A phase 1/2 investigation of safety/efficacy of nivolumab (Opdivo®) and ABI-009 (*nab*-rapamycin) in patients with advanced Ewing's sarcoma, PEComa, epithelioid sarcoma, desmoid tumor, chordoma, non-small cell lung cancer, small cell lung cancer, urethelial carcinoma, melanoma, renal cell carcinoma, squamous cell carcinoma of head and neck, hepatocellular carcinoma, classical Hodgkin's lymphoma, MSI-H/dMMR metastatic colorectal cancer, and tumors with genetic mutations sensitive to mTOR inhibitors

INVESTIGATIONAL PRODUCT (IP):	**ABI-009; Nivolumab (Opdivo ®)**
PROTOCOL NUMBER:	**SOC-1701**
Version History:	**Vs 6.0**
Date:	**September 26, 2019**
IND NUMBER:	**135985**
Cross Reference AADi IND NUMBER:	**125,669**
SPONSORS NAME/ ADDRESS:	**Sarcoma Oncology Research Center** **2811 Wilshire Blvd., Suite 414** **Santa Monica CA 90403**
Collaborator:	**AADi Bioscience, Inc** **1343 Luna Vista Dr** **Pacific Palisades, CA 90272**

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mm yyyy**
Erlinda M. Gordon, MD	
Printed Name of Site Principal Investigator	
Institution Name: Sarcoma Oncology Research Center	
By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from AADi representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

Co-Investigators: Doris Quon, MD
Steven Wong, MD
Ania Moradkhani, NP

Study Coordinators: Victoria Chua-Alcala, Katherine Kim

Sarcoma Oncology Research Center
2811 Wilshire Blvd., Suite 414
Santa Monica CA 90403

PROTOCOL SYNOPSIS

Study Title

A phase 1/2 investigation of safety/efficacy of nivolumab (Opdivo®) and ABI-009 (*nab*-rapamycin) in patients with advanced Ewing's sarcoma, PEComa, epithelioid sarcoma, desmoid tumor, chordoma, non-small cell lung cancer, small cell lung cancer, urethelial carcinoma, melanoma, renal cell carcinoma, squamous cell carcinoma of head and neck, hepatocellular carcinoma, classical Hodgkin's lymphoma, MSI-H/dMMR metastatic colorectal cancer, and tumors with genetic mutations sensitive to mTOR inhibitors

Study Number: SOC-1701

Study Phase: 1/2

Name of Investigational Product (IP)

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

Name of FDA Approved Study Agent

Nivolumab (Opdivo®), is a programmed death receptor-1 (PD-1) blocking monoclonal antibody indicated for the treatment of patients with (1) BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent, (2) BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent. This indication is approved under accelerated approval based on progression free survival. (3) Unresectable or metastatic melanoma, in combination with ipilimumab, (4) Metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy, (5) Advanced renal cell carcinoma who have received prior anti-angiogenic therapy, (6) Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin, (7) Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy, and (8) advanced or metastatic urothelial carcinoma who have progressed on platinum-containing chemotherapy.

Indication

Previously treated patients with advanced (metastatic or locally advanced) sarcoma, including desmoid tumor and chordoma

Objectives

Primary Objective

The primary objective of this study is to investigate the maximum tolerated dose of ABI-009, an mTOR inhibitor, when given sequentially with nivolumab in advanced UPS, LPS, OS, CS, Ewing's sarcoma.

Secondary Objectives

The secondary objectives are to investigate the disease control rate (DCR), progression free survival (PFS), recurrence-free survival (RFS) and overall survival using nivolumab/ABI-009 combination therapy in advanced Ewing's sarcoma, PEComa, epithelioid sarcoma, desmoid tumor, chordoma, non-small cell lung cancer, small cell lung cancer, urethelial carcinoma, melanoma, renal cell carcinoma, squamous cell carcinoma of head and neck, hepatocellular carcinoma, classical Hodgkin's lymphoma, MSI-H/dMMR metastatic colorectal cancer, and tumors with genetic mutations sensitive to mTOR inhibitors.

Exploratory Objectives

- To correlate disease control rate (DCR) based on Immune-related Response Criteria (irRECIST) with that based on RECIST v1.1.
- To correlate PFS with PD-L1 and other biomarker expression in patients' tumors
- To correlate DCR with PTEN mutation in patient's archived tumor

Endpoints

Primary Endpoint

- Maximum tolerated dose (MTD)

Secondary endpoints

- Disease control rate (DCR) as determined by a local radiologic assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; objective response rate (ORR; CR + PR), progression free survival (PFS), and overall survival (OS).
- PFS rate at 3, 6, 9, and 12 months, RFS at 4 months, median PFS, median RFS and median OS will be assessed for all subtypes together, and separately in the five subtypes of patients with metastatic disease and locally advanced disease.

Exploratory endpoints

- Correlation between DCR based on Immune-related Response Criteria (irRECIST) with that based on RECIST v1.1.
- Correlation between DCR and PD-L1 and other biomarker expression in patients' tumors.
- Correlation between DCR and PTEN mutation in patient's archived tumor

Study Design

This is an open label, dose-seeking phase 1/2 study using a defined dose of nivolumab and escalating doses of ABI-009 given intravenously.

I. Dose Escalation Phase 1 Part of Study: The study will employ the standard "cohort of three" design (2). Three patients are treated at each dose level with expansion to six patients per cohort if DLT is observed in one of the three initially-enrolled patients at each dose level. If no DLT occurs after 2 doses, escalation to the next dose level will be permitted. The maximum tolerated dose is defined as the highest safely tolerated dose, where not more than one patient experienced DLT, with the next higher dose level having at least two patients who experienced DLT. Patients in the dose escalation study may continue treatment at their designated dose levels up to eighteen 3-week cycles or until significant disease progression or unacceptable toxicity occurs. No intra-patient dose escalation will take place.

Dose of nivolumab: 3 mg/kg IV over 30 min. q 3 weeks (Day 1 of every 21-day cycle)

Dose of ABI-009:

NB: ABI-009 will start after 2nd nivolumab dose and will be administered on D8 and D15 beginning in C2.

Escalating doses IV over 30 min for 2 of every 3 weeks:

Treatment Cycle	# Pts.	Dose Level	Dose, mg/m^2
Every 3 weeks	3-6	I	56
Every 3 weeks	3-6	II	75
Every 3 weeks	3-6	III	100

Note: DLT includes any $\geq$ Grade 3 colitis, hepatitis, or pneumonitis, any Grade 1-2 colitis, hepatitis or pneumonitis that recurs, worsens or persists with oral steroids longer than 14 days, symptoms of adrenal crisis, any Grade 4 hematologic toxicity or any $\geq$ Grade 3 non-hematologic toxicity. If DLT develops in more than 1 patient at Dose 56 mg/m2, the dose will be de-escalated to 45 mg/m2 and to 30 mg/m2 if DLT develops at 45 mg/m2.

II. Expansion Phase 2 Part of Study: Following dose escalation, an additional 22-28 patients will receive ABI-009 at the MTD and defined doses of nivolumab to assess overall safety and potential efficacy in a greater number of patients. Patients in the expansion phase of the study may continue treatment up to 18 3-week treatment cycles or until significant disease progression or unacceptable toxicity occurs.

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

Surgical Resection: After three or more treatment cycles, the principal investigator may recommend surgical debulking, complete surgical removal or a biopsy. If residual disease

is present either by histopathological examination or by CT scan/MRI, repeat treatment cycles may be given 2-4 weeks after surgery, if the surgical incision has healed, and if the patient has ≤ grade I toxicity.

Resected or biopsied tumors will be analyzed for the effects of this dual therapy on disease control rate, and immune cell trafficking in the tumor microenvironment. Fresh and paraffin embedded tissue blocks will be analyzed by FACS for PD-L1 and other biomarkers, including Tregs, CD8+, CD4+ cells etc. Immunohistochemistry for cyclin G1, cyclin D1 and Ki67 will be conducted to determine the tumor's proliferative state. Histopathologic examination for tumor necrosis and mitotic index will also be determined.

Conditions for Continuation of Treatment in the Presence of Increased Tumor Size by CT scan or MRI Indicating Progressive Disease by RECIST v1.1:

Treatment may be continued if:

1. There are no signs or symptoms indicating unequivocal progression.
2. There is no worsening of ECOG score attributable to progressive disease.
3. There is no tumor growth at critical sites that is life-threatening.
4. Patient signs an informed consent that he/she is aware of alternative therapies but wishes to defer these therapies.
5. There is clinical benefit, as determined by investigator

Sample Size

40-50 patients may be enrolled. Patients who fail to become evaluable for the secondary endpoint with a follow-up CT/MRI will be replaced.

Study Population

Histology of Ewing's sarcoma, PEComa, epithelioid sarcoma, desmoid tumor, chordoma, non-small cell lung cancer, small cell lung cancer, urethelial carcinoma, melanoma, renal cell carcinoma, squamous cell carcinoma of head and neck, hepatocellular carcinoma, classical Hodgkin's lymphoma, MSI-H/dMMR metastatic colorectal cancer, and tumors with genetic mutations sensitive to mTOR inhibitors, will be confirmed locally by the institution prior to enrollment.

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 Ewing's sarcoma, PEComa, epithelioid sarcoma, desmoid tumor, chordoma, non-small cell lung cancer, small cell lung cancer, urethelial carcinoma, melanoma, renal cell

carcinoma, squamous cell carcinoma of head and neck, hepatocellular carcinoma, classical Hodgkin's lymphoma, MSI-H/dMMR metastatic colorectal cancer, and tumors with genetic mutations sensitive to mTOR inhibitors, that is either metastatic or locally advanced and for which surgery is not a recommended option.

2. Patients must have one or more measurable target lesions by CT scan or MRI. Measurable disease by RECIST v1.1, confirmed by investigator
3. Previously treated patients with Ewing's sarcoma, PEComa, epithelioid sarcoma, desmoid tumor, chordoma, non-small cell lung cancer, small cell lung cancer, urethelial carcinoma, melanoma, renal cell carcinoma, squamous cell carcinoma of head and neck, hepatocellular carcinoma, classical Hodgkin's lymphoma, MSI-H/dMMR metastatic colorectal cancer, and tumors with genetic mutations sensitive to mTOR inhibitors, if treatment is completed after 5 half-lives or ≥28 days prior to enrollment, whichever is shorter.
4. Eligible patients, 12-17 years (≥40 kg) or 18 years or older, with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
5. 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/ALT ≤2.5 x ULN (≤5 x ULN if attributable to liver metastases); alk phos ≤ 3 x ULN (patients with alk phos >3ULN will be allowed if due to bone metastases)
    c. Serum creatinine ≤1.5 x ULN
6. 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.
7. Serum triglyceride <300 mg/dL; serum cholesterol < 350 mg/dL.
8. 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.

9. Life expectancy of >3 months, as determined by the investigator.
10. Ability to understand and sign informed consent.
11. 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. 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.
2. Active gastrointestinal bleeding.
3. Pre-existing thyroid abnormality is allowed provided thyroid function can be controlled with medication.
4. 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).
5. 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.
6. 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).
7. Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy.
8. Unstable coronary artery disease or myocardial infarction during preceding 6 months.
9. Receiving any concomitant antitumor therapy.

10. Patients with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension.
11. 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.
12. Active Hepatitis B or Hepatitis C.
13. Non-oncology vaccine therapy used for prevention of infectious disease within 4 weeks of trial enrollment
14. Autoimmune disease including rheumatoid arthritis, systemic progressive sclerosis (scleroderma), systemic lupus erythematosus, autoimmune vasculitis and motor neuropathy considered to be of autoimmune origin (e.g. Guillain-Barre Syndrome)
15. Systemic immunosuppression, including HIV positive status with or without AIDS
16. Skin rash (psoriasis, eczema) affecting > 25% body surface area
17. Inflammatory bowel disease (Crohn's or ulcerative colitis)
18. Ongoing or uncontrolled diarrhea within 4 weeks of trial enrollment
19. Recent history of acute diverticulitis, intraabdominal abscess or gastrointestinal obstruction within 6 months of trial enrollment, which are known risk factors for bowel perforation
20. Current, active or previous history of heavy alcohol abuse
21. Pituitary endocrinopathy
22. Adrenal insufficiency or excess

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 or nivolumab. 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 or nivolumab.

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 Treatment

Patients will receive nivolumab 3 mg/kg as IV infusion over 30 min every 3 weeks (Day 1 of every 21-day cycle), followed by escalating doses of ABI-009 30, 45, 75 mg/m^2 for 2 of every 3 weeks by IV infusion over 30 minutes. ABI-009 dosing will start after 2nd nivolumab dose and to be administered on Day 8 and Day 15 of every cycle beginning in Cycle 2. Patients will continue therapy until unequivocal clinical disease progression, unacceptable toxicity, or until in the opinion of the investigator the patient is no longer benefiting from therapy, or at the patient's discretion.

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 signs, laboratory assessments (e.g., serum chemistry, hematology), and ECOG performance status will be monitored. All SAEs (regardless of relationship to IP) will be followed until resolution. Local laboratory analysis will be performed as per study schedule.

The MTD for ABI-009 will be determined, and will be used in the Phase 2 part of the study.

Overview of Key Efficacy Assessments

Patients will be evaluated for disease control rate [complete response (CR), partial response (PR), and 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 the end of treatment. 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 efficacy endpoints, DCR (CR, PR and SD), OR (CR + PR), PFS, and RFS will be determined by a local radiologic assessment using RECIST v1.1. After end of treatment, patients will be followed for survival every 12 weeks (+/- 3 weeks), or more frequently as needed, until death, withdrawal of consent, or the study closes, whichever is the earliest.

Statistical Considerations

Safety Analyses:

Demographic and baseline information (e.g., extent of prior therapy) on study patients will be tabulated. The number of patients studied for the Phase 1 (dose escalation) part of study could range from 12 to 18 evaluable patients, and 22-28 evaluable patients for the Phase 2 (dose expansion) part of the study.

