Cover Page

Study COLO-007, NCT# 03439462

Protocol including Statistical Analysis Plan

Last Approved Version & Date: Amendment V2.1, 05-Sep-2019

Protocol Title:
A phase 1/2 multi-center investigation of ABI-009 (nab-sirolimus) in combination with FOLFOX and bevacizumab as first-line therapy in patients with advanced or metastatic colorectal cancer

A phase 1/2 multi-center investigation of ABI-009 (*nab*-sirolimus) in combination with FOLFOX and bevacizumab as first-line therapy in patients with advanced or metastatic colorectal cancer

Investigational Product:	**ABI-009**
Protocol Number:	**COLO-007**
Study Phase:	**1/2**
IND Number:	**138434**
Sponsor Name / Address:	**Aadi Bioscience, Inc** 17383 Sunset Blvd., Suite A250 Pacific Palisades, CA 90272
Principal Investigator:	[redacted]

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MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

[redacted]
[redacted]
[redacted]
[redacted]
[redacted]

Aadi OFFICIAL SIGNATURE PAGE

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

PROTOCOL SYNOPSIS

INVESTIGATIONAL PRODUCT	ABI-009, sirolimus albumin-bound nanoparticles for injectable suspension, *nab*-sirolimus, formerly *nab*-rapamycin
TITLE	A phase 1/2 multi-center investigation of ABI-009 (*nab*-sirolimus) in combination with mFOLFOX6 and Bevacizumab as first-line therapy in patients with advanced or metastatic colorectal cancer
PROTOCOL NUMBER	COLO-007
PHASE	Phase 1/2
STUDY OBJECTIVES	**Objectives in Phase 1** **Primary** • To identify the recommended phase 2 dose (RP2D) and schedule of ABI-009 in combination with mFOLFOX6 and bevacizumab **Secondary** • To evaluate the safety and preliminary efficacy of ABI-009 in combination with mFOLFOX6 and bevacizumab at the RP2D **Objectives in Phase 2** **Primary** • To evaluate the efficacy of ABI-009 in combination with mFOLFOX6 and bevacizumab at the RP2D for all patients as well as based on PTEN status **Secondary** • To evaluate the safety and toxicity profile of ABI-009 in combination with mFOLFOX6 and bevacizumab at the RP2D **Exploratory** • To identify predictive molecular biomarkers for patients treated with ABI-009 in combination with mFOLFOX6 and bevacizumab
STUDY ENDPOINTS	**Endpoints in Phase 1** **Primary Endpoint** • Dose-limiting-toxicities (DLTs) and maximum-tolerated dose (MTD) of ABI-009 in combination with mFOLFOX6 and bevacizumab **Secondary endpoint** • Safety profile of dose cohorts analyzed separately and together • Disease control rate (DCR) assessed by investigators, dose cohorts analyzed separately and together **Endpoints in Phase 2 – data both from phase 1 and 2** **Primary Endpoint** • Progression-free (PF) rate at 6 months **Secondary endpoints**

	• Median progression-free survival (PFS), overall response rate (ORR), duration of response (DOR), and DCR for all patients and based on PTEN status • PF rate at 6 months based on PTEN status • Safety at RP2D **Exploratory Endpoints** • Biomarkers: ○ Pre-treatment metastatic tumor biopsy: (fresh or archival) are required from all patients to assess baseline biomarker and mutational analysis, including PTEN loss evaluation, PIK3CA and Ras mutational status, and mTOR pathway markers (including, but not limited to S6K, 4EBP1). In particular, PIK3CA mutations and PTEN loss will be analyzed by IHC to evaluate as potential predictive biomarkers of response to mTOR inhibition. If tissue from metastatic site is not available, primary lesion tissue is acceptable. Reports on mutational status will be collected from all patients, if available. ○ Blood samples: for cell-free plasma DNA collection (pretreatment, C3 and C6 D1 post-treatment, upon disease progression, and/or end of last dose of treatment) for all patients. Molecular analysis of circulating DNA assay using next generation sequencing to assess changes over time as response to therapy of the prevalence of mutations identified in the baseline tumor samples ▪ Nucleic acids extracted from blood can also be used to investigate whether circulating tumor nucleic acids are associated with disease progression
STUDY DESIGN and DOSE-FINDING RULES	This study is a prospective phase 1/2, single arm, open-label, multi-institutional study to identify the RP2D and determine the efficacy and safety profile of ABI-009 administered as first-line therapy in combination with mFOLFOX6 and bevacizumab in patients with advanced or metastatic colorectal cancer. A cycle will consist of 28 days. The study will be conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs). In the dose-finding portion of the study (phase 1), dose levels of ABI-009 will be tested in cohorts of 3 patients each using the 3+3 dose-finding design, with the starting dose of 20 mg/m^2 given once every 2 week on Days 1 and 15 in a 28-day cycle.

	<table><tr><th>Dose Levels</th><th>ABI-009 in mg/m^2 IV every 2 week</th></tr><tr><td>-2</td><td>10</td></tr><tr><td>-1</td><td>15</td></tr><tr><td>1</td><td>20</td></tr><tr><td>2</td><td>30</td></tr><tr><td>3</td><td>45</td></tr></table> Escalation to the next dose level with a new cohort of 3 patients will occur after no DLT was observed in the first 1 cycle (28 days). There will be no intra-patient dose escalation allowed. If a DLT occurs in a cohort, additional 3 patients will be recruited to the cohort. If no further DLTs occur, then a new cohort of 3 patients at the next higher dose level can be enrolled. If 2/6 patients at dose level 1 experience a DLT, then that cohort will be closed to further enrollment and 3 patients will be enrolled at the next lower dose level, and so on. The MTD is the highest dose level in which ≤1 patient has a DLT. The RP2D is identified based of the totality of safety and efficacy data. The original schedule of ABI-009 given weekly for 3 weeks followed by a week of rest (qw3/4) has been changed to every 2 weeks with Amendment 2, to align with the dosing schedule of the standard of care, FOLFOX + bevacizumab. Patients receiving ABI-009 qw3/4, the original dosing schedule, will drop Day 8 ABI-009 and switch to the every-2-week schedule. Once the dose-finding portion of the study is concluded and RP2D is identified, patients receiving a lower dose may be allowed to receive ABI-009 at the RP2D, based on the investigator judgment and discussion with the medical monitor.
NUMBER OF PATIENTS	Up to 55 evaluable patients will be enrolled in this phase 1/2 study, with up to 18 patients in the dose-finding phase 1 portion, and 34-37 additional patients in phase 2 (total N = 40 in phase 2, including patients from phase 1 at the RP2D).
SAMPLE SIZE ESTIMATE	In phase 1, it is estimated that a maximum of 18 patients will be required to achieve the MTD; however, MTD could be reached with as few as 5 patients. In phase 2, 34-37 additional eligible patients will be enrolled at the RP2D, for a total of 40 evaluable patients (including 3-6 patients from phase 1 at the RP2D). Assuming a 10% attrition rate, at least 44 patients would need to be enrolled for the phase 2 portion of the study.

	The focus of the phase 2 portion of the study will be on the estimation of the magnitude of treatment effect, as measured by PF rate at 6 months. Based on an assumed 6-month PF rate of 90% and a sample size of 40 patients, the 95% confidence intervals for the 6-month PF rate will be 76.3% to 97.2%.
INCLUSION CRITERIA	A patient will be eligible for inclusion in this study only if all of the following criteria are met at screening: 1. Patients with histologically confirmed advanced or metastatic colorectal cancers for whom chemotherapy is indicated. If biopsy from metastatic site is not feasible, imaging may be used to confirm the presence of metastasis in a patient that is already previously histologically confirmed for colorectal cancer. 2. Patients must not have had prior chemotherapy for advanced or metastatic disease. Patients could have received adjuvant chemotherapy or adjuvant chemo-radiotherapy. 3. Patients must have at least 1 measurable site of disease according to RECIST v1.1 that has not been previously irradiated. If the patient has had previous radiation to the marker lesion(s), there must be radiological evidence of progression since the radiation. 4. Eligible patients, 18 years or older, with Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2. 5. Patients must not have been previously treated with an mTOR inhibitor. 6. Adequate liver function: a. Total bilirubin ≤1.5 x upper limit of normal (ULN) mg/dL (except in the dose escalation phase, in which total bilirubin is <ULN) b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN (<5 x ULN if the patient has liver metastases). 7. Adequate renal function: a. Serum creatinine ≤2 x ULN or creatinine clearance ≥50 cc/hr (Cockcroft-Gault). 8. Adequate biological parameters: a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L b. Platelet count ≥100,000/mm^3 (100 × 10^9/L) c. Hemoglobin ≥9 g/dL. 9. Fasting serum triglyceride ≤300 mg/dL; fasting serum cholesterol ≤350 mg/dL. 10. INR and PTT ≤1.5 x ULN (anticoagulation is allowed if target INR ≤1.5 on a stable dose of warfarin or on a stable dose of LMW heparin for >2 weeks at time of enrollment). 11. Minimum of 4 weeks since any major surgery, completion of radiation, or completion of all prior systemic anticancer therapy, and ≥6 months since adjuvant FOLFOX therapy (adequately recovered from the acute toxicities of any prior therapy, including neuropathy should be grade ≤1).

