.22-0.48/1,000,000 or approximately 77-168 patients in the USA. A recent report in 2014 [11] reviewed 36 consecutive patients with a diagnosis of malignant PEComa at the Dana Farber Cancer Institute (DFCI) treated in a 5-year period between 2007-2012; the number of cases reported at DFCI is consistent with the estimate above.

Treatment for Malignant PEComa

Currently, no effective medical treatment has been approved for patients with malignant PEComa; therefore it represents a clear unmet medical need and requires the development of effective therapeutic interventions.

The primary treatment option for localized malignant PEComa cases is surgery. However, there is no curative therapeutic option once the disease has spread and it is usually fatal. The majority (~70%) of patients with localized primary malignant PEComas develop metastatic disease over a median follow-up of 1 year [3, 11] and nearly one fifth of the patients have metastatic disease at presentation [11]. Lung, liver, peritoneum, and bones were the most common sites of metastases in an observational study with 36 patients [11]. There is no curative therapy once the disease has spread and it is usually fatal with a median survival of 12-17 months [3, 7-9].

Currently, no effective medical treatment has been evaluated and approved in this indication. While there has not been a single prospective clinical trial in patients with malignant or metastatic PEComa, in a restrospective analysis assembled from isolated case reports of 18 patients with unresectable or metastatic malignant PEComas, the median overall survival was 16 months (range: 4 to 30 months) [3]. Chemotherapy and radiotherapy have not been shown to provide significant clinical benefit [3]. Neoadjuvant treatment has been utilized in a small number of cases usually reporting either progression or minimal evidence of efficacy in the resected tumor. The role of adjuvant therapy is also unclear [3]. In the metastatic setting, systemic chemotherapy has shown little efficacy, as there were no objective responses reported with the use of cytotoxic drugs, including doxorubicin, ifosfamide, paclitaxel, carboplatin, and epirubicin [3, 12].

In metastatic soft tissue sarcoma in general, cytotoxic therapy remains a standard treatment in both chemotherapy-naive and previously treated patients and single-agent doxorubicin is still an appropriate first-line chemotherapy option. As a single agent it resulted in an ORR of 5-18% and median OS of 7.0-12.0 months independent of the schedule of administration [13-15]. Several randomized trials compared doxorubicin-based combinations such as high dose ifosfamide, imidazole carboxamide and/or gemcitabine versus doxorubicin single-agent. Response rates with combination were better than with single-agent doxorubicin (18-25% compared to 5-18%) [14, 16-18]. There were conflicting results in terms of PFS (2 to 8 months), only some trials reporting a benefit with the combination compared to doxorubicin alone, especially when high doses of both doxorubicin and ifosfamide were used [16]. Overall survival was not significantly improved but severity of AEs was significantly increased with the combination therapies [16]. Targeted therapies, such as ridaforolimus, imatinib, and pazopanib did not provide higher response rates in general soft tissue sarcomas (ORR 1.9%, 2.2% and 6.3% respectively) [19-21]. Thus, despite its modest activity, doxorubicin has remained the drug used either in monotherapy or combination in adult soft tissue sarcomas for several years. Overactivation of the mTOR pathway has been reported and mTOR inhibitors have shown some efficacy in this indication, described in Section 1.3.

Many benign PEComas such as renal AML and LAM are associated with the rare genetic mutation in the tuberous sclerosis complex (TSC). Patients presenting with both PEComa-NOS and TSC is even less common than TSC and LAM or AML [3]. Most malignant PEComas are sporadic and result from the loss of tumor suppressor gene *TSC2* [22]. The mTOR pathway, which is inhibited by TSC1/TSC2 complex, is frequently deregulated in PEComas, making it a promising target for treatment. This

study will assess the safety and efficacy of a novel mTOR inhibitor, ABI-009, *nab*-rapamycin, in patients with malignant PEComas.

Histology

Histologically, PEComas typically show a nested architecture, are characterized by a proliferation of usually epithelioid cells, which exhibit a focal association with blood vessels walls with subendothelial growth and a radial arrangement of tumor cells. The origin of perivascular epithelioid cells (PECs) remains unknown, with no normal counterpart identified so far. PECs generally have an epithelioid appearance, with a clear to granular eosinophilic cytoplasm, a round, centrally located nucleus and an inconspicuous nucleolus, although hyperchromasia and nuclear irregularity may be present. Ultrastructurally, PECs contain microfilament bundles with electron-dense condensation, numerous mitochondria and membrane-bound dense granules [22]. Immunohistochemically, PECs are usually characterized by positive staining for both melanocytic markers (HMB45, MelanA/Mart1, and microphthalmia transcription factor) and muscle markers (smooth muscle actin, pan-muscle actin, and calponin), with desmin and S100 expression being less common. Some PEComas (particularly those with clear cytoplasm) lack expression of muscle markers. The most sensitive melanocytic marker for the diagnosis of PEComa is HMB-45 [4].

1.2. ABI-009 Background

1.2.1. Rapamycin and Rapalogs

Rapamycin is a crystalline powder with the empirical formula C51H79NO13 and a molecular weight of 914.17. Rapamycin is a protein kinase inhibitor that is approved for immunosuppression in renal transplant patients, and is under investigation as a cancer treatment. Rapamycin 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 [23]. mTOR is a serine/threonine-specific protein kinase, downstream of the phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B) pathway, and a key regulator of cell survival, proliferation, stress, and metabolism. Additionally, mTOR is involved in regulating angiogenesis by controlling endothelial and smooth muscle cell proliferation via the hypoxia-inducible factor-1α and vascular endothelial growth factor [24]. 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 anti-cancer therapy. Rapamycin 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 [25].

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

- PI3K, TSC1, TSC2, PI3K, AKT, and PTEN gene mutations [26]
- Phosphorylated p-AKT, p-S6, p-4EBP1 expression [27]
- biomarkers for the proliferation (Ki-67) and apoptosis (PARP) [25]

However, no clinical studies have confirmed the importance of these biomarkers as predictive factors of efficacy, except PI3K mutation in non PEComa tumors such as breast carcinoma [26].

Although rapamycin, an oral therapeutic, is an efficacious mTOR inhibitor, it has poor solubility, low oral bioavailability, and dose-limiting toxicity [23, 28]. Marketed rapamycin analogs are temsirolimus and everolimus. Temsirolimus, approved for the treatment of kidney cancer, is a prodrug of rapamycin and requires conversion by the CYP3A enzyme. Everolimus is approved for pediatric and adult patients with subependymal giant cell astrocytoma, for advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane, progressive neuroendocrine tumors of pancreatic origin (PNETs), subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis and advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib [29-33].

Oral rapamycin 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) sometimes fatal [34-36]. The most frequently occurring grade 3 or 4 adverse events were hyperglycemia (17%), hypophosphatemia (13%), anemia (9%), and hypertriglyceridemia (6%) [37]. These side effects could lead to the discontinuation of the treatment in 60% of patients in some studies.

1.2.2. ABI-009 (*nab*-Rapamycin)

The novel nanoparticle albumin-bound rapamycin (*nab*-rapamycin, ABI-009) is freely dispersible in saline and is suitable for intravenous administration, and has produced both a favorable safety profile and evidence of efficacy in patients with metastatic solid tumors [38].

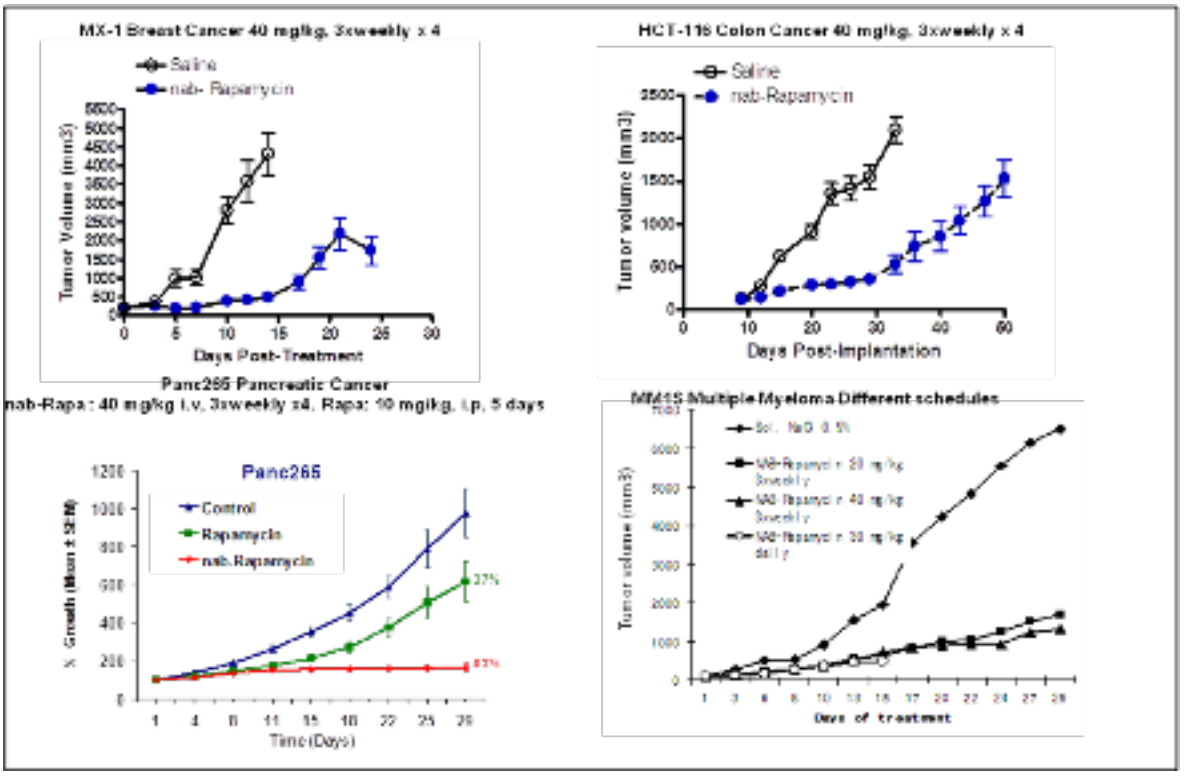
Nanoparticle albumin-bound or *nab*® technology (Abraxis BioScience, a wholly-owned subsidiary of Celgene Corporation) when applied to hydrophobic molecules, such as paclitaxel (*nab*-paclitaxel; Abraxane®), has led to improved drug delivery, safety, and efficacy in various solid tumors compared with the conventional paclitaxel formulation [39]. This suggests that the *nab* formulation of rapamycin may also produce similar advantages over the standard rapamycin.