For the Phase 1 part of the study, the following information will be reported for all adverse events observed in the study: dose level, type (organ affected or laboratory determination, such as absolute neutrophil count), severity (by NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 and most extreme abnormal values for laboratory determinations) and relatedness to study treatment. For each dose the number and percentage of patients experiencing any grade 3, 4, or 5 adverse event will be reported, as well as the number and percentage of patients who experienced selected specific types of adverse events. In addition, the DLTs will be summarized by dose level and the MTD will be determined.

The following table gives the probability of dose escalation at a single dose level as a function of the true probability of DLT at that level using the cohorts of 3 design (Objective #1) (2).

Table 1. Probability of Dose Escalation

True Rate of DLT (%)	Probability of Dose Escalation
10	0.91
20	0.71
30	0.49
40	0.31
50	0.17

For the Phase 1 part of the study, the entire treated population (Full Analysis Set) will be the analysis population for all safety analyses. Adverse events will be coded using the NIH CTCAE v4.03. 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 all patient groups together (metastatic and locally advanced). Although this study will not be large enough to allow firm conclusions about safety or efficacy, it will provide preliminary data on safety and efficacy that will be useful in planning future studies. Frequency tables, graphs, and summary statistics will be used for outcome data.

Patient incidence of all treatment-emergent AEs will be tabulated. Tables of fatal adverse events, serious adverse events, treatment-related AEs, and adverse events leading to withdrawal from investigation product will also be provided.

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

Efficacy Analyses:

The disease control rate (DCR; CR+PR+SD), objective response rate (ORR; CR + PR), progression free survival (PFS), and recurrence-free survival (RFS) will be assessed by a local radiologic assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and irRECIST.

The focus of the study is to estimate the DCR in patients treated with ABI-009 and nivolumab. Patients who progress before receiving ABI-009 will be replaced, and will not be included in the statistical analysis. The number and percentage of patients achieving response will be summarized.

Analysis of other efficacy endpoints, PFS at 4 months, RFS at 4 months, median PFS, and median OS will be assessed for all subtypes together, and separately in the five sarcoma subtypes.

PFS, RFS and OS will be summarized using Kaplan-Meier (KM) analysis. The number of patients in each category is expected to be small; therefore, PFS at 4 months, RFS at 4 months, median PFS, median RFS and median OS for these patients will be summarized by descriptive statistics.

Exploratory Analysis:

DCR based on RECIST v1,1 will be correlated with DCR based on Immune-related Response Criteria (irRECIST) and summarized by descriptive statistics.

PD-L1 and other biomarker expression in patients' tumors will be correlated with DCR PFS, and RFS and summarized by descriptive statistics.

DCR will be correlated with presence of PTEN mutation in patient's archived tumor and summarized by descriptive statistics.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
ANC	absolute neutrophil count
AST	aspartate transaminase (SGOT)
AUC	area under the time-concentration curve
BSA	body surface area
C_{max}	maximum plasma drug concentration
C_{min}	minimum plasma drug concentration
CBC	complete blood count
CI	confidence interval
CNS	central nervous system
CR	complete response
CS	chondrosarcoma
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
CRF	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
LPS	liposarcoma

IND	investigational new drug
IP	investigational product
IRB	Institutional Review Board
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	osteosarcoma
OS	overall survival
DCR	disease control rate
PD	progressive disease
PEComa	perivascular epithelioid cell tumors
PFS	Progression-free survival
RFS	Recurrence-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)
TBL	total bilirubin level
ULN	upper limit of normal
UPS	undifferentiated pleomorphic sarcoma

Abbreviation or Term	Definition/Explanation
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 or nivolumab which ever is later 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 or nivolumab whichever is later.
Primary Analysis	For this study will occur after all patients have either completed the study or completed 12 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 received at least two doses of ABI-009 and had a follow-up CT scan/MRI (modified treated population)
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 survival	The time from the first dose date to the first observation of a disease progression or death due to any cause.
Recurrence-free survival	The time from the first dose date to the first observation of disease progression or recurrence/progression after surgical resection, 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 a local radiologic assessment
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. Soft Tissue Sarcoma

Soft tissue sarcoma (STS) is a relatively rare neoplasm of mesenchymal origin, which includes a diversity of histological subtypes and occurs with an incidence of about 1% of all adult cancers. Surgical resection is still the treatment of choice for localized disease, along with radiation therapy for unresectable sarcomas. However, recurrence rate is high (~50%) and treatment options for metastatic/relapsed STS are limited to anthracycline-based chemotherapy (i.e., doxorubicin), administered alone or in combination with alkylating agents (ifosfamide and/or dacarbazine) (3, 4). Judging from studies conducted over the last 20 years, prognosis for advanced STS has been uniformly poor, with an estimated median survival of only 8 to 13 months (5-7). Recently, two new drugs for soft tissue sarcoma have been approved by the United States Food and Drug Administration (USFDA). The first drug, pazopanib (Votrient®, Novartis Pharma), is a multiple tyrosine kinase inhibitor, which hinders growth factor-mediated signal transduction pathways involved in tumor angiogenesis (8-10). The second drug, trabectedin/ET-743 (Yondelis®, Janssen Biotech, Inc.), is a natural alkaloid, originally isolated from the Caribbean tunicate, Ecteinascidia turbinata, which interacts with DNA in a complex manner that interferes with gene transcription and DNA repair (11). Following the approval of trabectedin in Europe for treatment-resistant STS (12, 13) and the results of a pivotal Phase 3 trial (14), which enabled its approval in the United States for liposarcoma and leiomyosarcoma in 2015, there is renewed optimism for improving the quality of life, progression-free survival, and potentially, the overall survival of advanced STS patients that have failed standard therapies (14, 15).

1.1.1 mTOR Inhibitors in Soft Tissue Sarcoma

Aberrant mammalian target of rapamycin (mTOR) signaling is common in sarcomas and other malignancies. Drug resistance and toxicities often limit benefits of systemic chemotherapy used to treat metastatic sarcomas. Ridaforolimus is an inhibitor of mammalian target of rapamycin, an integral component of the phosphatidyl 3-kinase/AKT signaling pathway, with early evidence of activity in sarcomas.

A multicenter, open-label, single-arm, phase II trial was conducted to assess the antitumor activity of ridaforolimus in patients with distinct subtypes of advanced sarcomas (Chawla et al. A total of 212 patients were treated in four separate histologic cohorts. In this heavily pretreated population, 61 patients (28.8%) achieved CBR. Median PFS was 15.3 weeks; median OS was 40 weeks. Response Evaluation Criteria in Solid Tumors (RECIST) confirmed response rate was 1.9%, with four patients achieving confirmed PR (two with osteosarcoma, one with spindle cell sarcoma, and one with undifferentiated pleomorphic sarcoma [formerly malignant fibrous histiocytoma]). Archival tumor protein markers analyzed were not correlated with CBR. Related adverse events were generally mild or moderate and consisted primarily of stomatitis, mucosal inflammation, mouth ulceration, rash, and fatigue. Conclusion: Single-agent ridaforolimus in patients with advanced and pretreated sarcomas led to PFS results that compare favorably with historical metrics.

A large randomized placebo-controlled phase III trial evaluated the mTOR inhibitor ridaforolimus to assess maintenance of disease control in advanced sarcomas after benefit from prior chemotherapy (16). Patients with metastatic soft tissue or bone sarcomas who achieved objective response or stable disease with prior chemotherapy were randomly assigned to receive ridaforolimus 40 mg or placebo once per day for 5 days every week. Primary end point was progression-free survival (PFS); secondary end points included overall survival (OS), best target lesion response, safety, and tolerability. A total of 711 patients were enrolled, and 702 received blinded study drug. Ridaforolimus treatment led to a modest, although significant, improvement in PFS per independent review compared with placebo (hazard ratio [HR], 0.72; 95% CI, 0.61 to 0.85; P < .001; median PFS, 17.7 v 14.6 weeks). Ridaforolimus induced a mean 1.3% decrease in target lesion size versus a 10.3%increase with placebo (P < .001). Median OS with ridaforolimus was 90.6 weeks versus 85.3 weeks with placebo (HR, 0.93; 95% CI, 0.78 to 1.12; P = .46). Adverse events (AEs) more common with ridaforolimus included stomatitis, infections, fatigue, thrombocytopenia, noninfectious pneumonitis, hyperglycemia, and rash. Grade 3 AEs were more common with ridaforolimus than placebo (64.1% v 25.6%). Conclusion: Ridaforolimus delayed tumor progression to a small statistically significant degree in patients with metastatic sarcoma who experienced benefit with prior chemotherapy. Toxicities were observed with ridaforolimus, as expected with mTOR inhibition. These data provide a foundation on which to further improve control of sarcomas.

Other mTOR inhibitors, including sirolimus and everolimus, have been tested or are being tested in clinical trials for advanced soft tissue sarcoma. For example, sirolimus, is currently approved for immunosuppression following organ transplantation. However, there is increasing interest in its role as a neoplastic agent. In a report of four cases of progressive metastatic sarcoma in patients who have progressed after 2–6 lines of chemotherapy, treatment with sirolimus resulted in minor radiographic improvement in three cases (17). Myxoid chondrosarcoma has also been reported to respond well to sirolimus in combination with cyclophosphamide (18).

Further, a phase II study investigating the efficacy of everolimus in patients with histological evidence of progressive or metastatic bone or soft tissue sarcoma is currently underway (19), as is a phase I/II study of everolimus in pediatric patients with recurrent or refractory solid tumors (20).

1.1.2 Immune Checkpoint Inhibitors in Soft Tissue Sarcoma

Immune check point inhibitors have become a mainstay of therapy for melanoma and are currently being developed for various solid tumors including renal cell carcinoma, non-small cell lung cancer, ovarian cancer, head and neck cancer and lymphoma. The underlying principle is to thwart the defenses (checkpoints) that tumors utilize to cripple the immune system. Examples of FDA-approved immune checkpoint inhibitors include monoclonal antibodies ipilimumab and nivolumab (21). Ipilimumab (Yervoy®) is a recombinant human IgG1 monoclonal antibody that blocks the human cytotoxic T-lymphocyte antigen (CTLA-4) which tumors use to overturn the immune system. CTL4 is one of several co-inhibitory molecules that help in controlling the T-cell response to stimuli/cancer cells. Cancer cells bind to the CTL-4 antigen to avoid the destruction by

cytotoxic T cells. In a pivotal phase III study, ipilimumab in combination with a glycoprotein 100 (gp100) peptide vaccine improved overall survival in Stage III or IV unresectable melanoma. These results, together with two other supportive studies, formed the basis of FDA approval for unresectable or metastatic melanoma (22, 23). Nivolumab (Opdivo®) is a human IgG4 monoclonal antibody that blocks the programmed death receptor-1 (PD-1). It is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. This indication is approved under accelerated approval by the USFDA (23).

Recently, the results of a multicenter phase 2 study (SARC028) investigating the safety and efficacy of pembrolizumab, a programmed death -1 (PD-1) inhibitor, in advanced soft tissue sarcoma and bone sarcoma (SARC028) showed that the ORR in the overall STS cohort was 18% and the 12-wk PFS 55% [95% CI, 42-71]). Clinical activity was variable by histologic subtype with 40% ORR in UPS (1 CR and 3PR out of 10 evaluable pts), 2 PR/10 were seen in DDLPS, 1PR/10 in SS and 0/10 in LMS. For BS, median follow-up was 12.3 months (ORR 5%; 12-wk PFS 28% [95% CI, 14-41]), with 1PR/22 OS, 1PR/5 CS and 0/13 ES. Seventy pre-pembrolizumab tissues were analyzed with PD-L1+ in 3/70 (4%); all 3 were UPS. Of the 2 evaluable pts, 1 had CR and 1 PR. Two OS were PD-L1+ on multi-color IHC, 1 had PR. All PD-L1+ samples had CD8+ T-cell infiltration. There were no post-pembro PD-L1+ samples. The authors concluded that pembrolizumab has clinical activity in UPS and LPS, and expansion cohorts in those subtypes are planned. Pre-treatment PD-L1 expression was infrequent, but correlated with T-cell infiltration and response in UPS & OS (24).

1.1.3 Combination Chemo-/Immuno- therapy for Soft Tissue Sarcoma

Understanding the bifunctional role that the immune system plays in tumor eradication vs growth promotion is critical in the design and timing of combination tumoricidal and immunologic therapies for sarcomas (25). Hence, immune checkpoint inhibitors that promote sustained T cell activation by suppressing T regs, may have synergistic activity with a tumoricidal agent, such as ABI-009, an mTOR inhibitor, whose plausible mechanism of action is to destroy the cancer cells and expose the tumor neoantigens for immune recognition.