	12. 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 throughout 3 months after last dose of IP 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 and throughout 3 months after last dose of IP. A second form of birth control is required even if he has undergone a successful vasectomy. 13. Life expectancy of >3 months, as determined by the investigator. 14. Ability to understand and sign informed consent. 15. 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. History of severe and uncontrolled allergic reactions to bevacizumab 2. Prior treatment with FOLFOX or bevacizumab within the preceding 4 weeks 3. Patients currently receiving or have received anticancer therapies within 4 weeks of the start of study treatment (including chemotherapy, radiation therapy, antibody-based therapy, etc.) 4. Patients, who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study 5. Chronic treatment with systemic steroids or another immunosuppressive agent; topical or inhaled corticosteroids are allowed 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. Patients who have any severe and/or uncontrolled medical or psychiatric conditions or other conditions that could affect their participation including: a. 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. b. Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease c. Pre-existing severely impaired lung function as defined as spirometry and DLCO that is 50% of the normal predicted value and/or O2 saturation that is 88% or less at rest on room air (Note: spirometry and PFTs not required to be performed unless clinically indicated). d. Uncontrolled diabetes as defined by fasting serum glucose >1.5x ULN or by HbA1c >8% despite adequate therapy. e. Any active (acute or chronic) or uncontrolled infection/ disorders. f. Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with the study therapy. Note, controlled non-melanoma skin cancers, carcinoma in situ of the cervix, resected incidental prostate cancer, or other adequately treated carcinoma-in-situ may be eligible, after documented discussion with the sponsor / medical monitor. g. Known liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh class C). h. Uncontrolled hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥90 mm Hg. 8. Patients with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension. 9. Patients with history of intestinal perforations, fistula, hemorrhages and/or hemoptysis ≤6 months prior to first study treatment. 10. A known history of HIV seropositivity. 11. Active Hepatitis B or Hepatitis C. Note: A detailed assessment of Hepatitis B/C medical history and risk factors must be done at screening for all patients. HBV DNA and HCV RNA PCR testing are required at screening for all patients with a positive medical history based on risk factors and/or confirmation of prior HBV/HCV infection. 12. Patients with an active bleeding diathesis or on oral anti-vitamin K medication (except low dose warfarin [Coumadin] or heparin). 13. 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.

DURATION OF TREATMENT AND STUDY PARTICIPATION	The study is expected to take approximately 24 months from first patient enrolled to last patient follow-up, including approximately 12 months of enrollment period, an estimated 12 months of treatment (or until treatment is no longer tolerated). End of Treatment (EOT) for a patient is defined as the date of the last dose of ABI-009. End of Treatment Visit for a patient is when safety assessments and procedures are performed after the last treatment, which must occur within 1 month after the last dose of ABI-009. 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. Follow-up period begins 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 of new 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 DRUG ADMINISTRATION	With Amendment 2, the starting dose and schedule of ABI-009 is 20 mg/m^2 given every-2-weeks (28-day cycle) by IV infusion over 30 minutes (+10 mins window allowed, ie 30-40 mins infusion). Bevacizumab and mFOLFOX6 will be administered every 2 weeks, starting Cycle 1, Day 1. Modified FOLFOX6 regimen: Oxaliplatin 85 mg/m^2 IV with LV 400 mg/m^2 IV over 2 hours plus 5FU 400 mg/m^2 IV bolus and 2,400 mg/m^2 continuous infusion over 46 hours every 2 weeks. Dose modifications of each agent in FOLFOX may be made independently based on the specific types of toxicities observed. Bevacizumab may be skipped or discontinued for bevacizumab-related toxicities, but the dose is not reduced. Patients will continue to therapy until disease progression, unacceptable toxicity, until in the opinion of the investigator the patient is no longer benefiting from therapy, or at the patient's discretion. Patients who remain on treatment for more than 6 months may be switched to mFOLFOX and bevacizumab every 3 weeks and ABI-009 given weekly for 2 weeks followed by a week of rest (qw2/3, 21-day cycle) at the discretion of the investigator. Single agent ABI-009 may be continued if mFOLFOX6 and/or bevacizumab are discontinued due to toxicity or achievement of maximum benefit in the opinion of the investigator and approval of the medical monitor and sponsor.

KEY EFFICACY ASSESSMENTS	Efficacy will be assessed by investigators using CT / PET scans and RECIST v1.1. Only RECIST v1.1 criteria will be used to assess response; PET will be used for qualitative purposes only. For the phase 2 portion of the study the primary endpoint is PF rate at 6 months. Progression-free rate at 6 months is the proportion of patients who are progression-free and alive at 6 months. The point estimate of the PF rate and the exact two-sided 95% confidence interval will be provided. Progression-free survival is defined as the time from the first day of study drug administration to disease progression or death due to any cause. For PFS, the KM estimates and corresponding two-sided 95% confidence intervals for the median and quartiles will be provided. The KM plot may also be provided. The ORR and DCR will be reported along with exact 95% confidence intervals computed by the Clopper-Pearson method. Additionally, all efficacy endpoints will also be analyzed based on PTEN status.
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) v5.0. Physical examination, vital signs, laboratory assessments (eg, serum chemistry, hematology), and ECOG performance status will be monitored. All serious AEs (regardless of relationship to IP) will be followed until resolution. Local laboratory analysis will be performed as per study schedule.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
ANC	absolute neutrophil count
AST	aspartate transaminase (SGOT)
AUC	area under the time-concentration curve
BSA	body surface area
C_{max}	maximum plasma drug concentration
C_{min}	minimum plasma drug concentration
CBC	complete blood count
CEA	carcinoembryonic antigen
CI	confidence interval
CNS	central nervous system
CR	complete response
CT	computed tomography
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DCR	disease control rate
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

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	overall survival
PD	progressive disease
PF rate	Progression-free rate
PFS	Progression-free survival
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

Term	Definition/Explanation
Study Day 1	First day that protocol-specified IP is administered to the patient.
End of Treatment	The date of the last dose of ABI-009 or mFOLFOX6/bev for an individual patient, whichever is later.
End of Treatment Visit	For a patient is when safety assessments and procedures are performed after the last treatment, which should occur within 1 week (±3 days) after the last dose of ABI-009 or mFOLFOX6/bev, whichever is later.
Follow-up Period	The 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 initiation of new 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.
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.
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.
Efficacy Analysis Dataset	All enrolled patients with measurable tumor per RECIST v1.1 at baseline who received at least 2 doses of ABI-009 and had a follow-up CT / PET (or MRI) (modified treated population).
Safety Analysis Set	All enrolled patients who receive at least 1 dose of ABI-009 (treated population).
Per-protocol Analysis Set	All enrolled patients who do not have any prospectively defined protocol violations.

Progression-free rate at 6 months	Progression-free rate at 6 months is the proportion of patients who are progression-free and alive at 6 months.
Progression-free survival	The time from the first dose date to the first observation of a disease progression, assessed radiologically, 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. Colorectal Cancer

Colorectal cancer is the 3rd most common cancer and one of the leading causes of death among cancer types (Siegel, 2017). In the early stage, colorectal cancer often does not present symptoms and usually becomes symptomatic when it progresses to more advanced stages. Surgery is the most common treatment for cancers that have not spread, and chemotherapy and/or targeted therapy is given for patients whose cancer metastasized. However, the 5-year survival rate is still a dismal 14% for patients with metastatic colorectal cancer (mCRC) (Siegel, 2017), and improved therapeutic options are needed.

1.2. Treatment Options in Colorectal Cancer

1.2.1. FOLFOX and Bevacizumab in Colorectal Cancer

Oxaliplatin with infusional 5-fluorouracil (5-FU) and leucovorin (LV) (FOLFOX) and irinotecan with infusional 5-FU and LV (FOLFIRI) are standard chemotherapy regimens for the first-line treatment of patients with mCRC (NCCN, 2017). Since its approval for the first-line treatment of mCRC in 2004, bevacizumab, a VEGF-A inhibitor, has become a standard treatment option in combination with chemotherapy for patients with mCRC. In particular, mFOLFOX6 combined with bevacizumab are now well established for treatment of metastatic colorectal carcinomas (Hochster, 2008; Saltz, 2008; Bendell, 2012; Strickler, 2012; Baba, 2017; Rivera, 2017). The median progression-free survival (PFS) were 9-11 months, with approximately 50% overall response rates (ORR) in most studies (Hochster, 2008; Saltz, 2008; Bendell, 2012; Strickler, 2012; Baba, 2017; Rivera, 2017), and improvement in reducing tumor burden and time to progression in the first-line setting is still needed. Improving efficacy of first-line treatments may help in optimizing the overall treatment plan and improve the outcome of subsequent therapies and overall survival (OS) for patients in colorectal cancer.

1.2.2. mTOR Inhibition in Colorectal Cancer

The mammalian target of rapamycin (mTOR) oncogenic pathways (PI3K/AKT/mTOR) are frequently dysregulated in human cancers, including colorectal cancer (Wu, 2015; Laes, 2017). mTOR is downstream of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and the tumor suppressor gene PTEN coding for the Phosphatase and Tensin Homolog, and a key regulator of cell survival, proliferation, and metabolism. Activating mutations in PIK3CA or null mutations in the tumor suppressor gene PTEN and subsequent loss of expression can lead to mTOR-pathway activation (Laes, 2017). 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 (VEGF) (Corradetti, 2006). Consistent with its role in cell proliferation, the mTOR pathway is frequently overactivated in a number of human malignancies and is considered to be an attractive target for anti-cancer therapy.

mTOR and PI3K inhibitors have been approved for the various cancer treatment, including renal cell carcinoma and breast cancer, and are under investigation for several cancer types, including mCRC. A recent phase 1/2 study that showed evidence for antitumor activity of everolimus, an mTOR inhibitor, in combination with mFOLFOX6 plus bevacizumab (standard of care) for the first-line treatment for mCRC (NCT01047293) (Gilcrease GW, 2012). The 6-month PF rate was 96%, at the maximum-tolerated dose (MTD) (Gilcrease GW, 2018), compared to a historical estimate of approximately 77% for mFOLFOX6 + bevacizumab (Saltz, 2008; Bendell, 2012; Baba, 2017; Rivera, 2017). The ORR was 53% in the intent-to-treat population and 86% for patients with PTEN loss, a population that typically has poorer prognosis. Evidence of anti-tumor activity correlated with mutation status (k-RAS, BRAF, PIK3CA) and PTEN deletion status. Thus, evaluation of PIK3CA or PTEN mutations or expression in combination with the mTOR activity status could provide additional information on disease prognosis and potential sensitivity to cancer treatments in future studies. While the efficacy of the mTOR inhibitor combined with FOLFOX/bev was highly promising, 62% patients developed grade 2 stomatitis, mainly related to the addition of everolimus.

A novel mTOR inhibitor, ABI-009 (albumin-bound sirolimus nanoparticles, *nab*-sirolimus), is a solvent-free, intravenous (IV) form of sirolimus and has relatively high bioavailability. Dose-limiting toxicities (DLT) including mucositis/stomatitis that were observed with other mTOR inhibitors were not dose-limiting with ABI-009 (Gonzalez-Angulo, 2013). The particularly safe toxicity profile of ABI-009 allows this mTOR inhibitor to be combined with other therapeutics, and offers a promising new therapeutic for colorectal cancer.