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 [40, 41]. Albumin circulating in the bloodstream can interact with gp60 to initiate caveolae-mediated transcytosis to reach tumor cells [42, 43]. Indeed, *nab*-paclitaxel transcytosis across the epithelial monolayer was dependent on caveolae formation [44]. 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 [44].

1.2.2.1. Preclinical Studies with ABI-009

Preclinical primary pharmacology studies in vivo demonstrated significant antitumor activity of ABI-009 as a single agent administered intravenously at 40 mg/kg, 3 times weekly for 4 weeks, across different tumor xenograft models in nude mice (see Figure 1 below), including breast, colorectal, multiple myeloma, and pancreatic cancer [45-49]. This dose level correlates to approximately 120 m g/m^2 in human. These findings are consistent with published information on rapamycin as an mTOR inhibitor and the role of mTOR in tumor growth [50]. In addition, recent preclinical study has demonstrated that combination of ABI-009 with the Akt inhibitor perifosine induced synergistic antitumor activity in multiple myeloma [48].

Figure 1: Antitumor Activity of ABI-009 in Tumor Xenografts



Preclinical pharmacokinetic (PK) studies in rats showed that intravenously administered ABI-009 exhibited linear PK with respect to dose and large volume of distribution (Vz), due to efficient tissue extraction of rapamycin from the central blood compartment [47]. Shortly after dosing, tissue rapamycin level was 3-5 fold higher than that of blood, indicating efficient extraction. The terminal half life of ABI-009 was long in rats, ranging from 13.4 - 25.8 hours and resulted in significant blood level at 48 hours (~10 ng/ml) and 120 hours (>1 ng/ml). Consistent with literature of rapamycin [51], excretion of ABI-009 was primarily through the fecal route (68.57 - 69.99%) with minimum contribution from the renal route (7.73 - 8.84%).

The safety and toxicity of ABI-009 were evaluated in a series of preclinical studies. In a GLP repeat-dose toxicity study in male and female rats, ABI-009 administered IV was well tolerated at doses up to 90 mg/kg (equivalent to 540 mg/m^2 human dose) when

delivered every four days for 3 cycles. Nonclinical toxicology studies of ABI-009 showed no new or unexpected toxicity compared to what is already known for rapamycin and other rapalogs [52-54].

1.2.2.2. Clinical Studies with ABI-009

In a phase 1 dose escalation, tolerability and pharmacokinetics study conducted at MD Anderson Cancer Center (Protocol CA-401), ABI-009 was well tolerated with evidence of responses and SD in various solid tumors including renal cell carcinoma and bladder cancer, both of which typically express mTOR [38]. Twenty-six patients were treated with 45, 56.25, 100, 125, 150 mg/m^2 ABI-009 per week for 3 weeks, followed by a week of rest (28-day cycle). ABI-009 was administered intravenously. The maximum tolerated dose was established at 100 mg/m^2.

Nineteen patients were evaluable for efficacy. One patient in the 45 mg/m^2 (95 mg actual rapamycin dose) cohort diagnosed with adenocarcinoma of the kidney and with bone and intrathoracic metastases had a confirmed PR. The target lesion of this patient was reduced by 35.1% and the duration of response lasted 183 days. Two (11%) patients (at doses 45 and 125 mg/m^2, with actual rapamycin doses of 88 mg and 193 mg, respectively) had an overall tumor evaluation of SD (confirmed): 1 patient with mesothelioma had SD for 365 days and 1 patient with a neuroendocrine tumor in the left axillary node had SD for 238 days.

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

The most common hematologic AEs, for all cohorts and grades, were thrombocytopenia (58%), followed by hypokalemia (23%), anemia and hypophosphatemia (19% each), and neutropenia and hypertriglyceridemia (15% each). Most of these events were grade 1/2, and only 1 grade 4 hematologic event occurred (thrombocytopenia in the 150 mg/m^2 arm). At the MTD, the only hematologic AE was a grade 3 anemia. In this clinical study, 16 of 26 patients (62%) had treatment-related adverse events (TRAEs) requiring a week dose delay:

- 9 of 17 (53%) who received dose levels considered acceptable for future therapeutic usage, ie doses ≤ 100 mg/m^2 :
  - 4 (57%) patients in the 45 mg/m^2 dose cohort
  - 1 (33%) in the 56 mg/m^2 dose cohort
  - 4 (57%) in the 100 mg/m^2 dose cohort

- 7 of 9 (78%) who received higher dosage:
  - 2 (100%) in the 150 mg/m^2
  - 5 (71%) in the 125 mg/m^2 cohort

The percentages of missing doses per dose level during the treatment period were:

- 45 mg/m^2: 20/86: 23%
- 56 mg/m^2: 2/21: 9.5%
- 100 mg/m^2: 11/72: 15.2%
- 75 mg/m^2: 7/27: 26% (75 mg/m^2 dose level was given to 2 patients because of prior toxicity at 100 mg/m^2; however this dosage was not part of the protocol, and as such has not been assessed)

The total percentage of missing dose was 19.4% at dose levels considered acceptable for future therapeutic usage ie doses ≤ 100 mg/m^2.

Most of the missing doses (83%) occurred at day 15, corresponding to the 3rd administration within a cycle. Thus, the present study will examine 100 mg/m^2 ABI-009 given weekly for 2 weeks followed by a week off (Section 1.3.2).

Table 1: Treatment-related Grade 1–4 Hematologic and Nonhematologic Adverse Events Reported in ≥10% of All Treated Patients

	MTD (100 mg/m^2) n = 7				All Treated Patients n = 26			
NCI CTCAE v 3.0	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**
Hematologic AEs, n (%)								
Anemia	0	0	1 (14)	0	0	3 (12)	2 (8)	0
Hypokalemia	1 (14)	0	0	0	5 (19)	0	1 (4)	0
Hypophosphatemia	0	1 (14)	0	0	1 (4)	2 (8)	2 (8)	0
Hypertriglyceridemia	1 (14)	1 (14)	0	0	2 (8)	1 (4)	1 (4)	0
Neutropenia	1 (14)	0	0	0	2 (8)	1 (4)	1 (4)	0
Thrombocytopenia	1 (14)	4 (57)	0	0	5 (19)	6 (23)	3 (12)	1 (4)
Nonhematologic AEs								
AST/SGOT	0	0	0	0	1 (4)	0	2 (8)	0
Constipation	0	1 (14)	0	0	1 (4)	2 (8)	0	0
Diarrhea	1 (14)	0	0	0	3 (12)	3 (12)	0	0
Dyspnea	0	1 (14)	1 (14)	0	1 (4)	2 (8)	1 (4)	0
Fatigue	1 (14)	4 (57)	0	0	1 (4)	6 (23)	0	0
Infection, oral cavity	1 (14)	1 (14)	0	0	3 (12)	2 (8)	0	0
Mucositis/stomatitis	3 (43)	2 (29)	0	0	7 (27)	3 (12)	0	0
Nausea	1 (14)	1 (14)	0	0	3 (12)	2 (8)	0	0
Rash	1 (14)	0	0	0	4 (15)	2 (8)	0	0
Weight loss	0	0	0	0	1 (4)	2 (8)	0	0

1.2.2.3. ABI-009 (*nab*-Rapamycin) Pharmacokinetics (PK)

ABI-009 produced a fairly dose proportional increase of C_{max} and AUC across the dose range tested, and it significantly inhibited mTOR targets S6K and 4EBP1.

ABI-009 has unique characteristics amongst the available mTOR inhibitors. The PK profile of rapamycin administered as ABI-009 is categorically different from those of the other oral or IV administered mTOR inhibitors. Intravenous infusion of ABI-009 results in high C_{max} of rapamycin upon administration followed by a long half-life of approximately 60 hrs that allows once weekly dosing. Peak levels of rapamycin after ABI-009 are well above 1000 ng/mL range that may have significant tumor penetration effect. Oral mTOR inhibitors such as rapamycin 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 (rapamycin) and as a result, high levels of rapamycin are

not achieved (< 100 ng/mL) [55]. The administration of ABI-009 led to a much higher exposure to rapamycin (sirolimus) as compared to sirolimus from temsirolimus (C_{max} almost 50 fold higher, AUC almost 12 fold higher for ABI-009) or everolimus (C_{max} 50-70 fold higher, AUC 85-200 fold higher for ABI-009) [38, 55]. Unlike with other mTOR inhibitors, micromolar concentrations are reached and maintained for several hours with ABI-009 which could potentially circumvent acquired resistance to mTOR inhibitors via retroactivation of AKT by TORC2 [56, 57]. The high exposure achieved with ABI-009 with acceptable safety profile could be highly relevant to the treatment of aggressive cancers such as malignant PEComas.