The initial results of our study on the feasibility of sequential administration of trabectedin and nivolumab support this concept. Trabectedin has direct cytotoxic activity in tumor cells and has also been shown to deplete pro-tumor macrophages in the tumor microenvironment (26). Nivolumab inhibits the immune checkpoint molecule, PD-1, which restores anti-tumor activity in tumor-infiltrating T cells. The objectives were to assess the safety/toxicity and efficacy of sequential administration of trabectedin and nivolumab in patients with advanced soft tissue sarcoma (STS). Fourteen patients with locally-advanced and/or metastatic STS were evaluated. Each patient received 1 dose of single-agent trabectedin (1.5 mg/kg continuous intravenous infusion, CIV, for 24 hours), followed by sequential administration of trabectedin CIV and nivolumab (3 mg/kg IV over 30 minutes) every 3-4 weeks, starting 3 weeks after the first trabectedin dose. Dexamethasone (6-20 mg IV over 30 minutes) was given prior to each trabectedin treatment. Safety/toxicity was analyzed using the NIH/NCI CTCAE v.4.03. Baseline and

follow-up CT scans or MRIs were performed after every 2 cycles of the sequential chemo-/immuno-therapy. Tumor responses were assessed by RECIST v1.1 and immune-related response criteria (irRC). Histologic subtypes include malignant fibrous histiocytoma / undifferentiated pleomorphic sarcoma (n = 6), leiomyosarcoma (n = 3), synovial sarcoma (n = 2), myxoid liposarcoma (n = 2) and chondrosarcoma (n = 1). All patients had metastatic disease and a median of 4 lines of prior chemotherapy. Safety analysis: Grade 3 treatment emergent adverse events include anemia (n=1), fatigue (n = 1), decreased platelet count (n=1), and increased creatine kinase (n=1). These AEs have been reported with trabectedin use. No immune-related adverse event has been observed so far. Efficacy analysis: Thirteen patients received 2 cycles of sequential chemo-/immuno-therapy, had follow-up CT scan or MRI, and were evaluated for objective response (OR), best overall response rate, (BORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). There were 2 partial responses (PR), with one biopsied nodule showing >90% liquefaction necrosis, 8 stable disease (SD) and 3 progressive disease (PD), with best overall response rate (BORR) of 15.3%, DCR of 76.9%, median PFS of >8 weeks (range: 8-21 weeks), and median OS of >8 weeks (12.3->21 weeks). To our knowledge, this study is the first to explore sequentially administered chemo-/immuno-therapy in patients with advanced STS. The initial data suggest that paired administration of trabectedin and nivolumab is safe. We continue to evaluate for safety as well as synergistic activity based on their mechanisms of action on the tumor-immune microenvironment (27).

1.1.4 Strategies to improve the efficacy of immune checkpoint inhibitors in other clinical indications.

Recently, several studies focused in modifying the tumor-immune microenvironment (TME) with small molecules that increase the number of activated T cells exerting tumoricidal activity and/or suppressing growth promoting macrophages in the TME. These drugs include microbiota modifiers, drugs targeting co-inhibitory receptors, anti-angiogenic therapeutics, small molecules, and oncolytic viruses.

The vascular network with its specific components (endothelial cells, pericytes, growth factors, and receptors) plays a key role in the regulation of inflammatory response, wound healing, and immune surveillance. The transit of immune cells in the tumor plays a critical role in the outcome of immunotherapeutic strategies, similarly to classical chemotherapeutic drugs. In particular, a normalized endothelium ensures the correct trafficking of T cells to the tumor bed (28). In fact, tumor angiogenesis contributes to the escape of the immune tumor through the immunosuppressive activity exerted by VEGF, PGE2, IL-10, and tumor hypoxia. In particular, VEGF acts through both the inhibition of lymphocyte adhesion to activated endothelial cells and the systemic effect on immune-regulatory cell function, including the suppression of DCs maturation, the inhibition of T cell development, and the increase of inhibitory immune cells. Therefore, the possibility of administering immune checkpoint inhibitors during an anti-angiogenic treatment has been studied in different types of cancers according to the hypothesis that anti-angiogenic drug-induced normalization of the vessels may improve immunotherapeutic strategies.

On the other hand, immune checkpoint inhibitor activation of Th1 cells blocked vessel normalization, suggesting the existence of a mutually regulatory circuit.

It is interesting to note that a combination of small molecules and immune checkpoint inhibitors have been evaluated in a mouse model of oral cancer. In this neoplasia, both activation of PI3K/mTOR and MEK/ERK pathways promoted the immunosuppressive tumor microenvironment [28]. In an immunogenic model of cancer of the oral cavity, rapamycin reduced tumor growth in a CD8-dependent manner (28). More recently, Moore et al. (28) demonstrated that rapamycin improved IFNγ production by peripheral and tumor-infiltrating CD8 T cells in a mouse model of oral cancer. Furthermore, antitumor efficacy was enhanced by the CD8 T cell but not by NK cell. Non-inflamed tumor models, which represent the low level of response to immune therapies, did not induce T cell or NK CD8 cell–mediated antitumor immunity when treated with combinations of targeted and immune checkpoint inhibitorss. In other models, antitumor immune responses to PD-L1 mAb treatment were enhanced when treated with mTOR inhibitors. These data suggested that a combination of mTOR and ICIs inhibitors should be evaluated in clinical trials setting. An appealing concept is to utilize a tumor targeted rapamycin, nab rapamycin (ABI-009) to enhance the efficacy of immune checkpoint inhibitors, specifically nivolumab in various cancer types wherein immune checkpoint inhibitors are already shown to be effective and are already FDA approved.

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 (29). 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 (30). 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 (31).

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 (32)
- Phosphorylated p-AKT, p-S6, p-4EBP1 expression (33)
- biomarkers for the proliferation (Ki-67) and apoptosis (PARP) (31)

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 (32).

Although rapamycin, an oral therapeutic, is an efficacious mTOR inhibitor, it has poor solubility, low oral bioavailability, and dose-limiting toxicity (29, 34). 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 (35-39).

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 (40-42). The most frequently occurring grade 3 or 4 adverse events were hyperglycemia (17%), hypophosphatemia (13%), anemia (9%), and hypertriglyceridemia (6%) (43). 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 (44).

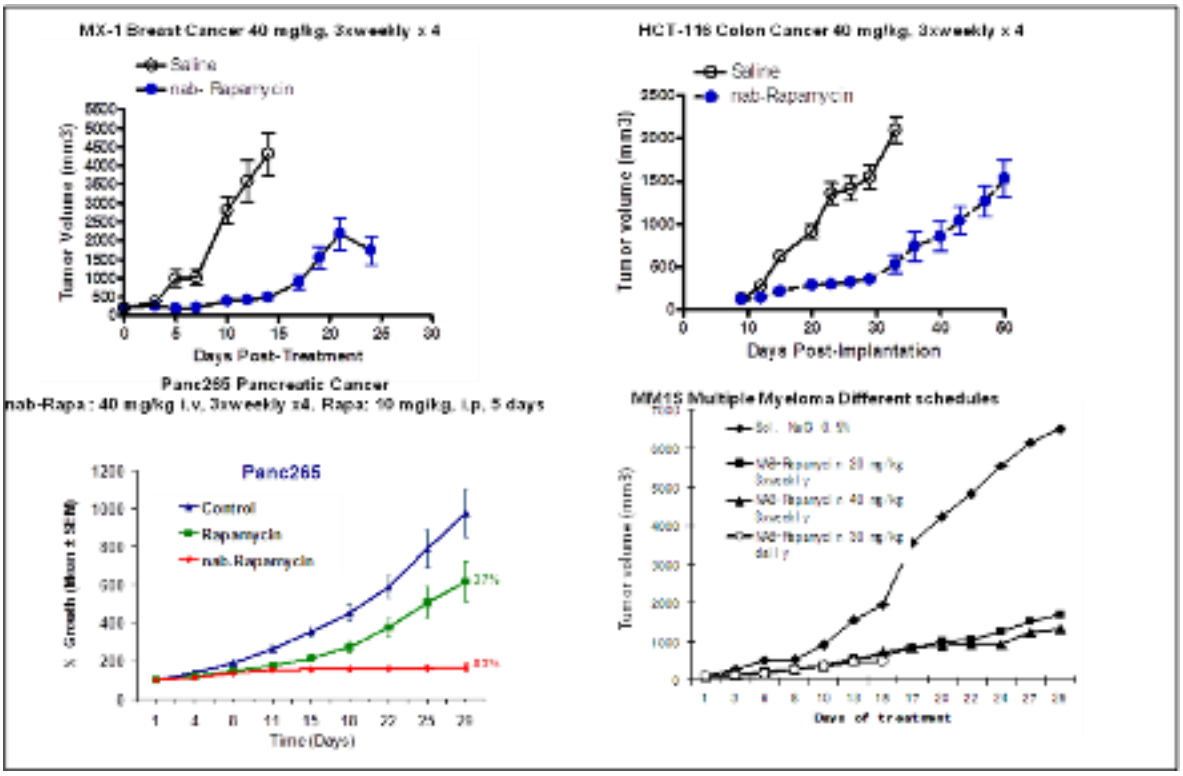
Nanoparticle albumin-bound or *nab*® technology (Abraxis BioScience, a wholly-owned subsidiary of Celgene Corporation) when applied to hydrophobic molecules, such as paclitaxel (*nab*-paclitaxel; Abraxane®), has led to improved drug delivery, safety, and efficacy in various solid tumors compared with the conventional paclitaxel formulation (45). 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 (45, 47). Albumin circulating in the bloodstream can interact with gp60 to initiate caveolae-mediated transcytosis to reach tumor cells (48, 49). Indeed, *nab*-paclitaxel transcytosis across the epithelial monolayer was dependent on caveolae formation (50). 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 (50).

1.2.3. 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 (51-55). 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 (56). In addition, recent preclinical study has demonstrated that combination of ABI-009 with the Akt inhibitor perifosine induced synergistic antitumor activity in multiple myeloma (54).

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 (53). 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 (57), 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 (58-60).

1.2.4. 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 (42). 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%). 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.

1.3. Nivolumab Background

Nivolumab is an FDA-approved human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa (64).

1.3.1. Nivolumab Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth (64).

1.3.2. Nivolumab Clinical Studies

Trial 1 was a multicenter, open-label trial that randomized (2:1) patients with unresectable or metastatic melanoma to receive either nivolumab administered intravenously at 3 mg/kg every 2 weeks or investigator's choice of chemotherapy, either single-agent dacarbazine 1000 mg/m2 every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m2 every 3 weeks. Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, ocular melanoma, active brain metastasis, or a history of Grade 4 ipilimumab-related adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter.

Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received nivolumab in Trial 1 and in whom the minimum duration of follow up was 6 months. The major efficacy outcome measures in this population were confirmed objective response rate (ORR) as measured by blinded independent central review using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and duration of response.

Among the 120 patients treated with nivolumab, the median age was 58 years (range: 25-88), 65% of patients were male, 98% were white, and the ECOG PS was 0 (58%) or 1 (42%). Disease characteristics were M1c disease (76%), BRAF V600 mutation positive (22%), elevated LDH (56%), history of brain metastases (18%), and two or more prior systemic therapies for metastatic disease (68%).

The ORR was 32% (95% confidence interval: 23, 41), consisting of 4 complete responses and 34 partial responses in nivolumab-treated patients. Of 38 patients with responses, 33 patients (87%) had ongoing responses with durations ranging from 2.6+ to 10+ months, which included 13 patients with ongoing responses of 6 months or longer.

There were objective responses in patients with and without BRAF V600 mutation positive-melanoma.

1.3.3. Nivolumab Adverse Events

The data described in the WARNINGS and PRECAUTIONS section of the nivolumab (Opdivo) product information and below reflect exposure to nivolumab in Trial 1, a randomized, open-label trial in which 370 patients with unresectable or metastatic melanoma received nivolumab 3 mg/kg every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102), either dacarbazine 1000 mg/m2 every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m2 every 3 weeks. The median duration of exposure was 5.3 months (range: 1 day-13.8+ months) with a median of eight doses (range: 1 to 31) in nivolumab-treated patients and was 2 months (range: 1 day-9.6+ months) in chemotherapy treated patients. In this ongoing trial, 24% of patients received nivolumab for greater than 6 months and 3% of patients received nivolumab for greater than 1 year.

Clinically significant adverse reactions were also evaluated in 574 patients with solid tumors enrolled in two clinical trials receiving nivolumab at doses of 0.1 to 10 mg/kg every 2 weeks, supplemented by immune-mediated adverse reaction reports across ongoing clinical trials.

In Trial 1, patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, prior ipilimumab-related Grade 4 adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event, patients with a condition requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, and a history of HIV.

The study population characteristics in the nivolumab group and the chemotherapy group were similar: 66% male, median age 59.5 years, 98% white, baseline ECOG performance status 0 (59%) or 1 (41%), 74% with M1c stage disease, 73% with cutaneous melanoma, 11% with mucosal melanoma, 73% received two or more prior therapies for advanced or metastatic disease, and 18% had brain metastasis. There were more patients in the nivolumab group with elevated LDH at baseline (51% vs. 38%).

- **Immune-mediated Grade 2 pneumonitis**

Severe pneumonitis or interstitial lung disease, including fatal cases, occurred with nivolumab treatment. Across the clinical trial experience in 574 patients with solid tumors, fatal immune-mediated pneumonitis occurred in 0.9% (5/574) of patients receiving nivolumab. No cases of fatal pneumonitis occurred in Trial 1; all five fatal cases occurred in a dose-finding study with nivolumab doses of 1 mg/kg (two patients), 3 mg/kg (two patients), and 10 mg/kg (one patient).

In Trial 1, pneumonitis, including interstitial lung disease, occurred in 3.4% (9/268) of patients receiving nivolumab and none of the 102 patients receiving chemotherapy. Immune-mediated pneumonitis, defined as requiring use of corticosteroids and no clear alternate etiology, occurred in 2.2% (6/268) of patients receiving nivolumab: one with Grade 3 and five with Grade 2 pneumonitis. The median time to onset for the six cases was 2.2 months (range: 25 days-3.5 months). In two patients, pneumonitis was diagnosed

after discontinuation of nivolumab for other reasons, and Grade 2 pneumonitis led to interruption or permanent discontinuation of nivolumab in the remaining four patients. All six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day); immune-mediated pneumonitis improved to Grade 0 or 1 with corticosteroids in all six patients. There were two patients with Grade 2 pneumonitis that completely resolved (defined as improved to Grade 0 with completion of corticosteroids) and nivolumab was restarted without recurrence of pneumonitis.