1.3. ABI-009 Background

1.3.1. Sirolimus and Rapalogs

Sirolimus (formerly rapamycin) is a protein kinase inhibitor that is approved for immunosuppression in renal transplant patients and for the treatment of lymphangioleiomyomatosis, and is under investigation for various cancer treatment. Sirolimus and its analogs (rapalogs) function as allosteric inhibitors of mTORC1. Rapalogs are currently used in the treatment of advanced renal cell carcinoma and other tumors (Dowling, 2010).

Although sirolimus is an efficacious mTOR inhibitor, it has poor solubility, low oral bioavailability, and produces DLTs, including mucositis and stomatitis (O'Donnell, 2008; Yuan, 2009). Marketed sirolimus analogs are temsirolimus and everolimus. Temsirolimus, a prodrug of sirolimus requiring conversion to sirolimus in vivo, is approved for the treatment of kidney cancer. Everolimus is approved for pediatric and adult patients with subependymal giant cell astrocytoma, 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(Hanna, 2008; Molina, 2011; Yao, 2011; Baselga, 2012; Thompson, 2012).

Oral sirolimus and currently available rapalogs induce common side effects including hypertension, maculopapular rash (75%), mucositis (50%), asthenia (40%), nausea (43%), thrombocytopenia, metabolic abnormalities and more rarely pneumonitis (8%, 3% grade 3) sometimes fatal (de Oliveira, 2011; Albiges, 2012; Qi, 2013). The most frequently occurring grade 3 or 4 adverse events (AEs) were hyperglycemia (17%), hypophosphatemia (13%), anemia (9%), and hypertriglyceridemia (6%) (Zhou, 2010).

1.3.2. ABI-009 (*nab*-Sirolimus)

The novel nanoparticle albumin-bound sirolimus (*nab*-sirolimus, ABI-009) is freely dispersible in saline and is suitable for IV administration, and has produced both a favorable safety profile and evidence of efficacy in patients with metastatic solid tumors (Gonzalez-Angulo, 2013).

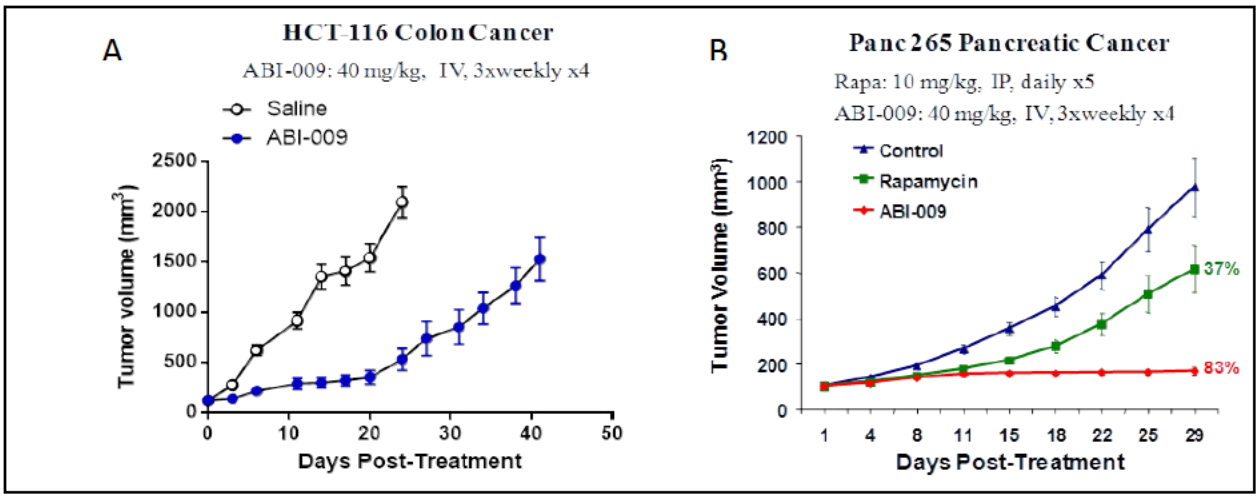
Nanoparticle albumin-bound or *nab*® technology (Abraxis BioScience, a wholly-owned subsidiary of Celgene Corporation) when applied to hydrophobic molecules, such as paclitaxel (*nab*-paclitaxel; Abraxane®), has led to improved drug delivery, safety, and efficacy in various solid tumors compared with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

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

1.3.3. Preclinical Studies with ABI-009

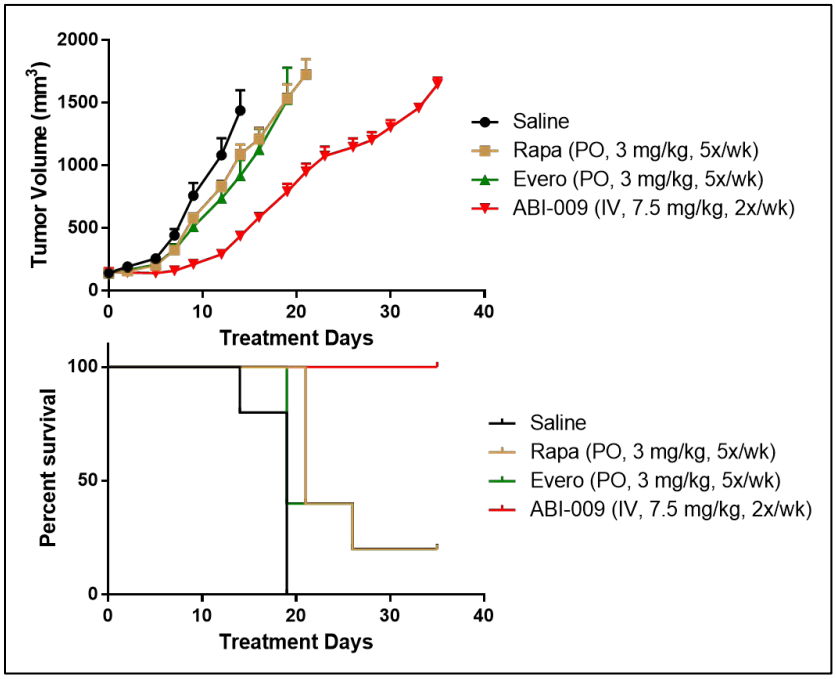
Preclinical primary pharmacology studies in vivo demonstrated significant antitumor activity of ABI-009 as a single agent administered intravenously at 40 mg/kg, 3 times weekly for 4 weeks, across different tumor xenograft models in nude mice (see Figure 1A and B, below), including colorectal and pancreatic cancer (De, 2007; Desai, 2009; Trieu, 2009; Cirstea, 2010; Kennecke, 2011). This dose level correlates to approximately 120 mg/m^2 in human. These findings are consistent with published information on sirolimus as an mTOR inhibitor and the role of mTOR in tumor growth (Fasolo, 2012).

Figure 1: Antitumor Activity of ABI-009 in Colon and Pancreatic Cancer Tumor Xenografts



A recent preclinical study demonstrated significantly greater antitumor activity and prolonged survival with ABI-009 administered IV compared with equal weekly dosing of oral sirolimus and oral everolimus (Aadi internal data, Figure 2). In athymic mice bearing UMUC3 human bladder cancer xenografts, ABI-009 was administered IV at 7.5 mg/kg, 2x weekly (total weekly dose: 15 mg/kg), whereas sirolimus and everolimus were administered PO at 3 mg/kg/day, 5 days per week to achieve the same weekly total dose. The tumor growth inhibition (TGI) was 69.6% with ABI-009, significantly greater than oral sirolimus (TGI 24.3%; $P < 0.00001$ vs ABI-009, ANOVA) and oral everolimus (TGI 36.2%; $P = 0.0023$ vs ABI-009, ANOVA). The median OS was also significantly longer with ABI-009 (not reached) compared with oral sirolimus (21 days; $P < 0.05$, log rank test) and oral everolimus (19 days; $P < 0.05$, log rank test). Results from this preclinical study clearly demonstrate superior therapeutic efficacy of ABI-009 to oral mTOR inhibitors in this setting.

Figure 2: ABI-009 Administered IV Compared with Equal Weekly Dosing of Oral Sirolimus and Oral Everolimus



Preclinical pharmacokinetic (PK) studies in rats showed that IV ABI-009 exhibited linear PK with respect to dose and large volume of distribution (Vz), due to efficient tissue extraction of sirolimus from the central blood compartment (De, 2007). Shortly after dosing, tissue sirolimus level was 3-5 folds 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 sirolimus literature (Sehgal, 2003), 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 Good Laboratory Practice (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 4 days for 3 cycles. Nonclinical toxicology studies of ABI-009 showed no new or unexpected toxicity compared to what is already known for sirolimus and other rapalogs (Pfizer, 2011a; Pfizer, 2011b; Novartis, 2017).

1.3.4. Clinical Studies with ABI-009

In a phase 1 dose-finding, tolerability, and PK study conducted at MD Anderson Cancer Center (Protocol CA401, NCT00635284), ABI-009 was well tolerated with evidence of responses and SD in various solid tumors including renal cell carcinoma, bladder cancer, and colorectal cancer, all of which typically overexpress mTOR (Gonzalez-Angulo, 2013). Twenty-six patients were treated with 45, 56.25, 100, 125, or 150 mg/m^2 ABI-009 per

week for 3 weeks, followed by a week of rest (28-day cycle, qw3/4). ABI-009 was administered IV. The MTD was established at 100 mg/m^2.

Nineteen patients were evaluable for efficacy. One patient in the 45 mg/m^2 (95 mg actual sirolimus dose) cohort, diagnosed with 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 sirolimus doses of 88 mg and 193 mg, respectively) had an overall tumor evaluation of stable disease (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 MTD of 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 (SAE), 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%), and 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.

Currently, there are several ongoing trials investigating the safety and efficacy of single-agent ABI-009 in various disease areas, including a trial in patients with malignant perivascular epithelioid tumors (PEComas), a rare type of soft-tissue tumors (NCT02494570). The particularly safe toxicity profile of ABI-009 allows this mTOR inhibitor to be combinable with other therapeutics and a trial in patients with advanced STS is currently evaluating the combination of ABI-009 and nivolumab (NCT03190174).