1.3. Rationale for the Study

1.3.1. Rationale for the Use of ABI-009 in Advanced Malignant PEComas

The rationale behind mTOR inhibitor use in PEComas lies in the fact that both classic PEComas and PEComa-NOS have been shown to frequently harbor mutations in the *TSC1* and/or *TSC2* genes, which regulate cell proliferation via the mTOR pathway [58]. Tumors of the PEComa family are rare and usually occur sporadically. Lymphangioleiomyomatosis and AML also are seen at high frequency in patients with TSC, a disorder caused by mutation of *TSC1* or *TSC2*, for which the gene products negatively regulate mTORC1 through inhibition of the mTOR kinase activator, RHEB [58]. Both *TSC1* and T*SC2* gene products are involved in multiple cellular pathways, including regulation of cell proliferation, migration and differentiation through inhibition of the Rheb/mTOR/p70S6 kinase-signaling pathway [58]. Inactivation of the tuberin/hamartin complex in TSC thus leads to the activation of mTOR and the phosphorylation of p70S6K and ribosomal protein S6, and further promotes translational initiation and cell growth. This mTOR pathway is reported to be up regulated not only in TSC-associated AML, but also in sporadic AML or PEComas [59]. A high frequency of loss of heterozygosity (LOH) in TSC2 gene is found in sporadic PEComas and sporadic classic renal and hepatic AMLs, with much lower LOH observed for TSC1 [60]. In a recent study, activation of mTORC1 pathway, manifested by increased phosphorylated p70S6K and decreased phospho-Akt levels, was observed in 100% non-TSC AMLs and 93% of extra-renal PEComas [61].

Initial trials of these agents in the classic PEComas (AML, LAM) have led to a number of meaningful responses [4, 62], sparking interest in their use for advanced or recurrent PEComa-NOS. Clinical benefits have been observed in a number of PEComa case studies using rapamycin [5, 63], temsirolimus [64], and everolimus [65], although these responses have not been uniform. Wagner et al reported a short series of 3 patients treated with rapamycin for metastatic malignant PEComas. Radiographic responses were observed in all 3 patients. Loss of TSC2 protein expression and evidence of baseline mTORC1 activation was found in all patients. Homozygous loss of *TSC1* was identified in one PEComa [5]. Dickson et al reported on the use of rapamycin in the treatment of 5 consecutive patients with extrarenal nonpulmonary PEComas with 3 CRs, 1 PR, and 1 case of progression [6]. In a retrospective study, the Royal Marsden Hospital reported that a population of 10 patients treated with either temsirolimus or rapamycin showed promising response rate but short remission duration [9]. It is

noteworthy that in a published clinical case, malignant PEComa tumors deemed inoperable or with borderline resectability achieved sufficient bulky tumor shrinkage with neoadjuvant rapamycin for a surgical resection. The option of neoadjuvant treatment may be considered for selected high-risk patients who can tolerate an mTOR inhibitor [63].

Additional justification for treating patients with malignant unresectable PEComa with ABI-009 instead of irradiation or doxorubicin-based chemotherapy: The available molecular and clinical evidence provides a strong rationale for using mTOR inhibitors in this disease. Thus participation in this clinical trial will be a reasonable option for many patients with advanced malignant PEComa. Most oncologists with expertise in sarcoma favor this approach since the disease is considered to be relatively insensitive to systemic chemotherapy and radiotherapy. Radiotherapy can be considered in selected cases, but may not be recommended depending on the location and/or extent of the tumor. Prior treatment with chemotherapy or radiotherapy would not exclude a patient from enrolling in the study and remain options at the discretion of the patient's treatment team.

The mechanisms of resistance to mTOR inhibition in malignant PEComa remain an important area for research [66, 67]. TFE3 gene rearrangement was recently reported in a small number of PEComas with no evidence of TSC2 mutation, which is suggested to cause resistance to mTOR inhibition, but this would need to be confirmed in a prospective study [68]. In addition, although rapamycin and rapalogs have shown some efficiency in the treatment of malignant PEComas, they induce AEs that can lead to treatment interruption, and thus compromising efficacy, and impact the quality of life, and lesions will typically regrow when the inhibitor is discontinued. More importantly, no formal clinical study has been conducted to investigate mTOR inhibitors safety and efficacy. These data clearly support the development of new mTOR inhibitors in an open study in the treatment of malignant PEComa.

It is estimated that 85% to 90% of the advanced malignant PEComas are metastatic and 10% to up to 15% are localized but unresectable. Allowing enrollment for both of these 2 subgroups of patients will permit assessing the efficacy of ABI-009 for response rate.

With favorable systemic safety at doses of 100 mg/m^2 given weekly IV observed in the phase 1 study, therapy with ABI-009 should result in manageable adverse events and provide significant therapeutic benefit to patients with malignant PEComas.

1.3.2. Rationale for the Schedule of Administration of ABI-009

A slightly different schedule of administration has been selected in the present study than was studied in the initial Phase 1 study CA401. In this study, 2 of 3 weekly schedule will be used instead of 3 of 4 weeks as in phase 1 clinical study CA-401.

The rationale for the modification to the schedule of administration of a dose of 100 mg/m^2 is to further improve the tolerance of ABI-009. As discussed in Section 1.2.2.2, 19.4% of doses were missed at doses ≤100 mg/m^2. Most of the missing doses (83%) occurred at day 15, corresponding to the 3rd administration within a cycle. Thus, the

present study will examine 100mg/m^2 ABI-009 given weekly for 2 weeks followed by a week off. This change in schedule will not substantially impact the total drug received by the patients. In a period of 6 months (24 weeks) of treatment, the 2/3 schedule will allow 16 administrations, while the 3/4 schedule will allow 18 administrations.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

To investigate the efficacy of the mTOR inhibitor ABI-009 in advanced malignant PEComa.

2.1.2. Secondary Objectives

The objectives are to further investigate the efficacy and safety of IV ABI-009 100 mg/m^2 given weekly for 2 of 3 weeks in patients with advanced malignant PEComa.

2.1.3. Exploratory Objectives

Exploratory Objectives

- To evaluate investigator assessed ORR
- To evaluate pharmacokinetic/pharmacodynamic relationships for safety and/or efficacy endpoints
- To evaluate tumor biomarkers:

2.2. Endpoints

2.2.1. Primary Endpoint

The primary endpoint is objective overall response rate (ORR), as determined by independent radiologic assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

2.2.2. Secondary Endpoints

The secondary endpoints are duration of response (DOR), progression-free survival (PFS) rate at 6 months, PFS, overall survival (OS), and safety/tolerability.

- DOR, PFS rate at 6 months, median PFS, and OS will be assessed separately in subgroups of patients with metastatic disease and locally advanced disease. Patients in the locally advanced tumor subgroup may be clinically indicated to receive surgery if there is sufficient tumor shrinkage, which could introduce a bias in the assessment of the DOR, PFS rate at 6 months, median PFS, and OS. Safety will be analyzed in all treated patients.

2.2.3. Exploratory Endpoints

- Investigator assessed ORR
- Pharmacokinetic/pharmacodynamic relationships for safety and/or efficacy endpoints

- To evaluate tumor biomarkers:
  - **Blood samples** will be obtained for cell-free plasma DNA collection (pretreatment, Cycle 4/Day 1, and post-treatment) for all patients.
    - Molecular analysis of cell-free plasma DNA assay using next-generation sequencing to assess the prevalence of mutations identified in the primary tumor sample over time as a measure of response to therapy.
  - **Tumor biopsy mutation analysis to assess resistance mechanisms.** Pre-treatment tumors (archival or fresh tissue biopsies) are required for all patients on this study to confirm diagnosis. This sample will also be used for baseline mutational analysis. In addition, an optional tumor biopsy will be collected for patients who provide additional consent at the end of treatment and/or if a patient experiences progression while on study.

3. OVERALL STUDY DESIGN

3.1. Study Design

This study is a prospective, single arm, phase 2, open label, multi-institutional study to determine the efficacy and safety profile of intravenous ABI-009 in patients with advanced malignant PEComa.

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

This study will be conducted at approximately 9 sites in the United States.

3.2. Study Duration

The duration of enrollment for this study will last approximately 24 months. A cycle will consist of 3 weeks, with ABI-009 given weekly for 2 weeks followed by a week of rest. Treatment will continue until disease progression or unacceptable toxicity.

It is anticipated that each study patient will be on study for approximately 2 weeks of screening, approximately 6 months of treatment and 4 weeks of safety follow up. The total duration of the study is expected to be approximately 32 months.

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

End of Study (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.

End of Treatment (EOT) is defined as the date of the last dose of ABI-009 for an individual patient

End of Treatment Visit for a patient is when safety assessments and procedures are performed after the last treatment, which must occur at least 4 weeks (± 7 days) after the last dose of ABI-009.

Primary analysis for this study will occur after all patients have either completed the study or completed 6 months of treatment. Patients who are still active at the time of the primary analysis may continue on study until disease progression or medication intolerance is observed.

Primary Completion is the time when the last patient is assessed or receives an intervention for the purposes of final collection of data for the primary analysis.

Follow-up period is the on-study time period after the EOT Visit. All patients that discontinue study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase for survival and anticancer therapy. Follow-up will continue approximately every 12 weeks (+/- 3 weeks), or more frequently as needed,

until death, withdrawal of consent, or the study closes, whichever is the earliest. This evaluation may be made by record review and/or telephone contact.