- **Immune-mediated Grade 2-3 colitis**

In Trial 1, diarrhea or colitis occurred in 21% (57/268) of patients receiving nivolumab and 18% (18/102) of patients receiving chemotherapy. Immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology, occurred in 2.2% (6/268) of patients receiving nivolumab: five patients with Grade 3 and one patient with Grade 2 colitis. The median time to onset of immune-mediated colitis from initiation of nivolumab was 2.5 months (range: 1-6 months). In three patients, colitis was diagnosed after discontinuation of nivolumab for other reasons, and Grade 2 or 3 colitis led to interruption or permanent discontinuation of nivolumab in the remaining three patients. Five of these six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 1.4 months (range: 3 days-2.4 months) preceding corticosteroid taper. The sixth patient continued on low-dose corticosteroids started for another immune-mediated adverse reaction. Immune-mediated colitis improved to Grade 0 with corticosteroids in five patients, including one patient with Grade 3 colitis retreated after complete resolution (defined as improved to Grade 0 with completion of corticosteroids) without additional events of colitis. Grade 2 colitis was ongoing in one patient.

- **Immune-mediated hepatitis.** Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN

In Trial 1, there was an increased incidence of liver test abnormalities in the nibolumab-treated group as compared to the chemotherapy-treated group, with increases in AST (28% vs. 12%), alkaline phosphatase (22% vs. 13%), ALT (16% vs. 5%), and total bilirubin (9% vs. 0). Immune-mediated hepatitis, defined as requirement for corticosteroids and no clear alternate etiology, occurred in 1.1% (3/268) of patients receiving nivolumab: two patients with Grade 3 and one patient with Grade 2 hepatitis. The time to onset was 97, 113, and 86 days after initiation of nivolumab. In one patient, hepatitis was diagnosed after discontinuation of nivolumab for other reasons. In two patients, nivolumab was withheld. All three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Liver tests improved to Grade 1 within 4-15 days of initiation of corticosteroids. Immune-mediated hepatitis resolved and did not recur with continuation of corticosteroids in two patients; the third patient died of disease progression with persistent hepatitis. The two patients with Grade 3 hepatitis that resolved restarted nivolumab and, in one patient, Grade 3 immune-mediated hepatitis recurred resulting in permanent discontinuation of nivolumab.

- **Immune-mediated nephritis and renal dysfunction. Creatinine greater than 1.5 and up to 6 times ULN or greater than 1.5 times baseline**

In Trial 1, there was an increased incidence of elevated creatinine in the nivolumab-treated group as compared to the chemotherapy-treated group (13% vs. 9%). Grade 2 or 3 immune-mediated nephritis or renal dysfunction (defined as > Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology) occurred in 0.7% (2/268) of patients at 3.5 and 6 months after nivolumab initiation, respectively. Nivolumab was permanently discontinued in both patients; both received high-dose corticosteroids (at least 40 mg prednisone equivalents). Immune-mediated nephritis resolved and did not recur with continuation of corticosteroids in one patient. Renal dysfunction was ongoing in one patient.

- **Immune-mediated hypothyroidism or hyperthyroidism**

In Trial 1, where patients were evaluated at baseline and during the trial for thyroid function, Grade 1 or 2 hypothyroidism occurred in 8% (21/268) of patients receiving nivolumab and none of the 102 patients receiving chemotherapy. The median time to onset was 2.5 months (range: 24 days-11.7 months). Seventeen of the 21 patients with hypothyroidism received levothyroxine. Fifteen of 17 patients received subsequent nivolumab dosing while continuing to receive levothyroxine.

Grade 1 or 2 hyperthyroidism occurred in 3% (8/268) of patients receiving nivolumab and 1% (1/102) of patients receiving chemotherapy. The median time to onset in nivolumab-treated patients was 1.6 months (range: 0-3.3 months). Four of five patients with Grade 1 hyperthyroidism and two of three patients with Grade 2 hyperthyroidism had documented resolution of hyperthyroidism; all three patients received medical management for Grade 2 hyperthyroidism.

- **Any other severe or Grade 3 treatment-related adverse reactions**

Other clinically significant immune-mediated adverse reactions can occur. Immune-mediated adverse reactions may occur after discontinuation of nivolumab therapy.

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of nivolumab-treated patients in Trial 1: pancreatitis, uveitis, demyelination, autoimmune neuropathy, adrenal insufficiency, and facial and abducens nerve paresis.

Across clinical trials of nivolumab administered at doses of 3 mg/kg and 10 mg/kg the following additional clinically significant, immune-mediated adverse reactions were identified: hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillain-Barré syndrome, and myasthenic syndrome.

Nivolumab was discontinued for adverse reactions in 9% of patients. Twenty-six percent of patients receiving nivolumab had a drug delay for an adverse reaction. Serious adverse reactions occurred in 41% of patients receiving nivolumab. Grade 3 and 4 adverse reactions occurred in 42% of patients receiving nivolumab. The most frequent Grade 3 and 4 adverse reactions reported in 2% to less than 5% of patients receiving nivolumab were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. Other adverse events that occurred in $\geq$10% of patients were rash, pruritus, cough, upper respiratory tract infection, peripheral edema, increased AST, increased alkaline phosphatase, hyponatremia, increased ALT, and hyperkalemia, with

no Grade 3-4 AE except for rash which was Grade 3-4 in 0.4%. Other clinically important adverse reactions in less than 10% of patients treated with nivolumab were:

Cardiac Disorders: ventricular arrhythmia

Eye Disorders: iridocyclitis

General Disorders and Administration Site Conditions: infusion-related reactions Investigations: increased amylase, increased lipase

Nervous System Disorders: dizziness, peripheral and sensory neuropathy

Skin and Subcutaneous Tissue Disorders: exfoliative dermatitis, erythema multiforme, vitiligo, psoriasis.

1.4. Rationale for the Schedule of the Study

In this study nivolumab will be given once every 3 weeks (D1 of a 3 week cycle) and ABI-009 will be administered on D8 and D15 of the 3 week cycle starting in Cycle 2 (C2). Thus, ABI-009 will be given weekly for 2 weeks with a 1 week break.

Although nivolumab is approved on a biweekly schedule, in this study, because nivolumab is being given in combination with ABI-009 which is administered 2 out of 3 weeks, a 3 weekly schedule for nivolumab was adopted. In a prior Phase 3 combination study with ipililumab, nivolumab 3 mg/kg was given every 3 weeks during the time when combination therapy was given (65). In this study, nivolumab and ABI-009 have different mechanisms of action. Therefore, it is not expected that the individual toxicities would significantly overlap. As a safety precaution, nivolumab will be given every three weeks (instead of every 2 weeks) when used in combination with ABI-009. Additionally, escalating doses of ABI-009 will start two dose levels below the MTD of 100 mg/m2 observed in the Phase 1 study (44), as well as a de-escalation schedule if DLT is noted at Dose Level 1 (See Dose Reduction in Section 6).

Nivolumab acts by blocking PD1, a negative regulator of T cell activation and response, thus promoting T cell activation and allowing the immune system to attack the tumor (66). Rapamycin suppression of mTOR results in a multitude of effects including a disruption of the G1/S transition of the proliferation cycle and results in a mid-to-late G1 arrest (67). Rapamycin, by disrupting cytokine signaling that promotes lymphocyte growth and differentiation, also promotes the expansion of Treg cells and depletes effector T cells, leading to immune suppression (68). It was therefore hypothesized that administering anti-PD1 antibody first will allow T cell activation, which will not be blunted by later administration of ABI-009. On the other hand, the addition of ABI-009 after anti-PD1 antibody also allows ABI-009 to exert its antiproliferative activity and potentially to increase autophagy for enhanced antigen presentation (30). In a recent study with syngeneic B16 mouse tumor model testing the combination and sequencing of anti-PD1 antibody and ABI-009, the administration of anti-PD1 antibody for one week before combining with ABI-009 demonstrated better antitumor efficacy compared to anti-PD1 /ABI-009 concurrent treatment or ABI-009 administered for one week before anti-PD1 antibody [privileged communication by AADi Bioscience Inc].

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

The primary objective of this study is to determine the maximum tolerated dose of ABI-009 when used in combination with nivolumab in advanced UPS, liposarcoma, osteosarcoma, chondrosarcoma and Ewing sarcoma.

2.1.2. Secondary Objectives

The secondary objectives are to investigate the disease control rate (DCR), progression free survival (PFS), recurrence-free survival (RFS) and overall survival (OS) using nivolumab/ABI-009 combination therapy in advanced Ewing's sarcoma, PEComa, epithelioid sarcoma, desmoid tumor, chordoma, non-small cell lung cancer, small cell lung cancer, urethelial carcinoma, melanoma, renal cell carcinoma, squamous cell carcinoma of head and neck, hepatocellular carcinoma, classical Hodgkin's lymphoma, MSI-H/dMMR metastatic colorectal cancer, and tumors with genetic mutations sensitive to mTOR inhibitors.

2.1.3. Exploratory Objectives

- To correlate DCR based on Immune-related Response Criteria (irRECIST) with that based on RECIST v1.1.
- To correlate DCR with PD-L1 and other biomarker expression in patients' tumors
- To correlate DCR with PTEN mutation in patient's archived tumor

2.2. Endpoints

2.2.1. Primary Endpoint

Maximum tolerated dose (MTD)

2.2.2. Secondary Endpoints

The secondary endpoints are

- Disease control rate (DCR), progression free survival (PFS), recurrence-free survival (RFS) as determined by the institution's radiologic assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and irRECIST criteria (Hodi et al., 2016); and overall survival (OS).
- PFS rate at 3, 6, 9, and 12 months, RFS at 4 months, median PFS, and median 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 PFS rate at 4 months, median PFS, and OS. Recurrence-free survival (RFS) defined as progression free

survival + absence of disease progression or recurrence after surgical resection has been added to the secondary endpoints to obviate this bias.

2.2.3. Exploratory Endpoints

- Correlation between DCR based on Immune-related Response Criteria (irRECIST) with that based on RECIST v1.1.
- Correlation between DCR with PD-L1 and other biomarker expression in patients' tumors.
- Correlation between DCR and PTEN mutation in patient's archived tumor

2.3. Study Design

This is an open label, dose-seeking phase 1/2 study using a defined dose of nivolumab and escalating doses of ABI-009 given intravenously.

I. Dose Escalation Phase 1 Part of Study: The study will employ the standard "cohort of three" design (Storer, 1989). Three patients are treated at each dose level with expansion to six patients per cohort if DLT is observed in one of the three initially-enrolled patients at each dose level. If no DLT occurs after 2 doses, escalation to the next dose level will be permitted. The maximum tolerated dose is defined as the highest safely tolerated dose, where not more than one patient experienced DLT, with the next higher dose level having at least two patients who experienced DLT. Patients in the dose escalation study may continue treatment at their designated dose levels up to eighteen 3-week treatment cycles or until significant disease progression or unacceptable toxicity occurs. No intra-patient dose escalation will take place.

Dose of nivolumab: 3 mg/kg IV over 30 min. q 3 weeks

NB: ABI-009 will start after 2nd Nivo dose, and will be administered on D8 and D15 beginning in C2.

Dose of ABI-009: Escalating doses IV over 30 min for 2 of every 3 weeks:

Treatment Cycle	# Pts.	Dose Level	Dose, mg/m2
Every 3 weeks	3-6	I	56
Every 3 weeks	3-6	II	75
Every 3 weeks	3-6	III	100

Note: DLT includes any $\geq$ Grade 3 colitis, hepatitis, or pneumonitis, any Grade 1-2 colitis, hepatitis or pneumonitis that recurs, worsens or persists with oral steroids longer than 14 days, symptoms of adrenal crisis, any Grade 4 hematologic toxicity or any $\geq$ Grade 3 non-hematologic toxicity.

II. Expansion Phase 2 Part of Study: Following dose escalation, an additional 22-28 patients will receive ABI-009 at the MTD and defined doses of nivolumab to assess overall safety and potential efficacy in a greater number of patients. Patients in the expansion

phase of the study may continue treatment up to 18 3-week treatment cycles or until significant disease progression or unacceptable toxicity occurs.

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

Surgical Resection: After three or more treatment cycles, the principal investigator may recommend surgical debulking, complete surgical removal or a biopsy. If residual disease is present either by histopathological examination or by CT scan/MRI, repeat treatment cycles may be given 2-4 weeks after surgery, if the surgical incision has healed, and if the patient has ≤ grade I toxicity.

Resected or biopsied tumors will be analyzed for the effects of this dual therapy on disease control rate, and immune cell trafficking in the tumor microenvironment. Fresh and paraffin embedded tissue blocks will be analyzed by FACS for PD-L1 and other biomarkers, including Tregs, CD8+, CD4+ cells etc. Immunohistochemistry for cyclin G1, cyclin D1 and Ki67 will be conducted to determine the tumor's proliferative state. Histopathologic examination for tumor necrosis and mitotic index will also be determined.

Conditions for Continuation of Treatment in the Presence of Increased Tumor Size by CT scan or MRI Indicating Progressive Disease by RECIST v1.1:

Treatment may be continued if:

1. There are no signs or symptoms indicating unequivocal progression.
2. There is no worsening of ECOG score attributable to progressive disease.
3. There is no tumor growth at critical sites that is life-threatening.
4. Patient signs an informed consent that he/she is aware of alternative therapies but wishes to defer these therapies.
5. There is clinical benefit, as determined by investigator

2.4. Study Duration

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 or nivolumab.

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 or nivolumab.

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.

2.5. 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 or nivolumab 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 or nivolumab.

Primary analysis for this study will occur after all patients have either completed the study or completed 12 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 nivolumab, 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

3. STUDY POPULATION

3.1. Number of Patients

The anticipated enrollment into this study will be approximately 12-18 patients for the Phase 1 part of the study and approximately 22-28 evaluable patients for the Phase 2 part of the study. The rationale for the number of patients is detailed in Section 8.

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

Before any study-specific procedure, the appropriate written informed consent must be obtained (see Section 11.5).