1.4. Rationale for Combination of ABI-009 with FOLFOX and Bevacizumab in Colorectal Cancer

In the phase 1/2 study (NCT01047293) of everolimus added to mFOLFOX6 + bevacizumab described in Section 1.2.2, the observed 96% PF rate at 6 months (compared with a historical estimate of approximately 77% for mFOLFOX6 + bevacizumab) (Saltz, 2008; Bendell, 2012; Baba, 2017; Rivera, 2017) and the observed 86% ORR in patients with PTEN loss (compared with 53% in the all patients) suggest that mTOR inhibition may be beneficial when added to the standard of care treatment. On the basis of the safety profile of single agent ABI-009, the evidence of antitumor activity in

various solid tumors (Section 1.3.4, NCT00635284), as well as the tumor xenograft study demonstrating improved therapeutic potential of ABI-009 vs oral sirolimus or everolimus, we propose a phase 1/2 assessment of the combination of ABI-009 with mFOLFOX6 and bevacizumab as first-line treatment for patients with mCRC. The goal of this study is to demonstrate that ABI-009 combined with the standard of care a) is safe and efficacious and b) suggests an improved benefit in patients with PTEN loss.

1.5. Rationale for Starting Dose selection and Schedule of ABI-009, mFOLFOX6, and Bevacizumab

Considering the safety profile of FOLFOX and bevacizumab, a dose lower than the MTD of single-agent ABI-009 is recommended when combined FOLFOX/bevacizumab. The original planned starting dose of 30 mg/m^2 ABI-009 given IV weekly for 3 weeks with a week of rest (qw3/4) gives a wide >3x safety margin for patients with advanced colorectal cancer over the established MTD of 100 mg/m^2. This dose, assuming a body surface area (BSA) of 1.7, is 51 mg/week (or 38 mg/week on average in a 4-week cycle), which is within the therapeutic range for rapalogs:

- In the phase 1/2 study with everolimus combined with mFOLFOX6 and bevacizumab NCT01047293) (Gilcrease GW, 2012), the MTD of everolimus was 7.5 mg/day (52.5 mg/week), which is similar to the dose range evaluated in this study.
- Using the PK data from the phase 1 study (Gonzalez-Angulo, 2013), linear modeling of sirolimus blood concentration predicts that 1 week after 10 and 20 mg/m^2 ABI-009 IV administration, therapeutic trough sirolimus levels are still maintained (7.11 and 14.22 ng/mL, respectively, Aadi data on file). Thus, potential dose reduction from the starting dose of 30 mg/m^2 should still result in therapeutic levels.
- ABI-009 has shown similar safety profile to other rapalogs, even at a higher dose of 100 mg/m^2. In particular, mucositis/stomatitis that were observed with other mTOR inhibitors has not been dose-limiting with ABI-009.

The qw3/4 schedule allows for coordinating the every-2-week administration of mFOLFOX6 and bevacizumab and was the studied schedule in the first-in-human study for ABI-009 (CA401, NCT00635284).

mFOLFOX6 and bevacizumab will be given as in the phase 1/2 study (NCT01047293). mFOLFOX6: oxaliplatin 85 mg/m^2 IV with leucovorin 400mg/m^2 IV over 2 hours plus FU 400 mg/m^2 IV bolus and 2,400 mg/m^2 continuous infusion over 46 hours every 2 weeks. Bevacizumab will be given at 5 mg/kg every 2 weeks.

While the original qw3/4 schedule starting at 30 mg/m^2 was based on the studied schedule, with Amendment 2, the every-2-week ABI-009 dosing schedule with a lower starting dose of 20 mg/m^2 has been implemented based on a) alignment with the every-2-week standard of care (FOLFOX + bevacizumab) dosing schedule and b) to allow sufficient time to recover from the potential cumulative myelosuppressive effect of the FOLFOX+bevacizumab+ABI-009 regimen given on Day 1.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Objectives in Phase 1

Primary

- To identify the recommended phase 2 dose (RP2D) of ABI-009 in combination with mFOLFOX6 and bevacizumab

Secondary

- To evaluate preliminary efficacy and safety of ABI-009 in combination with mFOLFOX6 and bevacizumab at the RP2D

Objectives in Phase 2

Primary

- To evaluate the efficacy of ABI-009 in combination with mFOLFOX6 and bevacizumab at the RP2D for all patients as well as based on PTEN status

Secondary

- To evaluate the safety and toxicity profile of ABI-009 in combination with mFOLFOX6 and bevacizumab at the RP2D

Exploratory

- To identify predictive molecular biomarkers for patients treated with ABI-009 in combination with mFOLFOX6 and bevacizumab

2.2. Endpoints

Endpoints in Phase 1

Primary Endpoint

- Identify DLTs and the MTD (defined as ≤1 of 6 patients with a DLT) of ABI-009 in combination with mFOLFOX6 and bevacizumab

Secondary Endpoints

- Safety profile of dose cohorts analyzed separately and together
- Disease control rate (DCR) assessed by investigators based on RECIST v1.1, dose cohorts analyzed separately and together

Endpoints in Phase 2 – Data from both phase 1 and 2

Primary Endpoint

- PF rate at 6 months in patients treated with ABI-009 in combination with mFOLFOX6 and bevacizumab at the RP2D based on investigator assessment (RECIST v1.1)

Secondary Endpoint

- Median PFS, ORR, duration of response (DOR), and DCR at the RP2D and all dose cohorts, based on investigator assessed RECIST v1.1 for all patients and based on PTEN status
- PF rate at 6 months based on PTEN status
- Safety at RP2D, including patients from phase 1, based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Exploratory endpoints

- Biomarkers:
  - Pre-treatment metastatic tumor biopsy: (fresh or archival) are required from all patients to assess baseline biomarker and mutational analysis, including PTEN loss evaluation, PIK3CA and Ras mutational status, and mTOR pathway markers (including, but not limited to S6K, 4EBP1). In particular, PIK3CA mutations and PTEN loss will be analyzed by IHC to evaluate as potential predictive biomarkers of response to mTOR inhibition. If tissue from metastatic site is not available, primary lesion tissue is acceptable. Reports on mutational status will be collected from all patients, if available.
  - Blood samples: for cell-free plasma DNA collection (pretreatment, C3 and C6 D1 post-treatment, upon disease progression, and/or end of last dose of treatment) for all patients. Molecular analysis of circulating DNA assay using next generation sequencing to assess changes over time as response to therapy of the prevalence of mutations identified in the baseline tumor samples
    - Nucleic acids extracted from blood can also be used to investigate whether circulating tumor nucleic acids are associated with disease progression

2.3. Study Design

This study is a prospective phase 1/2, single arm, open-label, multi-institutional study to identify the RP2D and determine the efficacy and safety profile of ABI-009 administered as first-line therapy in combination with mFOLFOX6 and bevacizumab in patients with advanced or mCRC. A cycle will consist of 4 weeks, ie 28 days.

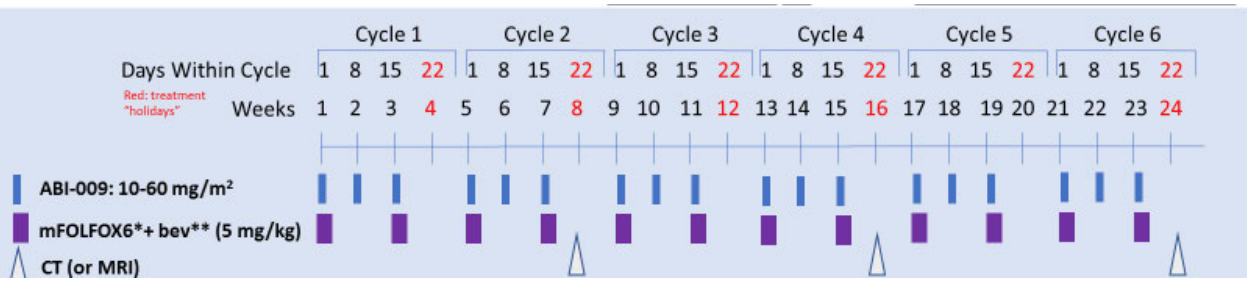
The study will be conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs).

The starting dose and schedule of ABI-009 is 20 mg/m^2 every 2 weeks on Days 1 and 15 (28-day cycle) by IV infusion over 30 minutes (+10 mins window allowed, ie 30-40 mins infusion). Bevacizumab and mFOLFOX6 will be administered every 2 weeks, starting Cycle 1, Day 1. Patients receiving ABI-009 qw3/4, the original dosing schedule prior to Amendment 2, will drop Day 8 ABI-009 and switch to the every-2-week schedule.

Modified FOLFOX6 regimen: Oxaliplatin 85 mg/m^2 IV with LV 400 mg/m^2 IV over 2 hours plus FU 400 mg/m^2 IV bolus and 2,400 mg/m^2 continuous infusion over 46 hours every 2 weeks. Dose modifications of each agent in FOLFOX may be made independently based on the specific types of toxicities observed. Bevacizumab may be skipped or discontinued for bevacizumab-related toxicities, but the dose is not reduced.

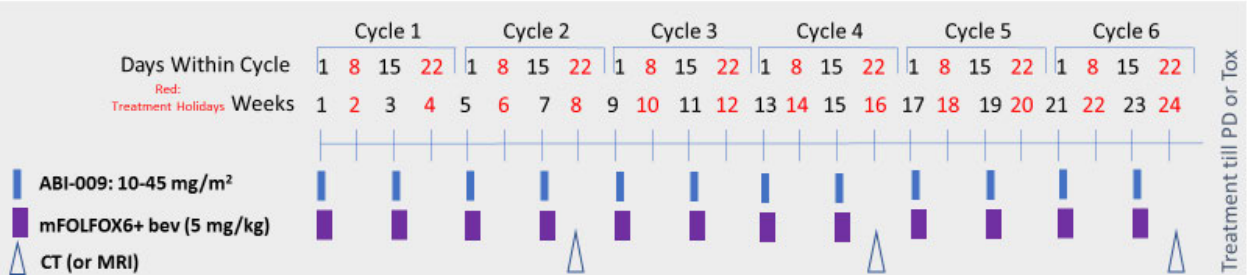
Patients will continue to therapy until disease progression, unacceptable toxicity, until in the opinion of the investigator the patient is no longer benefiting from therapy, or at the patient's discretion. After 6 months of therapy, single agent ABI-009 may be continued at the discretion of the investigator if mFOLFOX6 and/or bevacizumab are discontinued due to toxicity or achievement of maximum benefit per treating physician.