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

- When the last patient on study has completed their Safety follow-up visit, or
- When the last patient on study has documented toxicities to ABI-009 and the toxicity has resolved, returned to baseline or is deemed irreversible after the Safety follow-up visit or
- When the last patient completes or discontinues the follow-up phase

4. STUDY POPULATION

4.1. Number of Patients

The anticipated enrollment into this study will be at least 30 evaluable patients. The rationale for the number of patients is detailed in Section 10.

Investigators will be expected to maintain and submit every other week 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 refused to participate).

Investigators will also be expected to document the reasons for which any patient enrolled on the trial with locally advanced malignant PEComa disease is not a suitable candidate for local treatment (eg, surgery or irradiation).

Before any study-specific procedure, the appropriate written informed consent must be obtained (see Section 13.1).

If for a given patient, the appropriate tumor tissue is not made available for centralized retrospective confirmation of malignant PEComa tumor type, this patient may be replaced. Additional patients may be enrolled if the Sponsor determines that the minimum required number of patients with evaluable tissue samples have not been enrolled.

4.2. Inclusion Criteria

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

1. Patients must have a histologically confirmed diagnosis of malignant PEComa that is either metastatic or locally advanced and for which surgery is not a recommended option.
2. Patients must have available tumor block along with the corresponding pathology report (or approximately 30 unstained slides, with a minimum of 16 slides), and/or fresh biopsy to allow retrospective centralized confirmation of malignant PEComa and for mTOR pathway analysis and biomarker analysis.
3. Patients must have one or more measurable target lesions by CT scan or MRI. Measurable disease by RECIST v1.1.
4. Patients must not have been previously treated with an mTOR inhibitor.
5. Prior treatment (investigational or other), chemotherapy, radiotherapy, surgery, or other therapeutic agents (except mTOR inhibitors) is allowed, if completed after 5 half-lives or ≥28 days prior to enrollment, whichever is shorter.
6. Eligible patients, 18 years or older, with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

7. Patients must have the following blood chemistry levels at screening (obtained ≤14 days prior to enrollment (local laboratory):
    a. total bilirubin ≤1.5 x upper limit of normal (ULN) mg/dl
    b. AST ≤2.5 x ULN (≤5 x ULN if attributable to liver metastases)
    c. serum creatinine ≤1.5 x ULN
8. Adequate biological parameters as demonstrated by the following blood counts at screening (obtained ≤14 days prior to enrollment, local laboratory):
    a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L;
    b. Platelet count ≥100,000/mm3 (100 × 10^9/L);
    c. Hemoglobin ≥9 g/dL.
9. Serum triglyceride <300 mg/dL; serum cholesterol < 350 mg/dL.
10. Male or non-pregnant and non-breast feeding female:
    - Females of child-bearing potential must agree to use effective contraception without interruption from 28 days prior to starting IP and while on study medication and have a negative serum pregnancy test (β -hCG) result at screening and agree to ongoing pregnancy testing during the course of the study, and after the end of study treatment. A second form of birth control is required even if she has had a tubal ligation.
    - Male patients 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. A second form of birth control is required even if he has undergone a successful vasectomy.
11. Life expectancy of >3 months, as determined by the investigator.
12. Ability to understand and sign informed consent.
13. Willingness and ability to comply with scheduled visits, laboratory tests, and other study procedures.

4.3. Exclusion Criteria

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

1. Patients with lymphangioleiomyomatosis (LAM) are excluded.
2. Known active uncontrolled or symptomatic CNS metastases. A patient with controlled and asymptomatic CNS metastases may participate in this study. As such, the patient must have completed any prior treatment for CNS metastases ≥28 days (including radiotherapy and/or surgery) prior to start of treatment in this study and should not be receiving chronic corticosteroid therapy for the CNS metastases.
3. Active gastrointestinal bleeding.

4. Pre-existing thyroid abnormality is allowed provided thyroid function can be controlled with medication.
5. Uncontrolled serious medical or psychiatric illness. Patients with a “currently active” second malignancy other than non-melanoma skin cancers, carcinoma in situ of the cervix, resected incidental prostate cancer (staged pT2 with Gleason Score ≤6 and postoperative PSA <0.5 ng/mL), or other adequately treated carcinoma-in-situ are ineligible. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are free of disease for ≥1 year).
6. Liver-directed therapy within 2 months of enrollment. Prior treatment with radiotherapy (including radio-labeled spheres and/or cyberknife, hepatic arterial embolization (with or without chemotherapy) or cyrotherapy/ablation) is allowed if these therapies did not affect the areas of measurable disease being used for this protocol.
7. Recent infection requiring systemic anti-infective treatment that was completed ≤14 days prior to enrollment (with the exception of uncomplicated urinary tract infection or upper respiratory tract infection).
8. Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy.
9. Unstable coronary artery disease or myocardial infarction during preceding 6 months.
10. Receiving any concomitant antitumor therapy.
11. Patients with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension.
12. Use of strong inhibitors and inducers of CYP3A4 within the 14 days prior to receiving the first dose of ABI-009. Additionally, use of any known CYP3A4 substrates with narrow therapeutic window (such as fentanyl, alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, terfanide) within the 14 days prior to receiving the first dose of ABI-009.
13. Known Human Immunodeficiency Virus (HIV).
14. Active Hepatitis B or Hepatitis C.

5. TABLE OF EVENTS

The schedule of assessments in Table 2 outlines the specific time points for study assessments.

Table 2: Schedule of Assessments

Assessment [a]	Screening [b] (Day -14 to - 1)	Cycle 1 through Last Cycle (Treatment Period)		End of Treatment (EOT) Visit [d]	Follow-up Period [e]
		Day 1 [c]	Day 8		
General Assessments, Biomarkers, PK samples					
Informed Consent	X				
Demographics	X				
Medical History	X				
Physical Examination	X	X		X	
Vital Signs, Height and Weight	X	X [f]	X [f]	X [f]	
BSA Calculation		X [m]			
Prior/Concomitant Medication Evaluation [g]	X	X	X	Until 28 days after the last dose of IP	
Prior/Concurrent Procedures Evaluation [g]	X	X	X	Until 28 days after the last dose of IP	
ECOG PS	X	X		X	
Pregnancy Test [h]	X			X	
ECG (12 lead) [i]	X	X	X		
Survival status					X
Pre-treatment tissues (archival or fresh) (mandatory) [j]	X				
Tumor biopsy for Biomarkers [k]	X	Upon disease progression and/or end of last dose of IP			
Blood Sample for Biomarkers	X	Cycle 4/D1 and Upon disease progression and/or end of last dose of IP			
Blood Sample for Rapamycin (PK) [l]		Pre-treatment and at 0.5, 1, 2, 4 hrs post-treatment	Pre-treatment and at 0.5, 1, 2, 4 hrs post-treatment		
Adverse Events	Continuous starting from signing of Informed Consent until 28 days after last dose of IP				

Assessment [a]	Screening [b] (Day -14 to - 1)	Cycle 1 through Last Cycle (Treatment Period)		End of Treatment (EOT) Visit [d]	Follow-up Period [e]
		Day 1 [c]	Day 8		
ABI-009 Dosing		X	X		
Local Laboratory Assessments					
Clinical Chemistry Panel	X	X		X	
CBC, Differential, Platelet Count	X	X	X	X	
PT, PTT, INR	X				
Urinalysis	X				
Thyroid function	X	X			
HIV, HBV sAg, HBV cAb, HCV Ab	X				
Fasting Lipids	X	X [n]			
Imaging and Efficacy Assessments					
CT/MR [o]	X	Every 6 weeks after C1 D1 for the first year, then every 12 weeks thereafter		X	

a. Unless otherwise specified, visits must occur within ± 2 days of the planned visit date.
b. Screening evaluations to be obtained ≤14 days prior to enrollment unless specified otherwise.
c. Day 1 evaluations can be omitted if screening evaluations are performed within 72 hours of Cycle 1 Day 1.
d. End of Treatment Visit must occur at least 4 weeks (± 7 days) after the last dose of ABI-009.
e. Follow-up for survival and initiation of anticancer therapy can be performed by telephone contact every 12 weeks (+/- 3 weeks) or more frequently if needed, from EOT Visit. All patients that discontinue study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase for survival and anticancer therapy. This evaluation may be made by record review and/or telephone contact.
f. Vitals and weight only.
g. Prior: record all medications taken and procedures done ≤ 28 days prior to screening; Concomitant: any medications or procedures after the signing of informed consent.
h. For females of childbearing potential only. A serum β-hCG pregnancy test must be performed to assess patient eligibility at screening prior to first IP administration (negative results required for IP administration). Urine pregnancy test will be performed at EOT Visit (can be done locally) and as clinically indicated as per institutional guidelines.
i. ECG to be monitored at screening, Cycle 1 Day 1 and Day 8, and thereafter on Day 1 of every treatment Cycle. In each case ECG is to be monitored during infusion around the 30 min time point after start of infusion to coincide with the end of infusion period which lasts 30 minutes (+/- 10 min).
j. Ensure the surgical pathology report is submitted with tumor tissue sample (either tumor block or unstained slides [min 6]).
k. Biopsy tumor sample: formalin-fixed, paraffin-embedded (FFPE) tumor tissue or unstained slides from biopsy will be collected (tumor blocks are preferred – refer to Instruction Sheet for details). Screening tumor tissue (fresh/archival) required for biomarker analysis for all patients. On study tumor tissue collection is optional only for patients who provide additional consent.
l. PK samples to be taken only at Cycle 1 on Day 1 and Day 8 (pre-treatment and at 0.5, 1, 2, and 4 hrs (+/- 10 min) post-treatment) and in Cycle 2 Day 1, when only a pre-treatment sample is required.
m. Calculated ONLY on C1/D1; to be recalculated only if the weight changes by > 10% in subsequent cycles.
n. Every even numbered cycle starting with Cycle 2, eg C2, C4, C6, etc.

o. Screening CT/MRI scans must be performed within 28 days prior to study day 1, preferably as close to the day of enrollment as possible. Tumor evaluation by contrast-enhanced CT or MRI of the chest, abdomen, and pelvis will be performed during screening; every 6 weeks (± 3 days after C1D1 for the first year then every 12 weeks (± 7 days) thereafter until disease progression. EOT visit CT/MRI should be performed only for those patients that discontinue treatment for a reason other than disease progression per RECIST 1.1. If an initial observation of objective response (CR or PR) is made, a confirmation scan should be done at 6 weeks after initial observation.