3.2. 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 Ewing's sarcoma, PEComa, epithelioid sarcoma, desmoid tumor, chordoma, non-small cell lung cancer, small cell lung cancer, urethelial carcinoma, melanoma, renal cell carcinoma, squamous cell carcinoma of head and neck, hepatocellular carcinoma, classical Hodgkin's lymphoma, MSI-H/dMMR metastatic colorectal cancer, and tumors with genetic mutations sensitive to mTOR inhibitors, that is either metastatic or locally advanced and for which surgery is not a recommended option.
2. Patients must have one or more measurable target lesions by CT scan or MRI. Measurable disease by RECIST v1.1, confirmed by investigator.
3. Previously treated patient with Ewing's sarcoma, PEComa, epithelioid sarcoma, desmoid tumor, chordoma, non-small cell lung cancer, small cell lung cancer, urethelial carcinoma, melanoma, renal cell carcinoma, squamous cell carcinoma of head and neck, hepatocellular carcinoma, classical Hodgkin's lymphoma, MSI-H/dMMR metastatic colorectal cancer, and tumors with genetic mutations sensitive to mTOR inhibitors, if treatment is completed after 5 half-lives or ≥28 days prior to enrollment, whichever is shorter.
4. Eligible patients, 12-17 years (≥40 kg) or 18 years old or older, with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
5. 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/ALT ≤2.5 x ULN (≤5 x ULN if attributable to liver metastases); alk phos < 3 x ULN (patients with alk phos >3ULN will be allowed if due to bone metastases) AST ≤2.5 x ULN (≤5 x ULN if attributable to liver metastases)

c. serum creatinine ≤1.5 x ULN

6. 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 × 109/L; b. Platelet count ≥100,000/mm3 (100 × 109/L); c. Hemoglobin ≥9 g/dL.

7. Serum triglyceride <300 mg/dL; serum cholesterol < 350 mg/dL.

8. 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.

9. Life expectancy of >3 months, as determined by the investigator.

10. Ability to understand and sign informed consent.

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

3.3. Exclusion Criteria

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

1. 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.

2. Active gastrointestinal bleeding.

3. Pre-existing thyroid abnormality is allowed provided thyroid function can be controlled with medication.

4. 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).

5. 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.
6. 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).
7. Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy.
8. Unstable coronary artery disease or myocardial infarction during preceding 6 months.
9. Receiving any concomitant antitumor therapy.
10. Patients with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension.
11. 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.
12. Known Human Immunodeficiency Virus (HIV).
13. Active Hepatitis B or Hepatitis C.
14. Non-oncology vaccine therapy used for prevention of infectious disease within 4 weeks of trial enrollment
15. Autoimmune disease including rheumatoid arthritis, systemic progressive sclerosis (scleroderma), systemic lupus erythematosus, autoimmune vasculitis and motor neuropathy considered to be of autoimmune origin (e.g. Guillain-Barre Syndrome)
16. Systemic immunosuppression, including HIV positive status with or without AIDS
17. Skin rash (psoriasis, eczema) affecting > 25% body surface area
18. Inflammatory bowel disease (Crohn's or ulcerative colitis)
19. Ongoing or uncontrolled diarrhea within 4 weeks of trial enrollment
20. Recent history of acute diverticulitis, intraabdominal abscess or gastrointestinal obstruction within 6 months of trial enrollment, which are known risk factors for bowel perforation
21. Current, active or previous history of heavy alcohol abuse
22. Pituitary endocrinopathy and Adrenal insufficiency or excess

4. 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	Day 15		
General Assessments						
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]	X[f]	
BSA Calculation		X[j]				
Prior/Concomitant Medication Evaluation [g]	X	X	X	X	Until 28 days after the last dose of IP	
Prior/Concurrent Procedures Evaluation [g]	X	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					
Survival status						X
Adverse Events		Continuous starting from signing of Informed Consent until 28 days after last dose of IP				
Dexamethasone (every cycle)			X			
Nivolumab Dosing		X				
ABI-009 Dosing: ***To Start after 2nd Nivo dose***			X	X		
Local Laboratory Assessments						
Clinical Chemistry Panel	X	X	X	X	X	
CBC, Differential, Platelet Count	X	X	X	X	X	

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	Day 15		
PT, PTT, INR	X					
Urinalysis	X					
Thyroid function	X	X				
HIV, HBV sAg, HBV cAb, HCV Ab	X					
Fasting Lipids	X	X				
Trough rapamycin level [k]						
Immunohistochemistry for PTEN mutation in archived tumor	X					
Imaging and Efficacy Assessments						
CT/MR [l]	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 except for thyroid and fasting lipids every 12 weeks.
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, and as clinically indicated following standard of care procedures.
j. Calculated ONLY on C1/D1; to be recalculated only if the weight changes by > 10% in subsequent cycles.
k. Trough levels of rapamycin will be obtained immediately prior to ABI-009 infusion at Day 15 of the second and third cycles of ABI-009, a week after the first dose in both cycles.
l. 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.

5. PROCEDURES

5.1. Screening Evaluations

This study will be conducted at a single center, the Sarcoma Oncology Research Center, Santa Monica CA, USA. 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 have signed the informed consent.

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
- 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 2 weeks prior to study day 1, preferably as close to the day of enrollment as possible
- Immunohistochemistry for PTEN mutation on patient's archived tumor

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 (CRF).

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 4.

5.2. Treatment Period

All product administration (investigational or otherwise) 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 or up to 18 3-week treatment cycles.

5.2.1. 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
- 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 (every 12 weeks)
- Fasting lipids (every 12 weeks)
- Adverse Event assessment

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)

5.2.2. 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
- Clinical chemistry panel (including but not limited to sodium, potassium, chloride, glucose, alkaline phosphatase (ALP), AST/SGOT, ALT/SGPT, serum albumin)
- Trough levels of rapamycin will be obtained immediately prior to ABI-009 infusion at Day 15 of second and third cycles of ABI-009.
- Adverse Event assessment

5.2.3. Day 15 Assessment

The following assessments will be performed on Day 15 of each cycle, unless otherwise specified:

- Concomitant medication and procedures evaluation
- Vital signs
- CBC, differential and platelet count
- Adverse Event assessment

5.2.4. Response Assessment

Tumor response will be assessed by CT or MRI scan of the chest, abdomen, and pelvis (CAP); image preparation and evaluation will follow the specifications provided in the RECIST version 1.1. Immune RECIST (irRECIST) will also be obtained. 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:

- ≤2 weeks prior to C1D1 (screening)
- followed by every 6 weeks for the first year; then every 12 weeks until disease progression or unacceptable toxicity. 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. 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.

Conditions for Continuation of Treatment in the Presence of Increased Tumor Size by CT scan or MRI Indicating Progressive Disease by RECIST v1.1:

Treatment may be continued if:

1. There are no signs or symptoms indicating unequivocal progression.
2. There is no worsening of ECOG score attributable to progressive disease.
3. There is no tumor growth at critical sites that is life-threatening.
4. Patient signs an informed consent that he/she is aware of alternative therapies but wishes to defer these therapies.
5. There is clinical benefit, as determined by investigator

Table 3. Analyte Listing

Chemistry	Hematology	Coagulation	Urinalysis	Other Labs
Sodium	WBC	PT	Specific gravity	Pregnancy test
Potassium	RBC	PTT	pH	
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			PD-1\PD-L1
Total bilirubin	-Monocytes			
Alkaline phosphatase	-Eosinophils			
AST (SGOT)	-Basophils			
ALT (SGPT)				
Amylase				
Lipase				

5.3. 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 or

nivolumab. All efforts should be made to conduct this visit. If it is not possible to conduct the EOT Visit, documentation of efforts to complete the visit should be provided.

The following procedures will be completed at the EOT Visit as designated in the Schedule of Assessments (Table 2):

- 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

5.4. 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. DESCRIPTION OF STUDY TREATMENTS (ABI-009/NIVO)

6.1. ABI-009/Nivolumab Dosage, Administration, and Schedule

For the Phase 1 part of study, patients will receive nivolumab 3 mg/kg as IV infusion over 60 min every 3 weeks, followed by escalating doses of ABI-009 56, 75, 100 mg/m^2 for 2 of every 3 weeks by IV infusion over 30 minutes. ABI-009 will start on Day 8 of Cycle 2. If DLT develops in more than 1 patient at Dose 56 mg/m2, the dose will be de-escalated to 45 mg/m2 and to 30 mg/m2 if DLT develops at 45 mg/m2. Patients will continue therapy until unequivocal clinical disease progression, unacceptable toxicity, or until in the opinion of the investigator the patient is no longer benefiting from therapy, or at the patient's discretion.

For the Phase 2 part of study, patients will receive nivolumab 3 mg/kg as IV infusion over 30 min every 3 weeks, followed by ABI-009 at the MTD dose for 2 of every 3 weeks by IV infusion over 30 minutes. ABI-009 will start on Day 8 of Cycle 2. Patients will continue therapy until unequivocal clinical disease progression, unacceptable toxicity, or until in the opinion of the investigator the patient is no longer benefiting from therapy, or at the patient's discretion.

6.2. ABI-009 Dose Modification and Stopping Rules

6.2.1. 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.

If a Grade 4 hematologic toxicity occurs, the dose of ABI-009 is held until toxicity resolves to Grade 1 or less. The dose of ABI-009 is then modified according to the dose modification section. If a Grade 3 non-hematologic toxicity occurs, both nivolumab and ABI-009 are withheld until toxicity resolves to Grade 1 or less. The dose of ABI-009 is then modified according to the dose modification section. Nivolumab has no dose modification.

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.

During the Phase 2 part of the study, doses of ABI-009 will be reduced for hematologic and other toxicities. Two levels of dose modifications are permitted according to the criteria below. If MTD is determined to be 56 mg/m^2, dose reductions will occur sequentially (45 mg/m^2 and 30 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
1	Initial Dose: 56 mg/m^2
-1 (first dose reduction)	45 mg/m^2
-2 (second dose reduction)	30 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

6.2.2. 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.

6.2.2.1. 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)

6.2.2.2. 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.

6.2.2.3. 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 6.2.1) should never be rechallenged.

6.2.3. Overdose

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

6.3. Nivolumab Dose Modification and Stopping Rules

6.3.1. Dose Modification and Stopping Rules

Nivolumab (Opdivo®); see product information at www.accessdata.fda.gov)

Withhold nivolumab for any of the following:

- **Immune-mediated Grade 2 pneumonitis**

Monitor patients for signs and symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis, followed by corticosteroid taper. Permanently discontinue nivolumab for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold nivolumab until resolution for moderate (Grade 2) pneumonitis

- **Immune-mediated Grade 2-3 colitis**

Monitor patients for immune-mediated colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents. Withhold nivolumab for Grade 2 or 3 immune-mediated colitis. Permanently discontinue nivolumab for Grade 4 colitis or for recurrent colitis upon restarting nivolumab.

- **Immune-mediated hepatitis.** Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN

Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater transaminase elevations, with or without concomitant elevation in total bilirubin. Withhold nivolumab for moderate (Grade 2) and permanently discontinue nivolumab for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis

- **Immune-mediated nephritis and renal dysfunction. Creatinine greater than 1.5 and up to 6 times ULN or greater than 1.5 times baseline**

Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) serum creatinine elevation and permanently discontinue nivolumab. For severe (Grade 3) or moderate (Grade 2) serum creatinine elevation, withhold nivolumab and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper; if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue nivolumab.

- **Immune-mediated hypothyroidism or hyperthyroidism**

There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

Monitor thyroid function prior to and periodically during treatment. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. There are no recommended dose adjustments of nivolumab for hypothyroidism or hyperthyroidism.

- **Any other severe or Grade 3 treatment-related adverse reactions**

For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, withhold nivolumab, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting nivolumab after completion of corticosteroid taper based on the severity of the event.

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

Resume nivolumab in patients whose adverse reactions recover to Grade 0-1. Permanently discontinue nivolumab for any of the following:

- Any life-threatening or Grade 4 adverse reaction
- Grade 3 or 4 pneumonitis
- Grade 4 colitis
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
- Creatinine greater than 6 times ULN
- Any severe or Grade 3 treatment-related adverse reaction that recurs
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 treatment-related adverse reactions that do not recover to Grade 0-1 within 12 weeks after last dose of nivolumab

7. STUDY DRUG MANAGEMENT

7.1. Description of Study Drugs

7.1.1. 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.

7.1.2. Nivolumab Packaging, Labeling and Storage

Nivolumab (Opdivo) is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2 (64). Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

Nivolumab (OPDIVO) is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. OPDIVO injection for intravenous infusion is supplied in single-use vials. Each mL of OPDIVO solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

Nivolumab (OPDIVO) is available as 40 mg/4 ml and 100 mg/10 ml single use vials. Store nivolumab under refrigeration at 2°C to 8°C (36°F-46°F). Protect nivolumab from light by storing in the original package until time of use. Do not freeze or shake.

7.2. ABI-009 and Nivolumab Accountability, Disposal, and Compliance

For ABI-009, 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.

For ABI-009, 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 CRF 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.

For Nivolumab, the Investigator, or designee, shall record the dispensing of study drug to patients. The study drug record will be made available to AADi or authorized AADi-designated monitoring personnel for the purpose of accounting for the use of the drug.

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

7.3. 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:

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

   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).

7.4. 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. Investigator or designee will be responsible for drug inventory, drug accountability, and disposition of unused study drug.

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.

7.5. Nivolumab (Opdivo) Reconstitution

Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, is discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial (64).

Preparation of nivolumab:

- Withdraw the required volume of nivolumab and transfer into an intravenous container.
- Dilute nivolumab with 100 ml 0.9% Sodium Chloride Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of nivolumab.
    - Storage of Infusion
    - The product does not contain a preservative.

After preparation, store the nivolumab infusion either:

- at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation.
- Do not freeze.

Administration of nivolumab:

- Administer the infusion over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).
- Do not coadminister other drugs through the same intravenous line.
- Flush the intravenous line at end of infusion.

7.6. Concomitant Medications and Procedures

Dexamethasone, 10 mg IV, will be given on D8 of every cycle, beginning Cycle 2, to preempt or reduce the incidence/severity of pneumonitis and/or hepatitis with combined use of nivolumab and ABI-009.

All concomitant treatments, including blood and blood products, must be reported on the CRF. Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.8.

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 CRF(s).

7.7. 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 CRF. 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 CRF.