Figure 3A. Original Study Schema for ABI-009 given qw3/4 (original dosing schedule)



With Amendment 2, an alternate dosing schedule is implemented replacing the original schedule above to allow evaluation of ABI-009 given every 2 weeks, aligned with the dosing schedule of the standard of care, FOLFOX + bevacizumab. Study Schema for every-2-week dosing schedule implemented with Amendment 2. Patients receiving ABI-009 qw3/4 on the original schedule may permanently drop Day 8 dosing if ≥2 Day-8 ABI-009 had to be skipped due to toxicity.

Figure 3B. Study Schema for ABI-009 given every 2 weeks, implemented with Amendment 2



Dose-finding Phase 1 Portion of the Study:

Dose levels of ABI-009 will be tested in cohorts of 3 patients each using the 3+3 dose-finding design. The original starting dose was 30 mg/m^2 ABI-009 given weekly for 3 weeks followed by a week of rest (qw3/4, 28-day cycle), and dose levels could be escalated to 45 and 60 or de-escalated to 20 and 10 mg/m^2. With Amendment 2, the new starting dose was 20 mg/m^2 given once every 2 weeks on Days 1 and 15(28-day cycle).

Table 1. Dose Levels of ABI-009 Implemented with Amendment 2

Dose Levels	ABI-009 in mg/m^2 IV every 2 weeks
-2	10
-1	15
1	**20**
2	30
3	45

Escalation to the next dose level with a new cohort of 3 patients will occur after no DLT was observed in the first 2 cycles. There will be no intra-patient dose escalation allowed. If a DLT occurs in a cohort, additional 3 patients will be recruited to the cohort. If no further DLTs occur, then a new cohort of 3 patients at the next higher dose level can be enrolled. If 2/6 patients at dose level 1 experience a DLT, then that cohort will be closed to further enrollment and 3 patients will be enrolled at the next lower dose level, and so on.

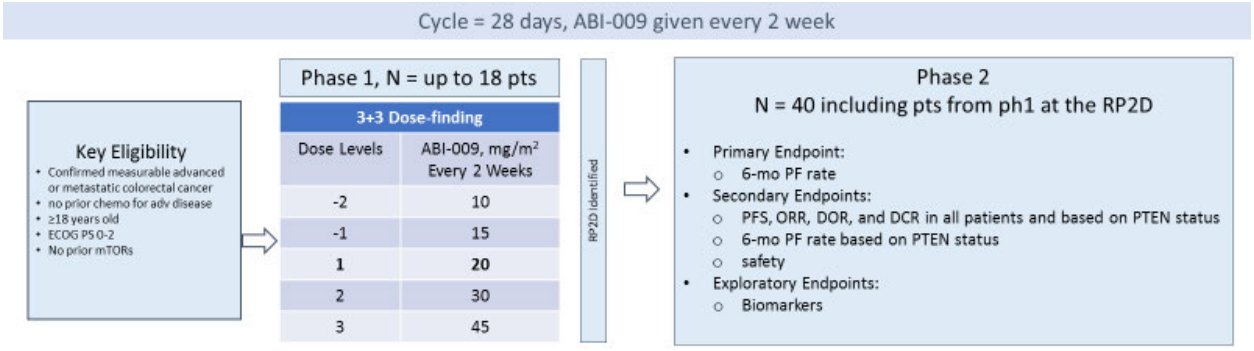
The MTD is the highest dose level in which ≤1 patient has a DLT. The RP2D is identified based on the totality of safety and efficacy data.

Once the dose-finding portion of the study is concluded and RP2D is identified, patients receiving a lower dose may be allowed to receive ABI-009 at the RP2D, based on the investigator judgment and discussion with the medical monitor.

Phase 2 Portion of the Study:

Phase 2 will be an open label single arm study in approximately 40 patients at the RP2D determined from phase 1. Assuming a 10% attrition rate, at least 44 patients would need to be enrolled for the phase 2 portion of the study. Patients enrolled in the phase 1 portion at the RP2D will be included in phase 2 for response and safety evaluation.

Figure 4. Study Design Implemented with Amendment 2



2.4. Study Duration, End of Study, End of Treatment, End of Treatment Visit, Follow-up Period

The study is expected to take approximately 24 months from first patient enrolled to last patient follow-up, including approximately 12 months of enrollment period, an estimated 12 months of treatment (or until treatment is no longer tolerated).

End of Treatment (EOT) for a patient is defined as the date of the last dose of ABI-009 or FOLFOX/bevacizumab, whichever is later. End of Treatment Visit for a patient is when safety assessments and procedures are performed after the last treatment (should be within 1 month of 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.

Follow-up period is the 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 of new 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.

3. STUDY POPULATION

3.1. Number of Patients

Phase 1: The sample size for phase 1 is anticipated to be 5 to 18 patients.

Phase 2: The sample size for phase 2 will be a total of approximately 40 patients, including the patients from phase 1 who initiated treatment at the RP2D.

Patients who fail to become evaluable for the primary endpoint because of a missing follow-up CT/PET (or MRI) will be replaced. Assuming a 10% attrition rate, at least 44 patients would need to be enrolled for the phase 2 portion of the study (inclusive of the phase 1 patients at RP2D).

3.2. Inclusion Criteria

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

1. Patients with histologically confirmed advanced or metastatic colorectal cancers for whom chemotherapy is indicated. If biopsy from metastatic site is not feasible, imaging may be used to confirm the presence of metastasis in a patient that is already previously histologically confirmed for colorectal cancer.
2. Patients must not have had prior chemotherapy for advanced or metastatic disease. Patients could have received adjuvant chemotherapy or adjuvant chemo-radiotherapy.
3. Patients must have at least 1 measurable site of disease according to RECIST v1.1 that has not been previously irradiated. If the patient has had previous radiation to the marker lesion(s), there must be radiological evidence of progression since the radiation.
4. Eligible patients, 18 years or older, with Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.
5. Patients must not have been previously treated with an mTOR inhibitor.
6. Adequate liver function:
   a. Total bilirubin ≤1.5 x upper limit of normal (ULN) mg/dL (except in the dose escalation phase, in which the total bilirubin is <ULN)
   b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN (<5 x ULN if the patient has liver metastases).
7. Adequate renal function:
   a. Serum creatinine ≤2 x ULN or creatinine clearance >50 cc/hr (Cockcroft-Gault).
8. Adequate biological parameters:
   a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L
   b. Platelet count ≥100,000/mm^3 (100 × 10^9/L)
   c. Hemoglobin ≥9 g/dL.
9. Fasting serum triglyceride ≤300 mg/dL; fasting serum cholesterol ≤350 mg/dL.
10. INR and PTT <1.5 x ULN (anticoagulation is allowed if target INR <1.5 on a stable dose of warfarin or on a stable dose of LMW heparin for >2 weeks at time of enrollment).

11. Minimum of 4 weeks since any major surgery, completion of radiation, or completion of all prior systemic anticancer therapy, and ≥6 months since adjuvant FOLFOX therapy (adequately recovered from the acute toxicities of any prior therapy, including neuropathy should be grade ≤1).
12. 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 throughout 3 months after last dose of IP 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 and throughout 3 months after last dose of IP. A second form of birth control is required even if he has undergone a successful vasectomy.

13. Life expectancy of >3 months, as determined by the investigator.
14. Ability to understand and sign informed consent.
15. 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 during screening:

1. History of severe and uncontrolled allergic reactions to bevacizumab.
2. Prior treatment with FOLFOX or bevacizumab within the preceding 4 weeks.
3. Patients currently receiving or have received anticancer therapies within 4 weeks of the start of study treatment (including chemotherapy, radiation therapy, antibody-based therapy, etc.).
4. Patients, who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study.
5. Chronic treatment with systemic steroids or another immunosuppressive agent; topical or inhaled corticosteroids are allowed.
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. Patients who have any severe and/or uncontrolled medical or psychiatric conditions or other conditions that could affect their participation including:
    a. 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.

b. Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease.
c. Pre-existing severely impaired lung function as defined as spirometry and DLCO that is 50% of the normal predicted value and/or O2 saturation that is 88% or less at rest on room air (Note: spirometry and PFTs not required to be performed unless clinically indicated).
d. Uncontrolled diabetes as defined by fasting serum glucose >1.5x ULN or by HbA1c >8% despite adequate therapy.
e. Any active (acute or chronic) or uncontrolled infection/ disorders.
f. Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with the study therapy. Note, controlled non-melanoma skin cancers, carcinoma in situ of the cervix, resected incidental prostate cancer, or other adequately treated carcinoma-in-situ may be eligible, after documented discussion with the sponsor / medical monitor.
g. Known liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh class C).
h. Uncontrolled hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥90 mm Hg.

8. Patients with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension.
9. Patients with history of intestinal perforations, fistula, hemorrhages and/or hemoptysis ≤6 months prior to first study treatment.
10. A known history of HIV seropositivity.
11. Active Hepatitis B or Hepatitis C. Note: A detailed assessment of Hepatitis B/C medical history and risk factors must be done at screening for all patients. HBV DNA and HCV RNA PCR testing are required at screening for all patients with a positive medical history based on risk factors and/or confirmation of prior HBV/HCV infection.
12. Patients with an active bleeding diathesis or on oral anti-vitamin K medication (except low dose warfarin [Coumadin] or heparin).
13. 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.