6. PROCEDURES

6.1. Screening Evaluations

This study will be conducted at approximately 10 sites in the US. Additional sites may be added.

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, including if a patient is rescreened.

Before patients may be entered into the study, the Sponsor requires a copy of the site's written IRB/IEC approval of the protocol, informed consent form, and all other patient information and/or recruitment material, if applicable. A signed and dated Institutional Review Board (IRB) 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 are signed the informed consent. The patients' tumor samples will be tested to confirm diagnosis and for biomarker analyses after informed consent form has been signed.

Screening evaluations will be performed for all patients to determine study eligibility. These evaluations must be obtained ≤14 days prior to enrollment. Any questions regarding patient eligibility should be directed to AADi or other sponsor-nominated representatives or designees for approval.

The following procedures are to be completed during the screening period, after signed informed consent has been obtained, designated in the Schedule of Assessments, Table 2.

- Demographics (if allowed by local regulations, date of birth, sex, race, and ethnicity)
- Physical examination as per standard of care (including physical exam, medical/cancer history, ECOG performance status assessment, height, weight)
- Prior/concomitant medication evaluation: all medications taken ≤28 days prior to screening
- Prior/concurrent procedures evaluation: all procedures done ≤28 days prior to screening

- Vital signs (eg, blood pressure, pulse, respiration rate, temperature)
- ECG
- Informed consent signed to collect for pre-treatment tumor sample (archived or fresh) along with pathology report for diagnosis confirmation and biomarker study for all patients
- Adverse event assessment
- Local Laboratory Assessments: chemistry, complete blood count (CBC), differential, platelet count, coagulation, urinalysis, thyroid function, pregnancy test (women of child-bearing potential, includes tubal ligations), HIV, hepatitis B surface antigen, hepatitis C antibody, fasting lipids
- Urinalysis (a urine dipstick may be used)
- CT or MRI, must be performed within 4 weeks prior to study day 1, preferably as close to the day of enrollment as possible

A patient is considered 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 14 days of study day 1, unless specified otherwise in the study procedures listed in Section 5. Once eligibility is confirmed, a site representative will complete and fax a patient eligibility criteria worksheet/tumor biopsy reference form to an AADi representative. The AADi representative will acknowledge receipt of the paperwork and confirm enrollment for that individual patient.

6.2. Treatment Period

A patient is considered enrolled on study day 1 when the IP, ABI-009, is first administered. ABI-009 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 therapy until disease progression or unacceptable adverse events.

6.2.1. Day 1 Assessment

The following assessments will be performed on Day 1 of each cycle, unless otherwise specified:

- Physical examination
- Weight assessment
- BSA calculation (Calculated ONLY on C1/D1; to be recalculated only if the weight changes by > 10% in subsequent cycles
- Concomitant medication and procedures evaluation
- Vital signs (temperature, systolic and diastolic blood pressure, and pulse)
- ECOG performance status

- ECG (12-lead ECG is to be conducted during infusion around the 30 min time point after start of infusion to coincide with the end of infusion period which lasts 30 minutes [+/- 10 min]). Day 1 ECG is conducted for every cycle.
- Clinical chemistry panel (including but not limited to sodium, potassium, chloride, glucose, alkaline phosphatase (ALP), AST/SGOT, ALT/SGPT, serum albumin)
- CBC, differential and platelet count
- Thyroid function
- Fasting lipids (every even numbered cycles starting with Cycle 2)
- Adverse Event assessment
- Pharmacokinetics assessment (only on Cycle 1 Day 1 at pre-treatment and at 0.5, 1, 2, 4 hrs post-treatment and Cycle 2 Day 1 at pre-treatment only)

Day 1 evaluations for Cycle 1 may be omitted if screening evaluations are performed within 72 hours of Cycle 1 Day 1. Laboratory assessments: chemistry, hematology, coagulation, urinalysis, pregnancy test (women of child-bearing potential, includes tubal ligation) (see Table 3 for analyte listing).

6.2.2. Day 8 Assessment

The following assessments will be performed on Day 8 of each cycle, unless otherwise specified:

- Concomitant medication and procedures evaluation
- Vital signs
- CBC, differential and platelet count
- Adverse Event assessment
- Pharmacokinetics assessment (only on Cycle 1 Day 8 pre-treatment and at 0.5, 1, 2, 4 hrs post-treatment)
- ECG (12-lead ECG is to be conducted during infusion around the 30 min time point after start of infusion to coincide with the end of infusion period which lasts 30 minutes [+/- 10 min]). Day 8 ECG is conducted only on Cycle 1.

6.2.3. Response Assessment

Tumor response will be assessed by CT or MRI scan of the chest, abdomen, and pelvis; image preparation and evaluation will follow the specifications provided in the RECIST version 1.1. The same modality (CT or MRI) must be used at screening and throughout the study.

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

- ≤4 weeks prior to C1D1 (screening)

- followed by every 6 weeks after C1D1 for the first 1 year (± 3 days)
- followed by every 12 weeks (± 7 days) thereafter until disease progression. End of Treatment Visit CT/MRI should be performed only for those patients that discontinue treatment for a reason other than disease progression.

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

At the time of disease progression, if a biopsy is performed, a tumor sample will be collected and sent to the central laboratory, if available. Ensure that the surgical pathology report is submitted with the tumor tissue sample. Refer to the Instruction Sheet for tissue handling instructions for processing and shipping details.

Table 3: Analyte Listing

Chemistry	Hematology	Coagulation	Urinalysis	Other Labs
Sodium	WBC	PT	Specific gravity	Pregnancy test
Potassium	RBC	PTT	pH	ABI-009 PK (central)
Bicarbonate	Hemoglobin	INR	Blood	TSH, T3, T4
Chloride	Hematocrit		Protein	HIV
Total protein	MCV		Glucose	HBV sAg
Albumin	MCH		Ketones	HBV cAb
Calcium	MCHC		Microscopic	HCV Ab
Magnesium	RDW			Total Cholestrol
Phosphorus	Platelets			HDL
Glucose	Differential:			LDL
BUN	-Neutrophils			Triglyceride
Creatinine	-Lymphocytes			Biomarker development (central)
Total bilirubin	-Monocytes			
Alkaline phosphatase	-Eosinophils			
AST (SGOT)	-Basophils			
ALT (SGPT)				
Amylase				
Lipase				

6.3. End of Treatment Visit Assessment

Patient participation is complete after the EOT Visit. The EOT Visit is a safety follow-up visit that is to be performed at least 4 weeks (+ 7 days) after the last dose of ABI-009. All efforts should be made to conduct this visit. If it is not possible to conduct the EOT Visit, documentation of efforts to complete the visit should be provided.

The following procedures will be completed at the EOT Visit as designated in the Schedule of Assessments (Section 5):

- Physical examination (including physical exam, ECOG Performance Status assessment, weight)
- Vital signs (eg, blood pressure, pulse, respiration rate, temperature)
- Laboratory assessments: chemistry, CBC, differential, platelet count, pregnancy test (women of child-bearing potential, includes tubal ligations)
- Imaging Assessment: CT/MRI is to be performed at the end of study visit only for those patients that discontinue treatment for a reason other than disease progression per RECIST v1.1

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

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

6.5. Pharmacokinetic Study

A PK study of rapamycin will be performed with limited PK sampling on all patients in this phase 2 study. Blood samples will be obtained during Cycle 1 Day 1 (C1D1) immediately predose (before infusion), 0.5 hr (immediately before termination of infusion), 1 hr, 2 hrs, and 4 hrs; during Cycle 1 Day 8 (C1D8) immediately predose (before infusion), 0.5 hr (immediately before termination of infusion), 1 hr, 2 hrs, and 4 hrs, and on Cycle 2 Day 1 (C2D1) immediately predose (before infusion). All samples should be collected within a window of +/- 10 minutes. Note that T = 0 is defined as the start of infusion, ie, all sample collection times are relative to the start of infusion. The sample at the end of the infusion (0.5 hour) is collected immediately before the infusion is stopped. If the duration of infusion is changed, the sample should be collected immediately before termination of the infusion.

Whole-blood samples will be collected in EDTA tubes for determination of rapamycin in a central laboratory.

Time Recording:

- The exact clock time for the start and end of infusion must be recorded.
- The exact clock time of each collection must be recorded.

6.6. Biomarker Development

The key objective of the tumor molecular profiling is to identify specific markers that are predictive of response to ABI-009. The key objective of the biomarker blood sampling is to investigate whether blood sampling can serve as a “liquid biopsy” to monitor disease progression.