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.

7.8. 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

8. STATISTICAL CONSIDERATIONS

8.1. Study Endpoints

Primary Endpoint:

- MTD

Secondary Endpoint(s):

- Disease control rate (DCR), ORR (CR+ PR)
- Progression-free survival
- Progression-free survival rate at 3,6,9,12 months
- Overall survival
- Incidence and grade of treatment-emergent AEs

Exploratory Endpoint(s):

- Correlation of response based on RECIST v1.1 and irRECIST
- Correlation between response and PD-L1 expression in patients' tumors
- Correlation between DCR and PTEN mutation in patient's archived tumor

8.2. Safety Analysis

Demographic and baseline information (e.g., extent of prior therapy) on study patients will be tabulated. The number of patients studied for the Phase 1 part of study could range from 12 to 18 evaluable patients, and 22-28 evaluable patients for the Phase 2 part of the study.

For the Phase 1 part of the study, the following information will be reported for adverse events observed in the study: dose level, type (organ affected or laboratory determination, such as absolute neutrophil count), severity (by NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 and most extreme abnormal values for laboratory determinations) and relatedness to study treatment. For each dose the number and percentage of patients experiencing any grade 3, 4, or 5 adverse event will be reported, as well as the number and percentage of patients who experienced selected specific types of adverse events. In addition, the DLTs will be summarized by dose level and the MTD will be determined.

The following table gives the probability of dose escalation at a single dose level as a function of the true probability of DLT at that level using the cohorts of 3 design (Objective #1) (2).

Table 1. Probability of Dose Escalation

True Rate of DLT (%)	Probability of Dose Escalation
10	0.91
20	0.71
30	0.49
40	0.31
50	0.17

For the Phase 2 part of the study, the entire treated population (Full Analysis Set) will be the analysis population for all safety analyses. Adverse events will be coded using the NIH CTCAE v4.03. 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 all patient groups together (metastatic and locally advanced). Although this study will not be large enough to allow firm conclusions about safety or efficacy, it will provide preliminary data on safety and efficacy that will be useful in planning future studies. Frequency tables, graphs, and summary statistics will be used for outcome data.

Patient incidence of all treatment-emergent AEs will be tabulated. Tables of fatal adverse events, serious adverse events, treatment-related AEs, and adverse events leading to withdrawal from investigation product will also be provided.

For select laboratory parameters, changes of laboratory values over time (e.g., 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.

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

8.3. Efficacy Analysis

The Efficacy Analysis Dataset includes all enrolled patients with measurable tumor per RECIST v1.1 at baseline who receive at least two doses of ABI-009 and had a follow-up CT scan/MRI.

The disease control rate (DCR; CR+PR+SD), objective response rate (ORR; CR + PR), progression free survival (PFS), recurrence-free survival (RFS) will be assessed by an local radiologic assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The focus of the study is to estimate the DCR in patients treated with ABI-009 and nivolumab. Patients who progress before receiving ABI-009 will be replaced, and will not be included in the statistical analysis. The number and percentage of patients achieving disease control (CR, PR or SD) will be summarized.

Analysis of other efficacy endpoints, PFS at 4 months, RFS at 4 months, median PFS, median RFS and median OS will be assessed for all subtypes together, and separately in the five sarcoma subtypes with metastatic disease and locally advanced disease. Patients may be stratified further as locally advanced or metastatic. 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 PFS at 4 months, median PFS, and OS. Recurrence-free survival (RFS) defined as progression free survival + absence of disease progression or recurrence after surgical resection has been added to the secondary endpoints to obviate this bias.

PFS, RFS and OS will be summarized using Kaplan-Meier (KM) analysis. The number of patients in each category is expected to be small; therefore, PFS at 4 months, RFS at 4 months, median PFS, and median OS for these patients will be summarized by descriptive statistics.

8.4. Exploratory Analysis

DCR based on RECIST v1.1 will be correlated with DCR based on Immune-related Response Criteria (irRECIST) and summarized by descriptive statistics and comparative KM analysis.

PD-L1 and other biomarker expression in patients' tumors will be correlated with DCR and summarized by descriptive statistics.

DCR will be correlated with presence of PTEN mutation in patient's archived tumor and summarized by descriptive statistics.

8.5. Covariates and Subgroups

Up to 20 clinical indications will be studied , including Ewing's sarcoma, PEComa, epithelioid sarcoma, desmoid tumor, chordoma, non-small cell lung cancer, small cell lung cancer, urethelial carcinoma, melanoma, renal cell carcinoma, squamous cell carcinoma of head and neck, hepatocellular carcinoma, classical Hodgkin's lymphoma, MSI-H/dMMR metastatic colorectal cancer, and tumors with genetic mutations sensitive to mTOR inhibitors, as well as those with metastatic disease and those with locally advanced disease for which surgery is not an option. The subgroups of patients will be assessed together and as subgroups for the efficacy endpoints,

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

8.6. Sample Size Considerations

The analyses of all study objectives is descriptive and hypothesis generating in nature. The sample size will not be enough to make any statistical conclusions about efficacy or safety, but will be useful for planning future Phase 2 clinical trials.

8.7. 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.

8.8. Planned Methods of Analysis

8.8.1. 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.

8.8.2. General Considerations

The secondary efficacy endpoint, DCR, will be determined by a local radiologic assessment.

The primary analysis will evaluate the DCR in patients treated with ABI-009 and nivolumab by providing the number and proportion of patients achieving disease control along with an exact binomial 95% CI for the proportion.

DCR is defined as the proportion of patients who achieve a confirmed CR, PR or SD per RECIST v1.1. If an initial observation of objective response (CR or PR) is made, a confirmation scan should be done at 6 weeks after initial observation.

8.8.3. Other Secondary Efficacy Endpoints

Analysis of other secondary efficacy endpoints PFS at 4 months, RFS at 4 months, median PFS, and median OS will be done separately for the 5 sarcoma subtypes groups. 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.

Recurrence-free survival (RFS) is defined as the time from the first dose date to the first observation of a disease progression or recurrence/progression after surgical resection of tumor, or death due to any cause. If a patient has not progressed or died by the data cutoff date, the RFS time will be censored at the time of the last evaluable tumor assessment.

Overall survival is defined as the time from the first dose date to the date of death due to any cause. If a patient is lost to follow-up before the data cutoff date or still alive by the data cutoff date the OS time will be censored at the last contact date.

9. MONITORING, RECORDING AND REPORTING OF ADVERSE EVENTS

9.1. 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 (58, 59).

9.2. Toxicities of Nivolumab

Nivolumab is an FDA approved monoclonal antibody for the treatment of advanced melanoma, non small cell lung cancer, renal cell carcinoma and bladder cancer. The toxicities of nivolumab are immune-related adverse events including immune-mediated pneumonitis, hepatitis, endocrinopathies and visual disorders. More details and known precautions, warnings and AEs are found in the product information (www.accessdata.fda.gov).

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 CRF 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 6.2.3 for the definition of overdose. Any sequela of an accidental or intentional overdose of the IP should be reported as an AE on the AE CRF. If the sequela of an overdose 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 CRF 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 CRF (eg, Adverse Event Summary CRF).

9.3. 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.

9.4. Serious Adverse Events

9.4.1. 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.

9.4.2. Reporting Procedures for Serious Adverse Events

All suspected unexpected serious adverse reactions (SUSARs) must be reported by the Investigator to their IRB in writing, and to the FDA within 7 days as required by law.

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 CRF. 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.

9.5. 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.

10. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

10.1. 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 CRF)

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

10.2. 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 CRF)

The reason for study discontinuation should be recorded in the CRF 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 (e.g., 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.

10.3. 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 Investigational Product 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's Investigational Product and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism.

11. REGULATORY OBLIGATIONS

11.1. 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 the investigator to AADi. 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.

11.2. 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.

11.3. 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.

11.4. Protocol Amendments

If investigator amends the protocol, agreement from AADi 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.

11.5. Termination of the Study

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.

12. DATA HANDLING AND RECORDKEEPING

12.1. 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 CRFs or CD-ROM.

12.2. Data Management

Data will be collected via CRF 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.

12.3. 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.

12.4 Research Use of Fresh and Stored Human Samples, Specimens or Data

- Intended Use: Samples and data collected under this protocol will be used to study the effects of combination therapy with ABI-009, an mTOR inhibitor that affects the differentiation of M1 and M2 macrophages in the tumor microenvironment (TME), and a immune checkpoint inhibitor, nivolumab, that inhibits CTLA4 and PD-1 and ligands in the TME. No genetic testing will be conducted.
- Resected or biopsied tumors that are $\geq$ than 500 mm^3 will be collected and cut into two pieces. One piece of tumor will be placed in media, processed and analyzed by flow cytometry (FACS). The second piece will be placed in 10% neutral-buffered formalin and later processed to formalin-fixed paraffin-embedded (FFPE) blocks. Tumors that are $\leq$ 500 mm^3 in volume will be not be cut and the whole tumor will be used for FACS analysis.
- For biomarker studies, flow cytometry analysis will be for human CD45, CD3, CD4, CD8, CD56, LAG-3, PD-1 and PD-L1 markers. Cell suspensions will be divided in two tubes, and each tube will be analyzed independently for the individual set of markers. Tube 1: CD45, CD3, CD4, CD8, CD56, PD-1, PD-L1, viability. Tube 2:

CD45, CD3, CD4, CD8, CD56, LAG-3, CD19 or CD20 (B cell marker), TIM3, 4-IBB, and FoxP3 regulatory T cells.

- Histopathologic examination of resected or biopsied tumors will be conducted, the degree of tumor necrosis and mitotic index will be assessed, and immunohistochemical analysis for expression of PD-1, PD-L1, CD8+, CD4+, CD19, CD20, CD45, NK, Ki67, cyclin G1, cyclin D1 will be conducted.
- Storage: Access to stored samples will be limited using a locked freezer. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- Tracking: Data will be tracked using a secure database system (e.g. Merge eCOS).
- Disposition at the completion of the study: All stored samples will be archived at the clinical site. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

12.5 Future Use of Stored Specimens

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. Data collected for this study will be analyzed and stored at the clinical site. After the study is completed, the de-identified, archived data will be transmitted to and stored in a secure database under the supervision of the principal investigator, for use by other researchers including those outside of the study. Permission to transmit data to the secure data base will be included 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 (e.g., the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). The patient has no commercial rights to the products and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

12.6 Sample Storage and Destruction

Any blood or tumor 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.

Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study.

The records should be retained by the Investigator/Sponsor according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer; but at a minimum, all study documentation must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of ABI-009.

Since the evaluations are not expected to benefit the patient directly or to alter the treatment course, the results of 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 (e.g., 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.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Study Monitoring

The Institution representative, 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, CRFs and other pertinent data) provided that patient confidentiality is respected.

The Institution representative together with the AADi representative are responsible for verifying the CRFs as needed 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, CRFs, 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 CRFs, are resolved.

13.2. 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.

14. 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.

15. REFERENCES

1. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. 2010.
2. Storer BE. Design and analysis of phase I clinical trials. Biometrics. 1989;45(3):925-37.
3. Judson I, Verweij J, Gelderblom H, Hartmann JT, Schoffski P, Blay JY, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol. 2014;15(4):415-23.
4. Wagner MJ, Amodu LI, Duh MS, Korves C, Solleza F, Manson SC, et al. A retrospective chart review of drug treatment patterns and clinical outcomes among patients with metastatic or recurrent soft tissue sarcoma refractory to one or more prior chemotherapy treatments. BMC Cancer. 2015;15:175.
5. Mocellin S, Rossi CR, Brandes A, Nitti D. Adult soft tissue sarcomas: conventional therapies and molecularly targeted approaches. Cancer Treat Rev. 2006;32(1):9-27.
6. Sharma S, Takyar S, Manson SC, Powell S, Penel N. Efficacy and safety of pharmacological interventions in second- or later-line treatment of patients with advanced soft tissue sarcoma: a systematic review. BMC Cancer. 2013;13:385.
7. Petek BJ, Loggers ET, Pollack SM, Jones RL. Trabectedin in soft tissue sarcomas. Marine drugs. 2015;13(2):974-83.
8. Gotink KJ, Verheul HM. Anti-angiogenic tyrosine kinase inhibitors: what is their mechanism of action? Angiogenesis. 2010;13(1):1-14.
9. van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379(9829):1879-86.
10. Coens C, van der Graaf WT, Blay JY, Chawla SP, Judson I, Sanfilippo R, et al. Health-related quality-of-life results from PALETTE: A randomized, double-blind, phase 3 trial of pazopanib versus placebo in patients with soft tissue sarcoma whose disease has progressed during or after prior chemotherapy-a European Organization for research and treatment of cancer soft tissue and bone sarcoma group global network study (EORTC 62072). Cancer. 2015;121(17):2933-41.
11. D'Incalci M, Galmarini CM. A review of trabectedin (ET-743): a unique mechanism of action. Mol Cancer Ther. 2010;9(8):2157-63.
12. Thornton K. Trabectedin: The evidence for its place in therapy in the treatment of soft tissue sarcoma. Core Evidence. 2009;4:191-8.
13. Reichardt P, Grünwald V, Kasper B, Schuler M, Gelderblom H. Efficacy of trabectedin in patients with some rare advanced soft tissue sarcoma subtypes other than liposarcoma and leiomyosarcoma. J Med Drug Rev. 2015;5:33-42.
14. Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. J Clin Oncol. 2016;34(8):786-93.
15. Samuels BL, Chawla S, Patel S, von Mehren M, Hamm J, Kaiser PE, et al. Clinical outcomes and safety with trabectedin therapy in patients with advanced soft tissue sarcomas following failure of prior chemotherapy: results of a worldwide expanded access program study. Ann Oncol. 2013;24(6):1703-9.
16. Demetri GD, Chawla SP, Ray-Coquard I, Le Cesne A, Staddon AP, Milhem MM, et al. Results of an international randomized phase III trial of the mammalian target of rapamycin inhibitor ridaforolimus versus placebo to control metastatic sarcomas in patients after benefit from prior chemotherapy. J Clin Oncol. 2013;31(19):2485-92.