4. TABLE OF EVENTS

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

Table 2. Schedule of Assessments

Assessments [a]	Baseline Screening [b]	Treatment Phase 28-day (4-week) Cycles Days		End of Treatment (EOT) Visit [d]	Follow-up [d]
		1	15		
Informed Consent	x				
Demographics / Medical History	x				
I/E Criteria	x				
HIV, HBV sAg, HBV cAb, HCV Ab	x				
PT/PTT/INR	x				
12-lead electrocardiogram [e]	x	C1 only [e]	C1 only [e]		
Pre-treatment metastatic tissue (archival or fresh) for biomarker analysis [f]	x				
Blood sample for biomarkers	x	D1 on C3 and C6, upon disease progression and/or end of last treatment			
Pregnancy Test [g]	x			x	
Physical Exam	x	x	x	x	
Vital signs, height, and weight [h]	x	x	x	x	
Prior / Concomitant Medications and Procedures	x	x	x	x	
CBC/Differential	x	x	x	x	
Chemistry Panel	x	x	x	x	
Urinalysis [i]	x	x	x		
Fasting Lipids	x	Even Cycles			
Sirolimus level [j]		C1 – C4	C1 – C4		
Carcinoembryonic antigen	x	x			
ECOG performance status	x	x		x	
CT / PET [k]	x	Every 8 weeks from 1st dose during the 1st year, then every 12 weeks until disease progressions or last treatment			
ABI-009 infusion [l]		x	x		
mFOLFOX6 / Bevacizumab [l]		x	x		
Adverse Event Assessment	Continuous from the signing of the informed consent to 28 days after last study treatment				

[a] All visits are allowed to occur in a window of ±3 days unless otherwise specified.

[b] Baseline screening visit will be done within 28 days prior to study treatment Day 1.

[c] Days 8 and 22 evaluations are not required with every-2-week dosing implemented with Amendment 2.

[d] End of Treatment-phase (EOT) Visit should be within 1 month of last study treatment with either ABI-009 or mFOLFOX6/bevacizumab, whichever is later. Follow up will be every 12 weeks, after EOT or last visit till study closes or withdrawal of consent, via phone call.

[e] Monitor ECG in all patients in Cycle 1 Days 1and 15, when ABI-009 infusion is given. In each case ECG is to be monitored during infusion at around the 30 min time point after start of infusion to coincide with the end of infusion ±10 mins.

[f] Ensure that metastatic tumor samples are collected from all patients for biomarker analysis, either fresh-frozen or formalin-fixed paraffin-embedded (FFPE) tumor blocks or unstained slides (min 6).

[g] For all female patients of childbearing potential, a serum pregnancy test will be done at screening. A urine pregnancy test will be repeated within 72 hours before first treatment if the serum pregnancy test occurred >72 hours before dosing, and at EOT. Pregnancy tests conducted after screening will be recorded in the source documentation only.

[h] Heights are measured only at screening. BSA will be capped at 2.0 m^2 for all therapeutics that require BSA calculation (ABI-009 and FOLFOX). Dose recalculation due to >10% weight change is from the last known value when the weight was used for dose calculation (applies to all therapeutics, including bevacizumab).

[i] Monitor proteinuria by dipstick urine analysis with serial urinalyses during bevacizumab therapy. For patients with a 2+ or greater urine dipstick reading bevacizumab treatment should be held. Patients should undergo further assessment with a 24-hour urine collection, if nephrotic syndrome is suspected. Suspend bevacizumab for >2 grams of proteinuria/24 hours and resume when proteinuria is < 2gm/24 hours. Discontinue bevacizumab in patients with nephrotic syndrome.

[j] Sirolimus levels are analyzed only for patients enrolled in the dose-finding phase (phase 1). C1D1 and C1D15 post-dose samples are done centrally; however, all trough levels (pre-dose) are done locally. C1D1: predose (anytime) and post-dose at 0.5 hr (end of infusion), 1, 2, and 4 hrs after start of infusion (±10 mins); C1D15: predose (anytime) and post-dose at 0.5 hr (end of infusion, ±10 mins). Additionally, pre-dose levels will be analyzed on these following infusion days C2D1, C2D15, C3D1, C3D14, C4D1, and C4D15. Note, pre-dose sample collection does not have a specific time and window; the collection should be made on the day of dosing, prior to dosing.

[k] Baseline imaging must be done within 2 weeks of C1D1, but preferably as close to the day of enrollment as possible, then every 8 weeks (±1 week) from first treatment during the 1st year, and every 12 weeks thereafter through disease progressions, regardless of missed or out of window doses. If a patient discontinued treatment other than disease progression, scan should be done at EOT visit. Either CT or CT/PET scans are acceptable for the study but if a CT/PET scan can be done, this is preferable. PET results are only used for qualitative assessments. MRI is allowed, if CT is contra-indicated for a patient. The same mode of imaging at screening must be used consistently throughout the study.

[l] ABI-009, mFOLFOX6, and bevacizumab must be administered after all study specific assessments are done in a visit, withABI-009 administered first followed by mFOLFOX6 + bevacizumab. It is recommended to limit the infusion to central line, which is used for the standard of care combination agents (FOLFOX + bevacizumab).

5. PROCEDURES

5.1. Screening Evaluations

This study will be conducted at least 2 US centers. Each patient who enters into the screening period for the study receives a unique patient identification number before any study-related procedures are performed. 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 sites' 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 ≤28 days prior to enrollment. Any questions regarding patient eligibility should be directed to Aadi Bioscience, Inc, 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)
- Medical history, prior/concomitant medications and procedures evaluation: all medications taken ≤28 days prior to screening
- ECG
- Physical examination as per standard of care (including physical exam, medical/cancer history, ECOG performance status assessment)
- Vital signs (eg, blood pressure, pulse, respiration rate, temperature, height, weight)
- Local Laboratory Assessments: chemistry, complete blood count (CBC), differential, platelet count, urinalysis, pregnancy test (women of child-bearing potential, includes tubal ligations), HIV, hepatitis B surface antigen, hepatitis C antibody, fasting lipids, carcinoembryonic antigen (CEA), blood for biomarkers
- Pre-treatment tissue collection for biomarkers

- CT/PET scans (or MRI, if CT is contraindicated), must be done within 2 weeks of C1D1, but preferably should be done as close to the day of enrollment as possible
- Adverse event assessment

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

5.2. Treatment Period

A patient is considered enrolled on study day 1 when the IP, ABI-009, is first administered. ABI-009, mFOLFOX6, and bevacizumab 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.

5.2.1. Day 1 Assessment

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

- Physical examination
- Vital signs
- Concomitant medication and procedures evaluation
- ECG, Cycle 1 only
- CBC, differential
- Clinical chemistry panel
- Urinalysis (to monitor proteinuria during bevacizumab therapy)
- Fasting lipids (every even cycles)
- Blood samples for biomarkers on C3 and C6
- Sirolimus level, Cycles 1 through 4
- CEA
- ECOG performance status
- Adverse events 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) (see Table 3 for analyte listing).

5.2.2. Day 15 Assessment

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

- Physical evaluation
- Vital signs
- Concomitant medication and procedures evaluation
- ECG, Cycle 1 only
- CBC, differential
- Clinical chemistry panel
- Urinalysis (to monitor proteinuria during bevacizumab therapy)
- Sirolimus level, Cycle 1 through 4
- Adverse event assessment

Table 3. Analyte Listing

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

5.2.3. Response Assessment

Tumor response will be assessed by CT / PET (or MRI, if CT is contra-indicated) scan of the chest, abdomen, and pelvis (CAP) per institutional guidelines; image preparation and evaluation will follow the specifications provided in the RECIST version 1.1. The same modality (CT or MRI) must be used at screening and throughout the study.

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

- ≤2 weeks prior to C1D1 (screening)
- followed by every 8 weeks for the first year; then every 12 weeks until disease progression or unacceptable toxicity. End of Treatment Visit CT/ PET (or 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.

5.3. End of Treatment Visit Assessment

The EOT Visit is a safety follow-up visit that is to be performed within 1 month after the last dose of ABI-009 or mFOLFOX6 / bevacizumab, whichever is later. 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
- Vital signs
- Concomitant medications and procedures evaluations
- Pregnancy test (urine test is sufficient)
- CBC /differential
- Chemistry panel
- ECOG performance status
- Imaging Assessment: CT/PET (or MRI) is to be performed at the EOT visit only for those patients that discontinue treatment for a reason other than disease progression per RECIST v1.1

5.4. Sirolimus Pharmacokinetic Analysis

Sirolimus assays will be done for patients enrolled in the dose-finding portion of the study. Pre-dose (trough levels) are done locally; post-dose levels are done centrally:

- Cycle 1 D1: pre-dose (anytime) and post-dose at 0.5 hr (±10 mins,end of infusion), and 1, 2, and 4hrs (±10 mins) after the start of the infusion;
- Cycle 1 D15: predose (anytime) and 0.5 hr ((±10 mins) after start of infusion
- Predose (anytime, prior to infusion) only on: Cycle 2 Days 1 and 15, Cycle 3 Days 1 and 15, and Cycle 4 Days 1 and 15.

5.5. 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 / mFOLFOX6 / BEVACIZUMAB)

6.1. ABI-009 plus mFOLFOX6 / Bevacizumab Dosage, Administration, and Schedule

Treatment with ABI-009 combined with mFOLFOX6 / bevacizumab will continue until disease progression or unacceptable toxicity. A physician must be available at the time of administration of IP on dosing days that correspond to study visits. Supportive care per the institution's normal standard of care including concomitant medications can be provided at the investigator's discretion.

As described in Section 2.3, with Amendment 2, an alternate dosing schedule is implemented to allow evaluation of ABI-009 given every 2 weeks, aligned with the dosing schedule of the standard of care, FOLFOX+ bevacizumab. The starting dose of the every-2-week schedule is 20 mg/m^{2,} see table below. Dose escalation to the next dose level will follow the same 3+3 dose-finding design as described in Section 2.3.Dose-escalation and de-escalation will follow the standard 3+3 rules, per Table 4.

Table 4. Dose Levels for ABI-009

Dose Levels	ABI-009 in mg/m^2 IV every 2 weeks
-2	10
-1	15
1	**20**
2	30
3	45

mFOLFOX6 (oxaliplatin 85 mg/m^2 IV with leucovorin 400mg/m^2 IV over 2 hours plus FU 400 mg/m^2 IV bolus and 2,400 mg/m^2 continuous infusion over 46 hours every 2 weeks) will be combined with bevacizumab given at 5 mg/kg every 2 weeks. If oxaliplatin is skipped, the 2-hr infusion time may be reduced as per institutional standards. Levoleucovorin (Fusilev) may be administered as a substitute for leucovorin. The levoleucovorin dose will be 200 mg/m^2 IV infusion over 2 hours, or as per institutional standards. The starting dose of FOLFOX + bevacizumab may also be modified as per the product labels and institutional standards.

