Cover Page

Study GBM-007, NCT03463265

Protocol Including Statistical Analysis

Last Approved Version 3.0
Date: December 02, 2019

Protocol Title
A Phase 2, Open-label Study of ABI-009 (nab-Rapamycin) in Bevacizumab-naïve Patients with Recurrent High-grade Glioma and in Patients with Newly Diagnosed Glioblastoma

A Phase 2, Open-label Study of ABI-009 (*nab*-Sirolimus) in Patients with Recurrent High-grade Glioma and in Patients with Newly Diagnosed Glioblastoma

Investigational Product:	**ABI-009**
Protocol Number:	**GBM-007**
Study Phase:	**2**
IND Number:	**138432**
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Lee Schacter, MD	
Printed Name	
By my signature, I indicate that I have reviewed this protocol and find its content to be acceptable.	

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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Institution Name:	

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

PROTOCOL SYNOPSIS

INVESTIGATIONAL PRODUCT	ABI-009, sirolimus albumin-bound nanoparticles for injectable suspension, *nab*-sirolimus, nanoparticle albumin-bound sirolimus
TITLE	A Phase 2, Open-label Study of ABI-009 (*nab*-Sirolimus) in Patients with Recurrent High-grade Glioma and in Patients with Newly Diagnosed Glioblastoma
PROTOCOL NUMBER	GBM-007
PHASE	Phase 2
STUDY OBJECTIVES	**Arm A: Recurrent High-grade Glioma** **Primary Objective** 1. To evaluate the efficacy of intravenous (IV) ABI-009 as a single agent and as a combination of ABI-009 + temozolomide (TMZ), ABI-009 + bevacizumab (BEV), ABI-009 + lomustine (CCNU), and ABI-009 + marizomib (MRZ) in patients with recurrent high-grade glioma. **Secondary Objective** 1. To evaluate the safety of ABI-009 as a single agent and in combination with TMZ, BEV, CCNU, or MRZ in patients with recurrent high-grade glioma. **Arm B: Newly Diagnosed Glioblastoma (ndGBM)** **Primary Objectives** 1. To evaluate the efficacy of the combination of ABI-009 and standard TMZ-based chemoradiotherapy in patients newly diagnosed with glioblastoma. **Secondary Objectives** 1. To evaluate the safety and efficacy of ABI-009 (Induction Treatment). 2. To evaluate the safety of the combination of ABI-009 + TMZ + radiotherapy (RT) (Concomitant Treatment). 3. To evaluate the safety of the combination of ABI-009 + TMZ (Adjuvant Treatment).

	Exploratory Objective for Arms A and B 1. To evaluate tumor biomarkers related to mTOR pathway using pre-study, archived tissue samples and if available, post-treatment tumor tissue samples. 2. To evaluate blood biomarkers and correlate to outcomes.
STUDY ENDPOINTS	**Primary Endpoint for Arms A and B** Objective overall response rate (ORR, according to RANO 2010 criteria) **Secondary Endpoints for Arms A and B** Progression-free survival (PFS) rate at 6 months, PFS rate at 12 months, median PFS, overall survival (OS) at 12 months, median OS, and adverse events (AEs) **Exploratory Endpoints for Arms A and B** • Assessment of pre-treatment archived tumor samples for the activity of mTOR pathway and correlation with activity/tolerability • If available, tumor biomarkers post-progression • To evaluate blood biomarkers and correlate to outcomes
STUDY DESIGN	This is a prospective, multi-cohort, non-randomized, open-label phase 2 study. Arm A will have 5 cohorts, aiming to determine the efficacy and safety profile of ABI-009 as a single agent and in combination with TMZ, BEV, CCNU, or MRZ in patients with recurrent high-grade glioma, who have not previously received any mTOR inhibitor. Arm A of the study will use Simon's two-stage design for each cohort. Up to 19 patients per cohort will be enrolled: there will initially be 9 patients enrolled with a stopping rule that only if there are 2 or more positive responses will the study proceed to further enrollment of the next 10 patients. 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 discretion of the patient. In Arm A (recurrent high-grade glioma) of the study, ABI-009 will be administered IV at 100 mg/m^2 as a single agent on Days 1 and 8 of every 21-day cycle (Cohort 1), or at 60 mg/m^2 on Days 1, 8, and 15 of every 28-day cycle in combination with TMZ (50 mg/m^2 PO daily), or with BEV (5 mg/kg IV on Days 1 and 15 of every 28-day cycle), or with MRZ (0.8 mg/m^2 IV on Days 1, 8, and 15 of every 28-day cycle), (Cohort 2, 3, and 5 respectively), or on Days 1 and 8 of every 21-day cycle with CCNU (90 mg/m^2 on Day 1 of every odd cycle, Cohort 4). At the discretion of the investigator, if ABI-009 is well tolerated (no DLTs, dose modifications, or dose delays) at 60 mg/m^2 in the