17. Schuetze S, Baker L, Maki R, editors. Sirolimus reduced tumor-related morbidity and resulted in biochemical and radiographic response in patients with progressive sarcoma. ASCO Annual Meeting; 2006; Chicago, IL: J Clin Oncol
18. Merimsky O, Bernstein-Molho R, Sagi-Eisenberg R. Targeting the mammalian target of rapamycin in myxoid chondrosarcoma. Anticancer Drugs. 2008;19(10):1019-21.
19. Novartis Pharmaceuticals Corporation. Treatment of Patients With RAD001 Who Have Progressive Sarcoma (NCT00767819). Available from: https://clinicaltrials.gov/ct2/show/NCT00767819.
20. St. Jude Children's Research Hospital. Everolimus for Treating Pediatric Patients With Recurrent or Refractory Tumors (NCT00187174). Available from: https://clinicaltrials.gov/ct2/show/NCT00187174.
21. Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. Science. 2015;348(6230):74-80.
22. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711-23.
23. Sharon E, Streicher H, Goncalves P, Chen HX. Immune checkpoint inhibitors in clinical trials. Chin J Cancer. 2014;33(9):434-44.
24. Burgess MA, Bolejack V, Van Tine BA, Schuetze S, Hu J, D'Angelo SP et al. Multicenter phase II study of pembrolizumab (P) in advanced soft tissue (STS) and bone sarcomas (BS): Final results of SARC028 and biomarker analyses. J Clin Oncol 35, 2017 (suppl; abstr 11008).
25. Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, et al. IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature. 2001;410(6832):1107-11.
26. Germano G, Frapolli R, Belgiovine C, Anselmo A, Pesce S, Liguori M, et al. Role of macrophage targeting in the antitumor activity of trabectedin. Cancer Cell. 2013;23(2):249-62.
27. Tseng WW, Somaiah N, Engleman EG. Potential for immunotherapy in soft tissue sarcoma. Human vaccines & immunotherapeutics. 2014;10(11):3117-24.
28. Longo V, Brunetti O, Azzariti A, Galetta D, Nardulli P, Leonetti F, Silvestris N. Strategies to Improve Checkpoint Inhibitors Efficacy, Other Than Abscopal Effect: A Systematic Review. Cancers. 2019;11(4):539.
29. Yuan R, Kay A, Berg WJ, Lebwohl D. Targeting tumorigenesis: development and use of mTOR inhibitors in cancer therapy. J Hematol Oncol. 2009;2:45.
30. Corradetti MN, Guan KL. Upstream of the mammalian target of rapamycin: do all roads pass through mTOR? Oncogene. 2006;25(48):6347-60.
31. Dowling RJ, Topisirovic I, Fonseca BD, Sonenberg N. Dissecting the role of mTOR: lessons from mTOR inhibitors. Biochim Biophys Acta. 2010;1804(3):433-9.
32. Weigelt B, Downward J. Genomic Determinants of PI3K Pathway Inhibitor Response in Cancer. Frontiers in oncology. 2012;2:109.
33. Li J, Zhu J, Cao B, Mao X. The mTOR signaling pathway is an emerging therapeutic target in multiple myeloma. Curr Pharm Des. 2014;20(1):125-35.
34. O'Donnell A, Faivre S, Burris HA, 3rd, Rea D, Papadimitrakopoulou V, Shand N, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral mammalian target of rapamycin inhibitor everolimus in patients with advanced solid tumors. J Clin Oncol. 2008;26(10):1588-95.
35. Baselga J, Campone M, Piccart M, Burris HA, 3rd, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012;366(6):520-9.
36. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):514-23.

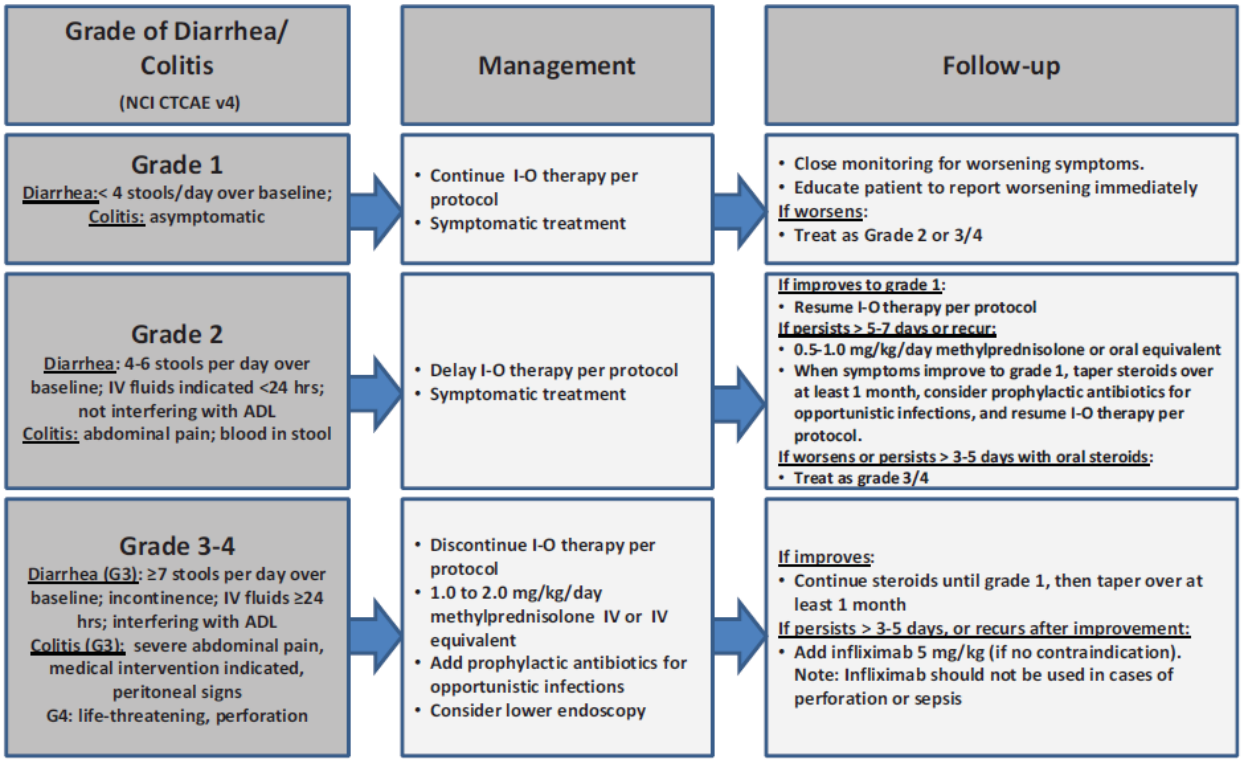
37. Hanna SC, Heathcote SA, Kim WY. mTOR pathway in renal cell carcinoma. Expert Rev Anticancer Ther. 2008;8(2):283-92.
38. Molina AM, Feldman DR, Voss MH, Ginsberg MS, Baum MS, Brocks DR, et al. Phase 1 trial of everolimus plus sunitinib in patients with metastatic renal cell carcinoma. Cancer. 2011;118(7):1868-76.
39. Thompson LA, Kim M, Wenger SD, O'Bryant CL. Everolimus: a new treatment option for advanced pancreatic neuroendocrine tumors. Ann Pharmacother. 2012;46(9):1212-9.
40. Albiges L, Chamming's F, Duclos B, Stern M, Motzer RJ, Ravaud A, et al. Incidence and management of mTOR inhibitor-associated pneumonitis in patients with metastatic renal cell carcinoma. Ann Oncol. 2012;23(8):1943-53.
41. de Oliveira MA, Martins EMF, Wang Q, Sonis S, Demetri G, George S, et al. Clinical presentation and management of mTOR inhibitor-associated stomatitis. Oral oncology. 2011;47(10):998-1003.
42. Qi WX, Huang YJ, Yao Y, Shen Z, Min DL. Incidence and risk of treatment-related mortality with mTOR inhibitors everolimus and temsirolimus in cancer patients: a meta-analysis. PLoS One. 2013;8(6):e65166.
43. Zhou H, Luo Y, Huang S. Updates of mTOR inhibitors. Anticancer Agents Med Chem. 2010;10(7):571-81.
44. Gonzalez-Angulo AM, Meric-Bernstam F, Chawla S, Falchook G, Hong D, Akcakanat A, et al. Weekly nab-Rapamycin in Patients with Advanced Nonhematologic Malignancies: Final Results of a Phase I Trial. Clin Cancer Res. 2013;19(19):5474-84.
45. Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 2005;23(31):7794-803.
46. Kratz F. Albumin as a drug carrier: design of prodrugs, drug conjugates and nanoparticles. J Control Release. 2008;132(3):171-83.
47. Kremer P, Hartung G, Bauder-Wust U, Schrenk HH, Wunder A, Heckl S, et al. Efficacy and tolerability of an aminopterin-albumin conjugate in tumor-bearing rats. Anticancer Drugs. 2002;13(6):615-23.
48. Schnitzer JE. gp60 is an albumin-binding glycoprotein expressed by continuous endothelium involved in albumin transcytosis. Am J Physiol. 1992;262(1 Pt 2):H246-54.
49. Schnitzer JE, Oh P, Jacobson BS, Dvorak AM. Caveolae from luminal plasmalemma of rat lung endothelium: microdomains enriched in caveolin, Ca(2+)-ATPase, and inositol trisphosphate receptor. Proc Natl Acad Sci U S A. 1995;92(5):1759-63.
50. Desai N, Trieu V, Yao Z, Louie L, Ci S, Yang A, et al. Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. Clin Cancer Res. 2006;12(4):1317-24.
51. Kennecke H, Rahman M, Yip S, Woods R, Schaeffer D, Tai I, editors. Effect of nab-rapamycin versus rapamycin in colorectal cancer cell lines and associations with KRAS and PI3K mutations. Proceedings of the 47th American Society of Clinical Oncology (ASCO) Annual Meeting; 2011 June 3-7; Chicago, IL,: J Clin Oncol
52. Trieu V, Ran S, Volk L, Stutzman A, D'Cruz O, Desai N, editors. CNS safety, antitumor activity, and antiangiogenic activity of nab-rapamycin (ABI-009). Proceedings of the 100th American Association for Cancer Research Annual Meeting (AACR); 2009 Apr 18-22; Denver CO: AACR.
53. De T, Trieu V, Yim Z, Cordia J, Yang A, Beals B, et al., editors. Nanoparticle albumin-bound (nab) rapamycin as an anticancer agent. Proceedings of the 98th American Association for Cancer Research Annual Meeting (AACR); 2007 Apr 14-18; Los Angeles CA: AACR.

54. Cirstea D, Hideshima T, Rodig S, Santo L, Pozzi S, Vallet S, et al. Dual inhibition of akt/mammalian target of rapamycin pathway by nanoparticle albumin-bound-rapamycin and perifosine induces antitumor activity in multiple myeloma. Mol Cancer Ther. 2010;9(4):963-75.
55. Desai N, D'Cruz O, Trieu V, editors. Potent antitumor effects of nab-rapamycin (ABI-009) in combination with kinase inhibitors erlotinib and perifosine. Proceedings of the 100th American Association for Cancer Research Annual Meeting (AACR); 2009 Apr 18-22; Denver CO: AACR.
56. Fasolo A, Sessa C. Targeting mTOR pathways in human malignancies. Curr Pharm Des. 2012;18(19):2766-77.
57. Sehgal SN. Sirolimus: its discovery, biological properties, and mechanism of action. Transplant Proc. 2003;35(3 Suppl):7S-14S.
58. Wyeth Pharmaceuticals Inc. Rapamune® Package Insert. 2015.
59. Wyeth Pharmaceuticals Inc. TORISEL® Package Insert. 2015.
60. Novartis Pharmaceuticals Corporation. Afinitor® Package Insert. 2014.
61. Danesi R, Boni JP, Ravaud A. Oral and intravenously administered mTOR inhibitors for metastatic renal cell carcinoma: pharmacokinetic considerations and clinical implications. Cancer Treat Rev. 2013;39(7):784-92.
62. Banaszynski LA, Liu CW, Wandless TJ. Characterization of the FKBP.rapamycin.FRB ternary complex. J Am Chem Soc. 2005;127(13):4715-21.
63. Shor B, Zhang WG, Toral-Barza L, Lucas J, Abraham RT, Gibbons JJ, et al. A new pharmacologic action of CCI-779 involves FKBP12-independent inhibition of mTOR kinase activity and profound repression of global protein synthesis. Cancer Res. 2008;68(8):2934-43.
64. Bristol-Myers Squibb Company. Nivolumab® Package Insert 2015 [cited Reference ID: 3831673]. Available from: www.accessdata.fda.org.
65. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015;372(21):2006-17.
66. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252-64.
67. Dumont FJ, Su Q. Mechanism of action of the immunosuppressant rapamycin. Life Sci. 1996;58(5):373-95.
68. Battaglia M, Stabilini A, Migliavacca B, Horejs-Hoeck J, Kaupper T, Roncarolo MG. Rapamycin promotes expansion of functional CD4+CD25+FOXP3+ regulatory T cells of both healthy subjects and type 1 diabetic patients. J Immunol. 2006;177(12):8338-47.
69. Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika. 1934;26(4):404-13.
70. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53(282 (Jun 1958)):457-81.
71. Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38:29-41.