Screening or day 1 weight will be used to calculate BSA for ABI-009 and FOLFOX (leucovorin included) dosing; BSA will be capped at 2.0 m^2 for all therapeutics that require BSA calculation (ABI-009 and FOLFOX). Bevacizumab dose will be calculated based on the actual patient weight in kilograms.

Dose modification for weight change:

- In the event of a ≥10% weight loss or gain, BSA will be recalculated. Dose recalculation is from the last known value when the weight was used for dose calculation (applies to all therapeutics, including bevacizumab).

6.2. ABI-009 Dose Modification and Stopping Rules

If treatment cannot be administered on the planned visit date, ABI-009 may be administered ±3 days from the scheduled date. Prior to ABI-009 administration, patients must meet the following hematological requirements:

- ANC ≥1.0 x 10^9/L
- Platelet count ≥75 x 10^9/L
- Hemoglobin ≥9 g/dL

ABI-009 will be on hold up to 28 days until the patient has fulfilled these criteria. The maximum delay between a missed scheduled ABI-009 dose and the next one (whichever dose was missed) should not be longer than 28 days. Approval from the medical monitor is required to restart study treatment after ≥28 days of interruption

In the event of clinically significant AE related to ABI-009 in any part of the study, ABI-009 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 28 days of stopping therapy, then ABI-009 may be restarted.

Dose reduction of ABI-009 to the next lower dose level should be considered as clinically indicated due to ABI-009-related toxicities for patients who are receiving ABI-009 at above the lowest dose level. In phase 1, once a dose has been reduced, it must not be increased to the previous level. In phase 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, based on the opinion of the investigator. A maximum of 2 dose level reductions are allowed for a patient.

Missed Doses

When ABI-009 is missed on any days (D1 or D15) but FOLFOX (or at least 5FU) was given on D1 and/or D15, the cycle follows the schedule set by FOLFOX, a standard of care.

Day 1 Dose Missed

When 5FU or the entire FOLFOX regimen is missed (not given within the 3-day window) on CXD1 visit, the next treatment (if counts and chemistries permit) becomes Day 1 of a new cycle.

Day 15 Dose Missed

When 5FU or the entire FOLFOX regimen is missed (not given within the 3-day window) on CXD15 visit, the next treatment, if occurs >28 days from the previous treatment will become Day 1 of a new cycle.

Dose-limiting Toxicity

Dose-limiting toxicities will be assessed in the first 28 days of dosing (1 cycle). Patients need to receive 2 rounds/sessions of all chemotherapy agents in the first 28 days in order to be evaluable for DLT assessment, unless a delay was due to toxicity in cycle 1. Patients who did not receive 2 rounds of all chemotherapy agents within 28 days due to

toxicity will be evaluable for DLT assessment. The first 2 doses of chemotherapy can be given over a longer period of time but a minimum assessment of 2 weeks will be required for toxicity assessment after the second dose of chemotherapy.

Definition of DLT for the Phase 1 part of the trial:

- Any grade ≥3 nonhematologic toxicity (NCI CTCAE v5.0), including febrile neutropenia, thought to be related to the regimen, with the exception that grade 3 nausea, vomiting, or diarrhea shall not be considered a DLT if they last less than 5 days
- Grade 3 thrombocytopenia with associated bleeding
- Grade 4 anemia or thrombocytopenia related to the regimen
- Grade 4 neutropenia

ABI-009 dose modification guidelines are outlined in Table 5 for clinically significant toxicities that are deemed related to ABI-009.

Table 5. Dose Modification Algorithms for Adverse Events Possibly Related to ABI-009 and mFOFLOX6

System/Organ	Adverse Event	CTCAE Grade v5.0	ABI-009	FOLFOX
Mucosa [a]	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.	Hold chemotherapy with FOLFOX until ≤ Grade 1. FOLFOX dose reduction is permitted if the treating investigator and the medical monitor considers this toxicity due to the combination.
		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.	Hold chemotherapy with FOLFOX until ≤ Grade 1. FOLFOX dose reduction is permitted if the treating investigator and the medical monitor considers this toxicity due to the combination.
Skin and Subcutaneous Tissue Disorders	Skin rash	Grade 2	Tolerable: Continue ABI 009 at full dose, monitor as clinically indicated.	Treat with same dose.
			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.	Treat with same dose.
		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.	Hold chemotherapy with FOLFOX until ≤ Grade 1.
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	Hold chemotherapy with FOLFOX until ≤ Grade 1 if toxicity is with first administration of FOLFOX, for subsequent occurrences, FOLFOX dose reduction is permitted.

			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.	Hold chemotherapy with FOLFOX until ≤ Grade 1 if toxicity is with first administration of FOLFOX, for subsequent occurrences, FOLFOX dose reduction is permitted.
Metabolic disorders	Hyperlipidemia (cholesterol, triglycerides)	Grade 3	If this is persistent for 2 months, reduce by 1 dose level at start of next cycle.	Treat with same dose.
		Grade 4	If this is persistent for 1 month, reduce by 1 dose level at start of next cycle.	Treat with same dose.
	Hyperglycemia	Grades 1 and 2	Start at home 2x/day glucose monitoring; initiate medical management.	Treat with same dose.
		Grade 3	Initiate medical management; If recurrent post ABI-009 despite adequate medical management, reduce by 1 dose level.	Treat with same dose.
		Grade 4	Initiate medical management, hold ABI-009 until grade 2 or less, restart 1 dose level lower	Treat with same dose.
Hematologic toxicity	Thrombocytopenia, Neutropenia, Anemia	Grade 2	ABI-009 can be administered if meeting the following hematological requirements: ANC ≥1000 cells/mm^3, platelets ≥75,000 cells/mm^3 and hemoglobin ≥9 g/dL.	The ANC must be ≥1000 cells/mm^3 and the platelet count ≥75,000 cells/mm^3 on the day of planned treatment. If these minimum requirements are not met on the day of planned treatment, treatment with mFOLFOX6 chemotherapy will be delayed until recovery occurs.
		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 ≥1000	For grade 3 or 4 neutropenia or thrombocytopenia, delay chemotherapy until the ANC ≥1000 cells/mm^3 and the platelet count

			cells/mm^3, platelet count ≥75,000 cells/mm^3 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.	≥75,000 cells/mm^3, then resume 5-FU and oxaliplatin at 1 lower dose level. For febrile neutropenia (defined as ANC <1000 cells/mm^3 and T ≥38.5°C), delay chemotherapy until absolute granulocyte count ≥1200 cells/mm^3 and the platelet count ≥75,000 cells/mm^3, then resume 5-FU and oxaliplatin at 1 lower dose level.
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. For noninfectious pneumonitis, if cough is troublesome, prescribe corticosteroids.	Consider holding chemotherapy till resolution.
		Grade ≥3	Permanently remove patient from protocol treatment. For grade 3 noninfectious pneumonitis, prescribe corticosteroids if infection is ruled out. Hold ABI-009 until recovery to ≤ grade 1; may restart within 3 weeks at reduced dose level if evidence of clinical benefit. Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 within 3 weeks. For grade 4 noninfectious pneumonitis, discontinue ABI-009.	

[a] The combination of ABI-009 with mFOLFOX-6 and bevacizumab may potentiate the risk of stomatitis and prophylactic approaches to prevent stomatitis such as steroid mouthwash (10 mL dexamethasone 0.1 mg/mL oral solution four times daily) could be considered for those who develop or at risk for stomatitis.

6.3. mFOLFOX6 and Bevacizumab Dose Modification and Stopping Rules

Dose modifications should follow the package insert for each therapeutic agent. The table below indicates dose modification levels for each of the agents in mFOLFOX6 for which dose modifications will be allowed. Dose adjustments of each agent may be made independently based on the specific types of toxicities observed. Only those agents specified in the sections below should be dose reduced. If dose reduction beyond -3 levels for any chemotherapeutic agent is required, that agent should be discontinued.

Table 6. mFOLFOX6 Dose Reductions

Agent	Initial Dose	-1	-2	-3
Oxaliplatin (mg/m^2	85	65	50	40
5-FU bolus (mg/m^2)	400	320	270	230
5-FU infusion (mg/m^2 / 46-48 hrs)	2400	1920	1600	1360

Note: If any infusion of 5-FU is to be skipped, leucovorin must also be skipped. The 5-FU bolus, along with leucovorin may be dropped after the DLT observation period (1st cycle) in phase 1, and anytime in phase 2 based on the discretion of the investigator.

Bevacizumab dose is always 5 mg/kg. Bevacizumab may be skipped or discontinued as described below, but the dose is not reduced.

Patients may continue on study if bevacizumab, oxaliplatin, or 5-FU need to be discontinued. If bevacizumab is discontinued, the bi-weekly urine protein testing will not be required. Single agent ABI-009 may be continued if mFOLFOX6 and/or bevacizumab are discontinued due to toxicity or achievement of maximum benefit in the opinion of the investigator and approval of the medical monitor and sponsor.

Patients who have unacceptable toxicity (eg, cumulative neurotoxicity, allergy) due to oxaliplatin but do not have progressive disease may modify or discontinue oxaliplatin and continue on study with 5-FU/leucovorin, bevacizumab and ABI-009 until progressive disease or intolerance. Conversely, patients who have unacceptable toxicity due to bevacizumab or ABI-009 may discontinue bevacizumab and/or ABI-009 and continue on study with the other agents until progressive disease or intolerance.