	first 3 patients in the cohort, the dose may be increased to 75 mg/m^2 for subsequent patients in the cohort. Arm B (ndGBM) of the study will evaluate the efficacy of ABI-009 induction therapy (60 mg/m^2 IV every week for 4 weeks) followed by the combination of ABI-009 (60 mg/m^2 IV on Days 8 and 15 of every 21-day cycle for 2 cycles) with the standard of care treatment of TMZ (75 mg/m^2 PO daily for 6 weeks) + RT (30x 200 cGy, 5 days/week) (Concomitant Treatment) followed by ABI-009 (60 mg/m^2 IV on Days 1, 8, and 15 of every 28-day cycle for 6 cycles) + TMZ (150 mg/m^2 PO daily on Days 1-5 of every 28-day cycle for 6 cycles) (Adjuvant Treatment) in patients with ndGBM who can have either non-measurable disease or enhancing tumors after surgery and have not previously received any local or systemic therapy. Up to 19 patients will be enrolled in Arm B.
NUMBER OF PATIENTS	**Arm A** (recurrent high-grade glioma)**:** up to 95 response-evaluable patients will be enrolled (up to 19 per cohort; 5 cohorts). **Arm B** (ndGBM)**:** up to 19 response-evaluable patients will be enrolled.
SAMPLE SIZE ESTIMATE	Simon's two-stage design (Simon, 1989) will be used for Arm A of this study. The null hypothesis that the true response rate is 15% will be tested against a one-sided alternative. In the first stage, 9 patients will be accrued. If there are 1 or fewer responses in these 9 patients, the study will be stopped. Otherwise, 10 additional patients will be accrued for a total of 19. The null hypothesis will be rejected if 6 or more responses are observed in 19 patients. This design yields a type I error rate of 0.0497 and power of 0.8132 when the true response rate is 40%.
INCLUSION CRITERIA	**Inclusion Criteria Common for Both Arms A and B** A patient will be eligible for inclusion in this study only if all the following criteria are met: 1. Understand and voluntarily sign and date an informed consent document prior to any study related assessments/procedures. 2. Males and females of age ≥18 years at the time of signing the informed consent document. 3. Karnofsky Performance Status (KPS) score ≥70% (see Appendix 1. Karnofsky Performance Status). 4. No investigational agent within 4 weeks prior to the first dose of study drug. 5. All AEs resulting from prior therapy and surgery must have resolved to National Cancer Institute Common Terminology Criteria for Adverse

	Events (NCI-CTCAE) v5.0 grade ≤1 (except for laboratory parameters outlined below). 6. Adequate hematological, renal, and hepatic function (assessment performed within 14 days prior to study treatment): – Absolute neutrophil count (ANC) ≥1.5 x 10^9/L – Platelets ≥100 x 10^9/L – Hemoglobin ≥9 g/dL. Serum creatinine ≤1.5 x upper limit of laboratory normal (ULN); Total serum bilirubin ≤1.5 x ULN, or ≤3 x ULN if Gilbert's disease is documented – Aspartate Serine Transaminase (AST), Aspartate Leucine Transaminase (ALT), Alkaline Phosphatase (ALP) ≤2.5 x ULN – Serum triglyceride <300 mg/dL; serum cholesterol <350 mg/dL 7. Patients must be without seizures for at least 14 days prior to enrollment, and patients who receive treatment with anti-epileptic drugs (AEDs) must be on stable doses for at least 14 days prior to enrollment. Patients must be off enzyme-inducing anti-epileptic drugs (EIAEDs) for at least 14 days prior to enrollment and cannot be on EIAEDs at any time during the study. 8. Steroid therapy for control of cerebral edema is allowed at the discretion of the Investigator. Patients should be on stable or decreasing dose of corticosteroids for at least 1 week prior to the first dose of study drug. 9. 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. • Male patients with partners of child-bearing potential must agree to take contraceptive measures for the duration of treatment and for 3 months after the last study treatment. 10. Willing and able to adhere to the study visit schedule and other protocol requirements. **Inclusion Criteria Specific for Arm A** 1. All patients must have histologic evidence of high grade glioma (World Health Organization [WHO] grade 3 or grade 4) and radiographic evidence of recurrence or disease progression (defined as either a greater than 25% increase in the largest bi-dimensional product of