APPENDIX: ADVERSE EVENT MANAGEMENT ALGORITHMS FOR NIVOLUMAB

GI Adverse Event Management Algorithm

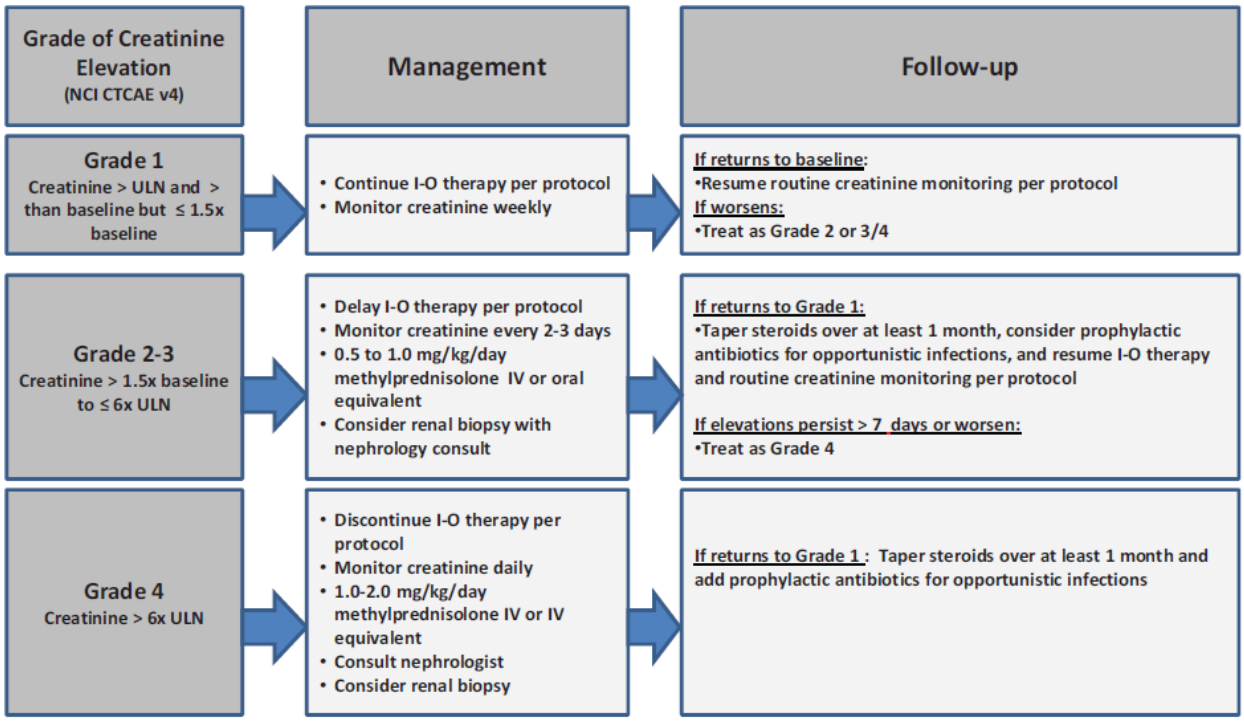
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

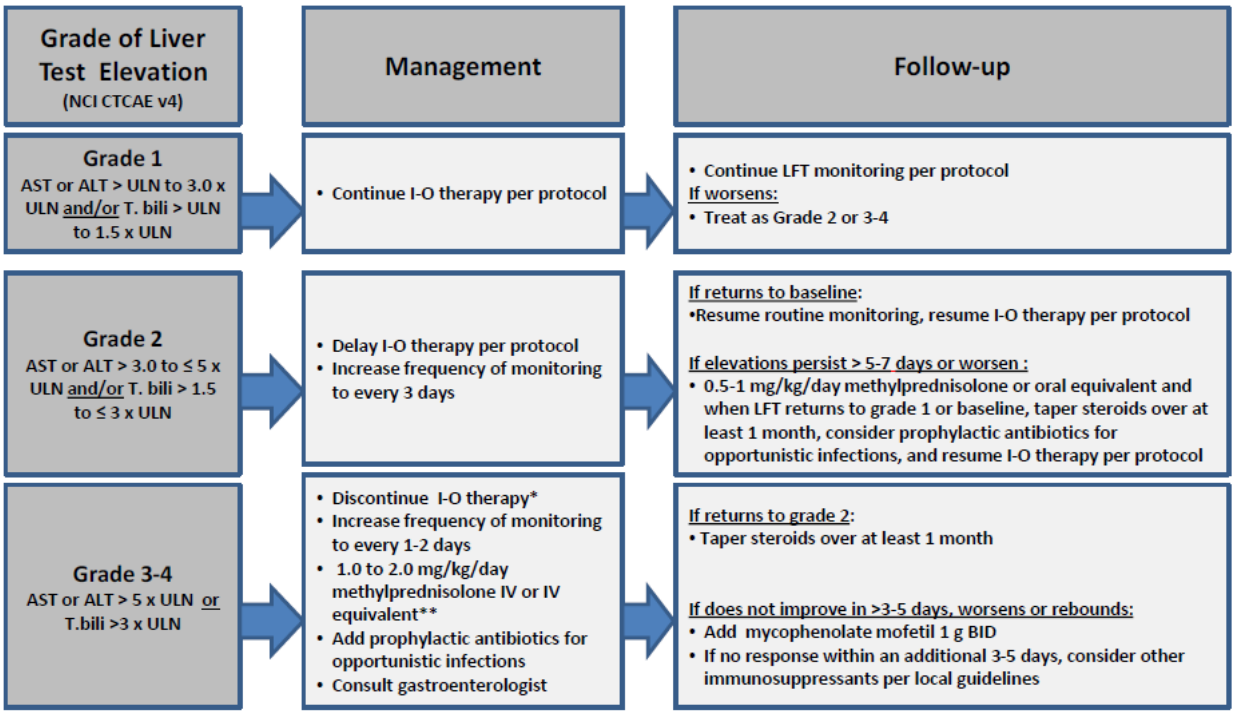
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



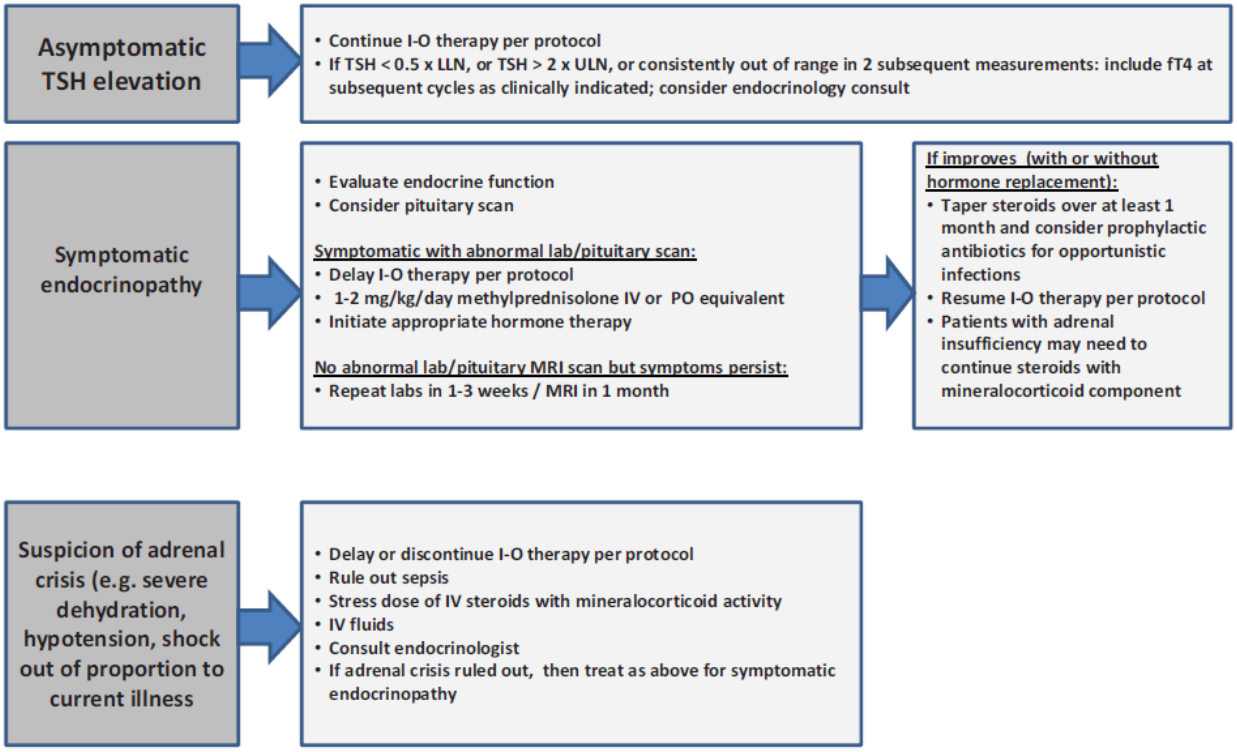
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Management Algorithm

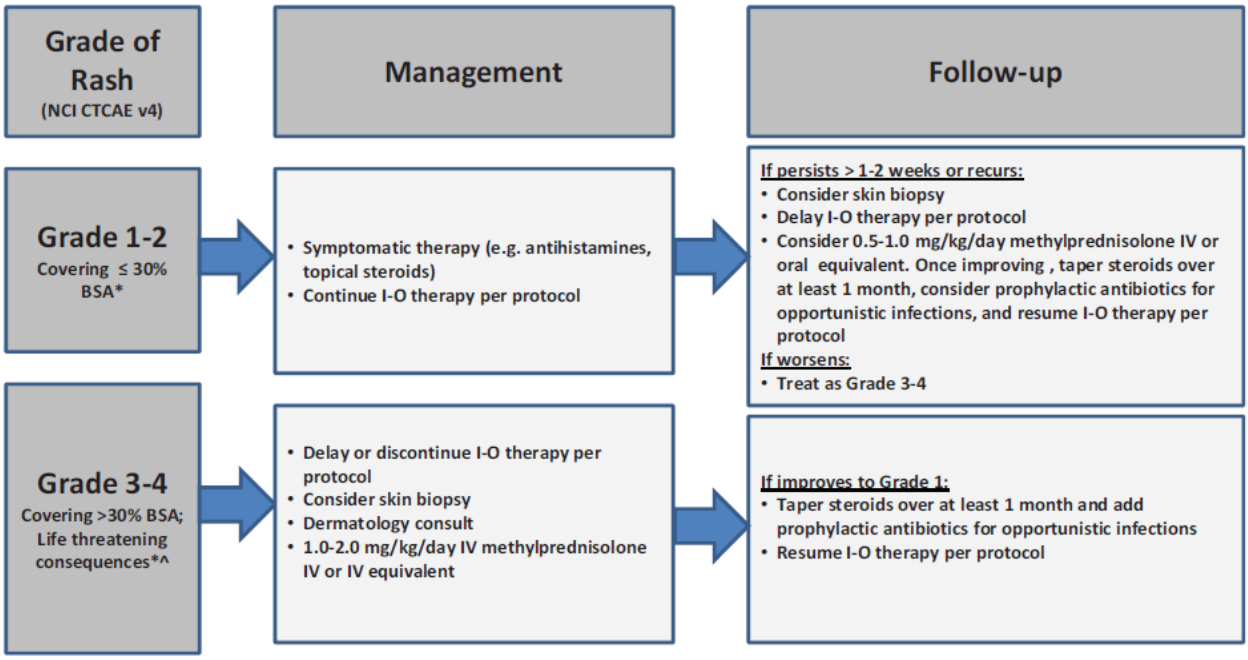
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

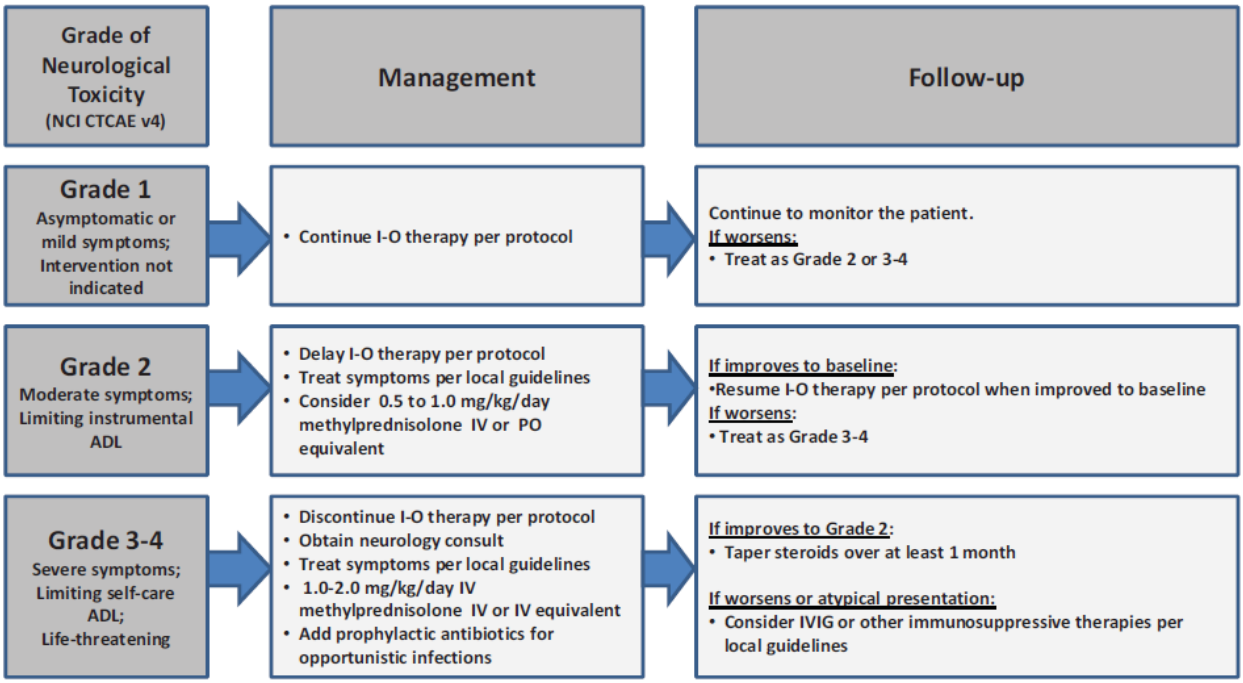
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.