- **Blood samples** will be obtained for cell-free plasma DNA collection (pretreatment, Cycle 4/Day 1, and post-treatment) for all patients:
  - **Molecular analysis of cell-free plasma DNA assay** using next-generation sequencing to assess the prevalence of mutations identified in the primary tumor sample over time as a measure of response to therapy.
- **Tumor biopsy mutation analysis to assess resistance mechanisms.** Pre-treatment tumors (archival or fresh tissue biopsies) are required for all patients on this study to confirm diagnosis. This sample will also be used for baseline mutational analysis. In addition, an optional tumor biopsy will be collected for patients who provide additional consent at the end of treatment and/or if a patient experiences progression while on study.

Tumor biopsies are to be collected and pharmacodynamic changes analyzed to determine the effect of the drug on target(s) in the tumor as well as to potentially analyze molecular mechanisms associated with acquired resistance.

- **Exome sequencing** using the Oncopanel test (BWH Pathology Department, CLIA certified) of approximately 300 genes will be performed to assess mutations in all the known mTOR pathway genes, including but not limited to PIK3CA, TSC1, TSC2, AKT, PTEN, MTOR, and RHEB. Rationale: TSC1 and TSC2 mutations are known to occur at high frequency in PEComa.
  - Evaluate correlation to clinical response to the therapy.
  - Test the correlation between biopsy and circulating DNA.
- FISH (fluorescence in-situ hybridization) analysis of translocations in TFE3. TFE3 translocations are known to occur at low frequency in PEComa. These studies will be performed centrally in a laboratory that is CLIA certified.
- **Immunohistochemistry** on relevant pathway markers, including but not limited to:
  - phosphoproteins p-AKT, p-S6, p-4EBP1, SPARC
  - proliferation marker, such as Ki-67
  - apoptosis marker, such as PARP
    - Post-treatment (progression) samples will be analyzed by similar exome sequencing as above, to search for causes of resistance, including secondary mutations and genomic amplification or deletion events.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. ABI-009 Dosage, Administration, and Schedule

Treatment cycles are 21 days in duration and patients are treated until disease progression or unacceptable toxicities. Patients will receive ABI-009 100 mg/m^2 (IV infusion over 30 minutes, +/- 10 min) weekly for 2 weeks followed by a week of rest (2/3 weekly schedule). The schedule 2 weeks out of a 3 weekly schedule will allow the patient to have 1 week rest, when most of the toxicities occur, based on experience in the phase 1 study of ABI-009 (Protocol CA401) [38]. In terms of dose intensity within 6 months (24 weeks), the 2 out of 3 weekly schedule will consist of 16 administrations compared to 18 administrations with the prior 3 out of 4 weekly schedule. This reflects a global dose intensity reduction of 11% when comparing the 2 schedules. Two dose reduction levels are allowed: 75 mg/m^2 and 56 mg/m^2. A physician must be available at the time of administration of IP on dosing days that correspond to study visits. Supportive care per the institution's normal standard of care including concomitant medications can be provided at the investigator's discretion.

7.2. Dose Modification and Stopping Rules

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

If, treatment cannot be administered on the planned visit date, ABI-009 may be administered +/- 2 days from the scheduled date. Prior to ABI-009 administration on Day 1 of each cycle, patients must meet the following hematological requirements:

- ANC ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Hemoglobin ≥9 g/dL

The treatment will be on hold up to 14 days until the patient has fulfilled these criteria.

Day 1 Dose Missed

If the dose held or missed was to be given on Day 1 of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the patient (ie, D1-D8-Rest, X-D1-D8-Rest, etc).

Day 8 Dose Is Missed

That week becomes the week of rest. Next dose (if counts and chemistries permit) becomes Day 1 of a new cycle (ie, D1-D8-Rest, D1-X, D1-D8-Rest, etc).

The maximum delay between a missed scheduled dose and the next one (whichever dose was missed) should not be longer than 14 days. Approval from the Medical Monitor is required to restart study treatment after ≥21 days of interruption.

Doses will be reduced for hematologic and other toxicities. Two levels of dose modifications are permitted according to the criteria below. Dose reductions will occur

sequentially (75 mg/m^2 and 56 mg/m^2), there should be no direct reduction by two dose levels. If a toxicity requiring dose modification occurs following the second dose reduction of ABI-009, further treatment should be discontinued. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI CTCAE Version 4.03.

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

- General guidelines for clinically significant toxicities related to study treatment

And

- Specific guidelines for adverse events of special interest, which are events that have been observed with higher frequency or severity.

In the event of clinically significant AE in any part of the study, treatment may be withheld and supportive therapy administered as clinically indicated. If the toxicity or event is not grade 3/4 and resolves to baseline or grade 1 in less than or equal to 14 days of stopping therapy, then treatment may be restarted. Dose reduction of ABI-009 should be considered as clinically indicated.

If the toxicity does not resolve to at least grade 1 in less than 14 days, withdrawal from treatment with the IP is recommended. However, if the investigator and AADi Medical Monitor agree that further treatment would benefit the patient, treatment can continue with at least one dose level dose reduction, per Table 4.

Table 4: Dose Level Reduction Guidelines

Dose level	ABI-009 Dose/Schedule
0	Initial Dose: 100 mg/m^2
-1 (first dose reduction)	25% reduction of initial dose of 100: 75 mg/m^2
-2 (second dose reduction)	25% reduction from 75 mg/m^2: 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.

Any patient meeting the criteria for Hy's Law case (i.e. severe drug-induced liver injury) will be considered a dose-limiting toxicity. A Hy's Law case is defined as: AST or ALT values of ≥ 3 x ULN AND with serum total bilirubin level (TBL) of > 2 x ULN without signs of cholestasis and with no other clear alternative reason to explain the observed liver-related laboratory abnormalities.

ABI-009 dose modification guidelines are outlined in Table 4 and Table 5: for clinically significant toxicities that are deemed related. The dosing schedule is described in the Schedule of Assessments, Table 2.

Table 5: Dose Modification Algorithms for Adverse Events Possibly Related to ABI-009

System/Organ	Adverse Event	CTCAE Grade v4.03	Dose modification Algorithm
Mucosa	Stomatitis, mucosal inflammation	Grade 2	Hold ABI-009 until resolution to Grade 1 or baseline and restart at the same dose for 1st occurrence; for subsequent occurrences, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
		Grade ≥3	Hold ABI-009 until resolution to Grade 1 or baseline and restart at the same dose for 1st occurrence for subsequent occurrences, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
Skin and Subcutaneous Tissue Disorders	Skin rash	Grade 2	Tolerable: Continue ABI 009 at full dose, monitor as clinically indicated
			Intolerable: Hold ABI-009 until resolution to Grade 1 or baseline and restart at the same dose for 1st occurrence; for subsequent occurrences, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
		Grade ≥3	Hold ABI-009 until resolution to Grade 1 or baseline; for subsequent events, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
Gastrointestinal Disorders	Diarrhea despite optimal medication	Grade 2	Hold ABI-009 until resolution to Grade 1 or baseline and restart at the same dose for 1st occurrences; for 2nd and subsequent events, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
		Grade ≥3	Hold ABI-009 until resolution to Grade 1 or baseline; for subsequent events, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
Metabolic disorders	Hyperlipemia (cholesterol, triglycerides)	Grade 3	If this is persistent for 2 months, reduce by 1 dose level at start of next cycle

		Grade 4	If this is persistent for 1 month, reduce by 1 dose level at start of next cycle
	Hyperglycemia	Grades 1 and 2	Start at home 2x/day glucose monitoring; initiate medical management
		Grade 3	Initiate medical management ; If recurrent post ABI-009 despite adequate medical management, reduce by 1 dose level
		Grade 4	Initiate medical management, hold ABI-009 until grade 2 or less, restart 1 dose level lower
Hematologic toxicity	Thrombocytopenia, Neutropenia, Anemia	Grade 2	ABI-009 can resume once meeting the following hematological requirements: ANC > 1.5 x 10^9/L, platelets > 100 x 10^9/L and hemoglobin ≥9 g/dL
		Grade ≥3	Hold ABI-009 immediately for the remainder of that cycle. Repeat blood collection within 3 days. ABI-009 can resume once meeting following requirements: absolute ANC >1.5 x 10^9/L, platelet count > 100 x 10^9/L and hemoglobin ≥9 g/dL. For 2nd and subsequent events, drug will be restarted at a reduced dose; G-CSF may be given as deemed indicated.
Respiratory events	Pneumonitis, bronchiolitis obliterans, and/or organizing pneumonia	Grade 2	Hold ABI-009 immediately for up to 3 weeks until resolved to ≤ grade 1, then reduce by 1 dose level. If it is still a Grade 2 after 3 weeks, discontinue treatment. If > Grade 2 recurs after resuming ABI-009 at a reduced dose level, discontinue treatment
		Grade ≥3	Permanently remove patient from protocol treatment

7.2.2. Hepatotoxicity Stopping Rules

Patients with abnormal hepatic laboratory values (ie, ALP, AST, ALT, total bilirubin TBL) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis may meet the criteria for withholding or permanent discontinuation of ABI-009 as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

7.2.2.1. Criteria for Permanent Discontinuation of ABI-009 Due to Potential Hepatotoxicity

ABI-009 should be discontinued permanently and the patient should be followed for possible drug-induced liver injury (DILI), if **ALL** of the criteria below are met:

- TBL > 2x upper limit of normal (ULN) or INR > 1.5x
- AND increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT elevation
< ULN	≥ 3x ULN

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

7.2.2.2. Criteria for Conditional Withholding of ABI-009 Due to Potential Hepatotoxicity

For patients who do not meet the criteria for permanent discontinuation of ABI-009 and have no underlying liver disease, and eligibility criteria requiring normal transaminases and TBL at baseline or patients with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of ABI-009:

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

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

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

ABI-009 should be withheld pending investigation into alternative causes of DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, and ALP) and/or elevated TBL is discovered and the laboratory abnormalities resolve to normal or baseline.