6.3.1. Oxaliplatin-related Neurotoxicity

Dose-limiting neurotoxicity is common after oxaliplatin treatment, with both acute and chronic manifestations. Neuropathic symptoms may resolve within a week (acute); however, with increasing cumulative dose, severe chronic sensory neuropathy may, characterized by distal paresthesia and numbness, leading to functional disability. The following dose modifications are recommended for oxaliplatin-related neurotoxicity, Table 7:

Table 7. Oxaliplatin Dose Modification for Neurotoxicity

Paresthesias/dysesthesias	Duration of Acute Toxicity [a]		Persistent Toxicity [b]
	1-7 Days	>7 Days	Between Cycles
Grade 1: Paresthesias/dysesthesias[c] of short duration that resolve and do not interfere with function	No change	No change	No change
Grade 2: Paresthesias/dysesthesias[c] interfering with function, but not activities of daily living	No change	No change	Decrease oxaliplatin dose by one dose level
Grade 3: Paresthesias/dysesthesias[c] with pain or with functional impairment that also interfere with activities of daily living	No change	Decrease oxaliplatin dose by one dose level	Stop oxaliplatin (continue all other agents until PD)
Grade 4: Persistent Paresthesias/dysesthesias[c] that are disabling or life-threatening	Stop oxaliplatin (continue all other agents until PD)	Stop oxaliplatin (continue all other agents until PD)	Stop oxaliplatin (continue all other agents until PD)

[a] Acute toxicity is defined as reversible primary peripheral sensory neuropathy that is of early onset, occurring within hours or one to two days of dosing, that resolves within 14 days, and that frequently recurs with further dosing.
[b] Persistent toxicity (> 14 days) is defined as primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysesthesias, hypoesthesias, but may also include deficits in proprioception that can interfere with daily activities (e.g., writing, buttoning, swallowing, and difficulty walking from impaired proprioception).
[c] May be cold-induced.

6.4. 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.

6.4.1. 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 ≥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)

6.4.2. 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.

6.4.3. Overdose

On a per dose basis, an overdose is defined as 10% over the protocol-specified dose of ABI-009 or mFOLFOX6 / bevacizumab assigned to a given patient, regardless of any associated AEs or sequelae.

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

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

7. STUDY DRUG MANAGEMENT

7.1. Description of 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 sirolimus 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 Bioscience or sponsor nominated Contract Research Organization monitoring teams for verification of proper study drug storage.

7.2. ABI-009, FOLFOX, and Bevacizumab Accountability, Disposal, and Compliance

For ABI-009, only completely unused study drug vials should be retained by the site until a representative from Aadi Bioscience 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 Bioscience or authorized Aadi Bioscience-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 Bioscience 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 FOLFOX / bevacizumab, the investigator, or designee, shall record the dispensing of study drug to patients. The study drug record will be made available to Aadi Bioscience or authorized Aadi Bioscience-designated monitoring personnel for the purpose of accounting for the use of the drug.

Accurate recording of all FOLFOX / bevacizumab 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 and Use

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 the Pharmacy Manual, 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.

7.4. Receipt and Return of ABI-009

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

8. CONCOMITANT MEDICATIONS AND PROCEDURES

All concomitant treatments, including blood and blood products, must be reported on the 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 8.2.

Concomitant therapies are to be collected from the signing of informed consent through the EOT Visit. Use of prohibited medications and procedures will be evaluated and documented during screening and on study. Therapy name including indication, dose, frequency, route, start date and stop date will be recorded on each patient's CRF(s).

8.1. Permitted Medications and Procedures

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the 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-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. G-CSF 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.

8.2. Prohibited Medications and Procedures

The use of certain medications, and illicit drugs within 5 half-lives or 28 days, whichever is shorter prior to the first dose of study drug and for the duration of the study will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while study drug is held, the Aadi Bioscience 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.
- Sirolimus is metabolized primarily by CYP3A4. Drugs that are strong inhibitors or inducers of CYP3A4 may only be used under special circumstances (eg, as a single use for a procedure) while treatment with study drug is interrupted. The list may be modified based on emerging data.

- Use of any known CYP3A4 substrates with 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

9. STATISTICAL CONSIDERATIONS

9.1. Study Endpoints

Primary Endpoint:

- Phase 1: DLTs and MTD of ABI-009 in combination with mFOLFOX6 and bevacizumab
- Phase 2: PF rate at 6 months in patients treated with ABI-009 at the RP2D, in combination with mFOLFOX6 and bevacizumab, assessed by investigators

Secondary Endpoint(s): data both from phase 1 and 2

- Phase 1:
  - Safety profile of dose cohorts analyzed separately and together
  - DCR assessed by investigators, dose cohorts analyzed separately and together
- Phase 2:
  - Median PFS, ORR, DOR, and DCR assessed by investigator for all patients and based on PTEN status
  - PF rate at 6 months based on PTEN status
  - Safety at RP2D

Exploratory Endpoint(s):

- Biomarkers:
  - Pre-treatment metastatic tumor biopsy: (fresh or archival) are required from all patients to assess baseline biomarker and mutational analysis, including PTEN loss evaluation, PIK3CA and Ras mutational status, and mTOR pathway markers (including, but not limited to S6K, 4EBP1). In particular, PIK3CA mutations and PTEN loss will be analyzed by IHC to evaluate as potential predictive biomarkers of response to mTOR inhibition. If tissue from metastatic site is not available, primary lesion tissue is acceptable. Reports on mutational status will be collected from all patients, if available.
  - Blood samples: for cell-free plasma DNA collection (pretreatment, C3 and C6 D1 post-treatment, upon disease progression, and/or end of last dose of treatment) for all patients. Molecular analysis of circulating DNA assay using next generation sequencing to assess changes over time as response to therapy of the prevalence of mutations identified in the baseline tumor samples.
    - Nucleic acids extracted from blood can also be used to investigate whether circulating tumor nucleic acids are associated with disease progression

9.2. Safety Analysis

The safety analysis set includes all treated patients.

Safety and tolerability will be monitored through continuous reporting of treatment-emergent and treatment-related AEs, AEs of special interest, laboratory abnormalities, and incidence of patients experiencing dose modifications, dose delay/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 NCI CTCAE v5.0.

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

9.3. Efficacy Analysis

The Efficacy Analysis Set includes all enrolled patients with measurable tumor per RECIST v1.1 at baseline who received at least 2 doses of ABI-009 and had a follow-up CT / PET (or MRI).

Efficacy will be assessed by investigators using CT / PET scans and RECIST v1.1. Only RECIST v1.1 criteria will be used to assess response; PET will be used for qualitative purposes only.

For the phase 2 portion of the study the primary endpoint is PF rate at 6 months. Progression-free rate at 6 months is the proportion of patients who are progression-free and alive at 6 months. The point estimate of the PF rate and the exact two-sided 95% confidence interval will be provided.

Progression-free survival is defined as the time from the first day of study drug administration to disease progression or death due to any cause. For PFS, the KM estimates and corresponding two-sided 95% confidence intervals for the median and quartiles will be provided. The KM plot may also be provided.

The ORR and DCR will be reported along with exact 95% confidence intervals computed by the Clopper-Pearson method.

All efficacy endpoints will also be analyzed based on PTEN status.

9.4. Exploratory Analysis

Presence/level of expression of several tumor and blood biomarkers and their relationship to clinical responsiveness.

9.5. Sample Size Considerations

In phase 1, it is estimated that a maximum of up to 18 patients will be required to achieve the MTD; however, MTD could be reached with as few as 5 patients.

In phase 2, 34-37 additional eligible patients will be enrolled at the RP2D, for a total of 40 patients (including 3-6 patients from phase 1 at the RP2D). Patients without follow-up

scans will be replaced. Assuming a 10% attrition rate, 44 patients would need to be enrolled for the phase 2 portion of the study, inclusive of the phase 1 patients at RP2D.

The focus of the phase 2 portion of the study will be on the estimation of the magnitude of treatment effect, as measured by PF rate at 6 months. Based on an assumed 6-month PF rate of 90% and a sample size of 40 patients, the 95% confidence intervals for the 6-month PF rate will be 76.3% to 97.2%.

9.6. 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.

10. MONITORING, RECORDING AND REPORTING OF ADVERSE EVENTS

10.1. Toxicities of ABI-009

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

More details on the known precautions, warnings, and AEs of sirolimus and rapalogs are found in the Rapamune® and Torisel® Package Inserts (Pfizer, 2011a; Pfizer, 2011b).

10.2. Toxicities of FOLFOX

FOLFOX regimens combine oxaliplatin and leucovorin with bolus and infusional 5-fluorouracil (5-FU). Oxaliplatin is a DNA cross-linking agent consisting of a platinum ion chelated with1, 2-diaminocyclohexane (DACH) and an oxalate ligand. It undergoes spontaneous activation in aqueous solutions via displacement of the labile oxalate ligand by water. The activated compounds bind with DNA, resulting in inter- and intra-strand platinum-DNA crosslinks. 5-FU is an anti-metabolite that blocks the methylation reaction of deoxyuridylic acid to thymidylic acid, causing thymidine-less cell death in rapidly growing cells. Leucovorin is reduced folic acid that modulates the activity of 5-FU by stabilizing the ternary 5-FdUMP/ thymidylate synthetase complex. Side effects associated with FOLFOX include neuropathy including pharyngo-laryngodysesthesia, diarrhea, nausea, vomiting, and mild myelosuppression.

10.3. Toxicities of Bevacizumab

Per the prescribing information, the most common adverse reactions incidence (incidence > 10%) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis (Genentech, 2017).

Due to bevacizumab's influence on blood vessels, it causes coagulative side effects and conversely also bleeding and wound repair problems, including GI perforation and fistulae (Tahover, 2013).

10.4. 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 v5.0.

10.5. Serious Adverse Events

10.5.1. 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.

10.5.2. Reporting Procedures for Serious Adverse Events

All serious adverse experiences that are drug-related 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 Bioscience 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 Bioscience 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 Bioscience 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 Bioscience and the IRB/EC.

10.6. 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 Bioscience 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 Bioscience 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 Bioscience 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.

11. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

11.1. 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.

11.2. 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.

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

12. REGULATORY OBLIGATIONS

12.1. Informed Consent

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

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

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

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

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

12.2. Institutional Review Board/Independent Ethics Committee

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

12.3. Patient Confidentiality

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

- 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 Bioscience, 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 Bioscience (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

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

12.4. Protocol Amendments

If investigator amends the protocol, agreement from Aadi Bioscience 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 Bioscience.

12.5. Termination of the Study

Both Aadi Bioscience 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 Bioscience.

13. DATA HANDLING AND RECORDKEEPING

13.1. Data/Documents

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

13.2. 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.

13.3. Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including patients not receiving protocol-required therapies) as stipulated in the protocol for each patient in the study. For patients who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 2), the investigator can search publicly available records (where permitted) to ascertain survival status.

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

13.4. The investigator is responsible 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.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. Study Monitoring

The Institution representative, Aadi Bioscience representative(s) or designee 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 Bioscience representative or designee 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 Bioscience representative or designee 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.

14.2. 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 Bioscience's Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

15. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

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