7.2.2.3. Criteria for Rechallenge with ABI-009 After Potential Hepatotoxicity

The decision to rechallenge the patient should be discussed and agreed upon unanimously by the patient, investigator, and AADi medical monitor.

If signs or symptoms recur with rechallenge, then ABI-009 should be permanently discontinued. Patients who clearly meet the criteria for permanent discontinuation (as described in Section 7.2.1) should never be rechallenged.

7.2.3. Overdose

On a per dose basis, an overdose is defined as 10% over the protocol-specified dose of ABI-009 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.

8. STUDY DRUG MANAGEMENT

8.1. Description of ABI-009

8.1.1. ABI-009 Packaging, Labeling, and Storage

ABI-009 will be supplied by the Sponsor in single-use vials as lyophilized product. Each single-use 50-mL vial will contain 100 mg rapamycin and approximately 800 mg of human albumin as a stabilizer. Each vial will be labeled according to country-specific regulatory requirements for labeling of IPs.

Unopened vials of ABI-009 should be stored in a refrigerator (2°-8°C; 36°-46°F) in original cartons to protect from light. Reconstituted ABI-009 may be stored for up to 4 hours at 2-8°C (36°- 46°F), followed by 4 hours at room temperature (<25°C) in the IV bag. Both unopened vials of ABI-009 and reconstituted ABI-009 should be stored in an area free of environmental extremes and must be accessible only to study personnel.

Temperature records for ABI-009 must be made available to AADi or Sponsor nominated Contract Research Organization monitoring teams for verification of proper study drug storage.

8.2. ABI-009 Accountability, Disposal, and Compliance

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

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

Accurate recording of all ABI-009 administration will be made in the appropriate section of the patient's eCRF and source documents. The investigator or designee is responsible for accounting for all study-specific IP either administered or in their custody during the course of the study.

8.3. ABI-009 Reconstitution

NOTE: It is not a requirement to use filter needles in the preparation, or in-line filters during the administration of ABI-009. In any event, filters of pore size less than 15 microns (15 µm) must not be used.

ABI-009 will be reconstituted by appropriate study personnel and administered to the patient in the study site (see below). The Investigator will calculate the BSA of the patient in order to determine the total amount of ABI-009 to be administered.

Reconstitution and Use of ABI-009:

1. Calculate the patient's BSA according to standard institutional methods. BSA will be calculated at baseline and recalculated if the weight changes by >10%.

   Calculate the total dose (in mg) to be administered by:

   Total Dose (mg) = BSA × (study dose mg/m^2)

2. Calculate the total number of vials required by:

   $$\text{Total Number of Vials} = \frac{\text{Total dose (mg)}}{\text{100 (mg/vial)}}$$

   Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (e.g., if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).

3. Using sterile technique, prepare the vials for reconstitution.
4. Swab the rubber stoppers with alcohol.
5. Reconstitute each ABI-009 vial by using a 50-cc or 60-cc sterile syringe to inject 20 mL of 0.9% Sodium Chloride Injection into each vial over a period of not less than 1 minute (Note: Change the syringes after reconstituting every 3 vials).
   - Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection.
   - **Slowly** inject the 20 mL of 0.9% Sodium Chloride Injection over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the **INSIDE WALL OF THE VIAL.**
   - **DO NOT INJECT** the 0.9% Sodium Chloride Injection directly onto the lyophilized cake as this will result in foaming.
   - Once the injection is complete, allow the vial to sit for a **minimum of 5 minutes** to ensure proper wetting of the lyophilized cake/powder.
   - **Gently** swirl and/or invert the vial **slowly** for at least **2 minutes** until complete dissolution of any cake/powder occurs. **Avoid** generation of foam.
   - If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.
   - Each mL of reconstituted product will contain 5 mg of rapamycin.
6. Calculate the exact total dosing volume (to the nearest mL) of 5 mg/mL suspension required for the patient:

   Dosing volume (mL) = Total dose (mg)/5 (mg/mL)

7. The reconstituted sample should be translucent and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be **gently** inverted again to ensure complete resuspension, prior to use.
8. Using a new, sterile 50-cc or 60-cc syringe, withdraw the reconstituted ABI-009 solution. Do not remove the rubber stopper from the ABI-009 vials as this can compromise the sterility of the drug preparation.
9. Inject the calculated dosing volume of reconstituted ABI-009 suspension into an empty sterile, standard PVC or non-PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag. Repeat steps 9 and 10 until the patient's entire required dose is injected into the IV bag.
10. Remove the injection port.
11. Once the exact volume of reconstituted ABI-009 has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures for cytotoxic drugs.
12. Administer the calculated dosing volume of reconstituted ABI-009 suspension by IV infusion over 30 minutes (+/- 10 min). The use of in-line filters is not necessary; if used, in-line filters with pore sizes of < 15 microns (15 µm) should not be used. Upon completion of infusion, the infusion catheter should be flushed with ~2 mL normal saline to ensure all drug has been infused.
13. Reconstituted ABI-009 suspension in IV bag should be used immediately, but may be stored for up to 4 hours at 2-8°C (36°- 46°F), followed by 4 hours at room temperature (<25°C).

8.4. Receipt and Return of ABI-009

Upon receipt of the study drug supplies, the Investigator or designee will conduct an inventory and sign both copies of the study drug receipt and forward one copy to the address indicated on the form. One copy of the receipt and the packing slip must be retained in the Investigator's regulatory file records.

A representative from AADi or his/her designee will inspect the study drug inventory, Drug Accountability Record form(s), and will arrange for the disposition of any remaining unused study drug. No study drug may be returned to AADi without the representative from AADi or other AADi-designated personnel first inspecting the study drug inventory and accountability documentation.

9. 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 9.2.

Concomitant therapies are to be collected from enrollment/randomization 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).

9.1. Permitted Medications and Procedures

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

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

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.

9.2. Prohibited Medications and Procedures

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

The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on treatment in this study.
- 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.
- Rapamycin is metabolized primarily by CYP3A4. Drugs that are strong inhibitors or inducers of CYP3A4 may only be used under special circumstances (eg, as a single use for a procedure) while treatment with study drug is interrupted. The list may be modified based on emerging data.

- Use of any known CYP3A4 substrates with narrow therapeutic window (such as fentanyl, alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, terfanide) within the 14 days prior to receiving the first dose of ABI-009. Other medications may be allowed if there is agreement between the sponsor and investigator
- Use of strong inhibitors and inducers of CYP3A4 within the 14 days prior to receiving the first dose of ABI-009

10. STATISTICAL CONSIDERATIONS

10.1. Study Endpoints, Analysis Sets, and Covariates

10.1.1. Study Endpoints

Primary Endpoint:

- Objective Response Rate evaluated by independent review assessment

Secondary Endpoint(s):

- Duration of response
- Progression-free survival rate at 6 months
- Progression-free survival
- Overall survival
- Incidence and grade of treatment-emergent AEs

Note: Analysis of secondary efficacy endpoints DOR, PFS rate at 6 months, median PFS, and median OS will be done separately for 2 subgroups of patients: 1) those with metastatic disease; and 2) those with locally advanced disease for which surgery is not an option. Patients in the locally advanced tumor subgroup may receive surgery if there is sufficient tumor shrinkage, which could introduce a bias in the assessment of the DOR, PFS rate at 6 months, median PFS, and OS. Safety will be analyzed in both patient groups together.

Exploratory Endpoint(s):

- Investigator assessed ORR
- Pharmacokinetic/pharmacodynamic relationships for safety and/or efficacy endpoints
- ABI-009 pharmacokinetic parameters including, but not limited to, maximum observed concentration (C_{max}) of rapamycin, minimum observed concentration (C_{min}), and area under the plasma concentration-time curve (AUC)
- Presence/level of expression of several tumor biomarkers and their relationship to clinical responsiveness

10.1.2. Analysis Sets

Efficacy Analysis Set

The Efficacy Analysis Dataset includes all enrolled patients with measurable tumor per RECIST v1.1 at baseline who receive at least one dose of ABI-009, and have a confirmed diagnosis of PEComa. The primary analysis of all efficacy endpoints will be performed on the Efficacy Analysis Dataset.

Full Analysis Set (Treated Population)

The Full Analysis Set includes all enrolled patients who receive at least one dose of ABI-009. All efficacy analyses will be repeated using the Full Analysis Data Set as sensitivity analyses. Analyses of safety endpoints will be performed on the Full Analysis set.

Per-protocol Analysis Set

The Per-protocol Analysis Set includes all enrolled patients who do not have any prospectively defined protocol violation. A sensitivity analysis of the primary and secondary efficacy endpoints may be performed on the PP Analysis Set.

The relationship of the following covariates to efficacy endpoints will be explored if appropriate.

10.1.3. Covariates and Subgroups

Two groups of patients will be studied, those with metastatic disease and those with locally advanced disease for which surgery is not an option. The 2 subgroups of patients will be assessed together for the primary endpoint, ORR. However, because some of the patients in the locally advanced tumor subgroup may be clinically indicated to have surgery if there is sufficient tumor shrinkage, which would introduce a bias, the 2 groups will be analyzed separately for secondary endpoints, DOR, PFS rate at 6 months, PFS, and OS.

In addition the following covariates may be used to examine efficacy and/or safety in subgroup or covariate analyses, if sufficient number of patients are enrolled in the subgroups:

- Gender (male and female)
- Age at enrollment (<65 vs ≥65 and <75 vs ≥75 years)
- ECOG Performance Status at baseline (0 vs 1)
- Time from initial diagnosis to enrollment

10.2. Sample Size Considerations

Sample size estimation is based on the primary efficacy endpoint, confirmed ORR: proportion of patients who achieve an objective response.

A sample size of 30 patients will result in the half width of the 95% CI for the estimated ORR of no more than 18.7%. Assuming an observed ORR of 30%, the lower bound of the 95% CI for the estimated ORR will exclude values less than 14.7%.

10.3. Data Monitoring Committee (DMC)

An external DMC will assess safety approximately when a third of patients are enrolled and have completed at least 2 cycles. On the basis of their review the DMC will make recommendations to AADi regarding the continuation of the study. The DMC will consist of at least 2 clinicians with relevant specialties and one statistician. Details regarding the responsibilities of the DMC will be outlined in the DMC charter.

10.4. Primary Analysis

The objective of the primary analysis is to address all study objectives and it will be conducted when all patients have had the opportunity to be treated for at least 6 months. All primary, secondary, and exploratory efficacy and safety analyses will be conducted at the time of the primary analysis, with the exception of the biomarkers which may be analyzed at a later date.

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

10.5. Planned Methods of Analysis

10.5.1. General Considerations

A clinical study report will be generated for the primary analysis. The study report will be updated once the last data point is collected from the last patient that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol.

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

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

Point estimates for efficacy endpoint incidences will be accompanied by a 2-sided 95% exact binomial CI [69].

Time to event endpoints will be summarized descriptively using the KM method [70]. KM quartiles (when estimable) along with the 95% 2-sided CIs [71], the number of patients censored and the number of events will be provided. Kaplan Meier estimates will also be presented graphically.

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

10.5.2. Primary Efficacy Endpoint

The primary endpoint, ORR, will be determined by independent radiologist(s). The independent radiologic review will follow a separate imaging charter.

The primary analysis will evaluate the independently assessed ORR in patients treated with ABI-009 by providing the number and proportion of patients achieving OR along with an exact binomial 95% CI for the proportion.

Overall response rate is defined as the proportion of patients who achieve a confirmed PR or CR per RECIST 1.1. Patients without a post-baseline disease assessment will be considered not to have achieved a response. If an initial observation of objective response (CR or PR) is made, a confirmation scan should be done at 6 weeks after initial observation.

The analysis of ORR will be conducted on the Efficacy Analysis Dataset. A sensitivity analysis will also be conducted using the Full Analysis Dataset. Analysis of ORR will include both subgroups of patients: 1) those with metastatic disease and 2) those with unresectable locally advanced disease or resectable with multiple resections.

10.5.3. Secondary Efficacy Endpoints

Analysis of secondary efficacy endpoints DOR, PFS rate at 6 months, median PFS, and median OS will be done separately for the 2 subgroups of: 1) those with metastatic disease; and 2) those with locally advanced disease for which surgery is not an option.

The analysis of the DOR will be conducted on the Efficacy Analysis Dataset. A sensitivity analysis will also be conducted using the Full Analysis Dataset. For patients with metastatic disease the duration of response will be estimated by the KM method. The number of patients in the second subgroup: those with locally advanced disease, is expected to be small. The DOR for these patients will be summarized descriptively by case reports.

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 v 1.1 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 PFS rate at 6 months, PFS and OS will be conducted on the Efficacy Analysis Dataset. A sensitivity analysis will also be conducted using the Full Analysis Dataset. PFS rate at 6 months, median PFS, and OS for patients with metastatic disease will be summarized using KM methods.

The number of patients in the second subgroup: those with locally advanced disease, is expected to be small. The PFS rate at 6 months, PFS and OS for these patients will be summarized descriptively by case reports.

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.

10.5.4. Safety Endpoints

Safety (incidence and severity of adverse events and significant laboratory abnormalities) is a secondary endpoint. Safety analysis will be performed on all patients in the Full Analysis Set.

Patient incidence of all treatment-emergent AEs will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, treatment-related AEs, and adverse events leading to withdrawal from investigation product will

also be provided. The MedDRA will be used to code adverse events and the NCI CTCAE version 4.03 will be used to grade severity of adverse events and laboratory toxicities.

For ABI-009 exposure, summary statistic will be provided for total number of doses, average dose administered, and duration of treatment.

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

The ECG measurements from this study will be performed as per standard of care for routine safety monitoring.

10.6. Pharmacokinetic Analysis

Pharmacokinetic analysis will include all patients who received ABI-009. Pharmacokinetic analysis including but not limited to C_{max}, AUC, V_d and Half-life will be performed at Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 2 Day 1 on total rapamycin in all patients who received ABI-009 as described in Section 6.5.

11. MONITORING, RECORDING AND REPORTING OF ADVERSE EVENTS

11.1. Toxicities of ABI-009

ABI-009 is a formulation of rapamycin. No unexpected toxicities not already known for rapamycin (Rapamune®) or the rapamycin prodrug, temsirolimus (Torisel®), were identified in the nonclinical toxicity studies, or observed in the phase 1 studies for ABI-009.

More details on the known precautions, warnings, and AEs of rapamycin and rapalogs are found in the Rapamune® and Torisel® Package Inserts [52, 53].

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a patient during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the patient's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome. **Note:** Disease progression and death due will not be recorded as an AE.

Abuse, withdrawal, sensitivity or toxicity to the IP should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the appropriate CRF, see Section 7.2.3 for the definition of overdose. Any sequela of an accidental or intentional overdose of the IP should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

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.

All AEs will be recorded by the investigator from the time the patient signs informed consent until 28 days after the last dose of ABI-009 and those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. AEs and SAEs will be recorded on the AE page of the eCRF and in the patient's source documents. All SAEs must be reported to AADi Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

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 observed by the investigator or reported by the patient that occur after the first

dose of IP through the EOT Visit are reported using the applicable eCRF (eg, Adverse Event Summary CRF).

11.2. Evaluation of Adverse Events

The investigator must assign the following AE attributes:

- AE diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- Dates of onset and resolution (if resolved)
- Severity [and/or toxicity per protocol]
- Assessment of relatedness to the IP
- Assessment of relatedness to protocol-required procedures
- Action taken

The AE toxicity grading scale used will be the NCI CTCAE Version 4.03.

11.3. Serious Adverse Events

11.3.1. Definition of Serious Adverse Events

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

- fatal
- life-threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An AE would meet the criterion of “requires hospitalization”, if the event necessitated an in-patient admission to a health care facility (eg, overnight stay).

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.

Since the criteria for the CTCAE grading scale differs from the regulatory criteria for 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 also report these abnormalities as SAEs. For any AE that applies to this situation, comprehensive documentation of the event’s severity status must be recorded in the patient’s medical record.

11.3.2. Reporting Procedures for Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to AADi Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time of signing of the informed consent form to 28 days after the last dose of IP), and those made known to the investigator at any time thereafter that are suspected of being related to IP.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a patient died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to AADi Drug Safety as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to AADi Drug Safety.

Where required by local legislation, the investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The investigator must keep copies of all SAE information on file including correspondence with AADi and the IRB/EC.

11.4. Pregnancy and Breast Feeding Reporting

If a pregnancy occurs in a female patient, or female partner of a male patient, while the patient is taking protocol-required therapies report the pregnancy to AADi as specified below. In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur up to 3 months after the last dose of protocol-required therapies.

The investigator will follow the female patient until completion of the pregnancy, and must notify AADi Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form. If a lactation case occurs while the female patient is taking protocol-required therapies, report the lactation case to AADi as specified below. In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur up to 1 week after the last dose of protocol-required therapies.

12. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

12.1. Discontinuation from Investigational Product

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

- AE(s) (that are intolerable)
- Disease progression
- Physician decision
- Withdrawal of consent (from treatment only)
- Death
- Lost to follow up
- Protocol violation
- Other (to be specified on the eCRF)

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

12.2. Discontinuation from the Study

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

- Withdrawal of consent
- Death
- Lost to follow up
- Protocol violation
- 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.

12.3. Investigator or Sponsor Decision to Withdraw or Terminate Patient's Participation Prior to Study Completion

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

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

13. REGULATORY OBLIGATIONS

13.1. Informed Consent

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

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

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

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

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

13.2. Institutional Review Board/Independent Ethics Committee

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

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

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

13.3. Patient Confidentiality

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

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

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

13.4. 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.

13.5. 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.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

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

14.2. 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.

14.3. 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 2), the investigator can search publically available records (where permitted) to ascertain survival status.

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

14.4. Sample Storage and Destruction

Any blood, tumor, biomarker or pharmacokinetic sample collected according to the Schedule of Assessments (Table 2) 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 ABI-009*,* 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 the sponsor 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.

The sponsor 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, the sponsor 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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. 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, fax, or telephone. During monitoring visits, the facilities, IP storage area, eCRFs, patient's source documents, and all other study documentation will be inspected/reviewed by the AADi representative in accordance with the Study Monitoring Plan.

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

15.2. Audits and Inspections

In accordance with ICH GCP and the sponsor'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.

16. 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. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

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