	enhancement, a new enhancing lesion, or a significant increase in T2 FLAIR). Patients must have at least 1 measurable lesion by RANO criteria (≥10 mm in 2 perpendicular diameters). 2. Patients must have previously failed a treatment regimen, including radiation and/or chemotherapy. 3. No prior treatment with mTOR inhibitors. 4. No prior treatment with TMZ for the treatment of recurrent glioma for patients entering the ABI-009 + TMZ cohort. 5. No prior treatment with BEV or any other anti-angiogenic agents, including sorafenib, sunitinib, axitinib, pazopanib, or cilengitide, for patients entering the ABI-009 + BEV cohort. 6. No prior treatment with CCNU for the ABI-009 + CCNU arm. 7. No prior treatment with MRZ or any other proteasome inhibitors, including bortezomib (BTZ), carfilzomib (CFZ), or ixazomib (IXZ), for patients entering the ABI-009 + MRZ cohort. 8. At least 4 weeks from surgical resection and at least 12 weeks from the end of RT prior to enrollment in this study, unless relapse is confirmed by tumor biopsy or new lesion outside of radiation field, or if there are 2 magnetic resonance imaging (MRI) scans confirming progressive disease (PD) that are approximately 4 weeks apart. **Inclusion Criteria Specific for Arm B** 1. Histologically confirmed ndGBM. 2. Patients must have had surgery and can have either non-measurable disease or a measurable post-contrast lesion after surgery detected by MRI. 3. No prior treatment with mTOR inhibitors, and no prior local or systemic therapy for GBM.
EXCLUSION CRITERIA	**Exclusion Criteria Common for Both Arms A and B** A patient will not be eligible for inclusion in this study if any of the following criteria apply: 1. Co-medication or concomitant therapy that may interfere with study results, including anti-coagulants and enzyme-Inducing anti-epileptic drugs (EIAEDs). 2. History of thrombotic or hemorrhagic stroke or myocardial infarction within 6 months. 3. Pregnant or breast feeding. 4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring IV antibiotics & psychiatric illness/social situations that would limit compliance with study requirements, or disorders associated with significant immunocompromised state. 5. Active gastrointestinal bleeding.

	6. Uncontrolled hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥90 mm Hg. 7. Patients with history of intestinal perforations, fistula, hemorrhages and/or hemoptysis ≤6 months prior to first study treatment. 8. Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy. 9. Patients with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension. 10. Use of strong inhibitors and inducers of CYP3A4 (such as EIAEDs including carbamazepine, phenytoin, oxcarbazepine, topiramate, among others) 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. 11. Known other previous/current malignancy requiring treatment within ≤ 3 years except for limited disease treated with curative intent, such as in situ prostate cancer, intracapsular renal cancer, cervical carcinoma in situ, squamous or basal cell skin carcinoma, and superficial bladder carcinoma. 12. Any comorbid condition that restricts the use of study drug and confounds the ability to interpret data from the study as judged by the Investigator or Medical Monitor. 13. Known infection with human Immunodeficiency Virus (HIV), or active Hepatitis B or Hepatitis C.
DURATION OF TREATMENT AND STUDY PARTICIPATION	The Arm A of this study is expected to take approximately 32 months from first patient enrolled to last patient follow-up, including approximately 24 months of enrollment period, an estimated 6 months of treatment (or until unacceptable toxicity or disease progression) and an end of treatment visit (EOT) within 4 weeks after last treatment. The Arm B of this study is expected to take approximately 24 months from first patient enrolled to last patient follow-up, including approximately 16 months of enrollment period, up to 12 months of treatment (or until unacceptable toxicity or disease progression) and an EOT within 4 weeks after last treatment. End of Treatment 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 4 weeks 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 is the on-study 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 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	**Arm A (recurrent high-grade glioma):** **Cohort 1: ABI-009** ABI-009 will be administered at 100 mg/m^2 as a 30-minute IV infusion on Days 1 and 8 of every 21-day cycle. Two dose reduction levels will be allowed for toxicities: 75 mg/m^2 and 60 mg/m^2. **Cohort 2: ABI-009 + TMZ** ABI-009 will be administered at 60 mg/m^2 as a 30-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle. If ABI-009 is well tolerated at 60 mg/m^2 in the first 3 patients in the cohort, the dose may be increased to 75 mg/m^2. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2. Temozolomide will be administered PO at 50 mg/m^2 daily. **Cohort 3: ABI-009 + BEV** ABI-009 will be administered intravenously at 60 mg/m^2 as a 30-minute infusion on Days 1, 8, and 15 of every 28-day cycle. If ABI-009 is well tolerated at 60 mg/m^2 in the first 3 patients in the cohort, the dose may be increased to 75 mg/m^2. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2. Bevacizumab will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose, and 30 minutes afterward assuming tolerability) at a fixed dose of 5 mg/kg on Days 1 and 15 of every 28-day cycle. Bevacizumab will be administered approximately 10 minutes after the end of the ABI-009. **Cohort 4: ABI-009 + CCNU** ABI-009 will be administered at 60 mg/m^2 as a 30-minute IV infusion on Days 1 and 8 of every 21-day cycle. If ABI-009 is well tolerated at 60 mg/m^2 in the first 3 patients in the cohort, the dose may be increased to 75 mg/m^2. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2.

	Lomustine (CCNU) will be administered PO at 90 mg/m^2 on Day 1 of each odd 21-day cycle (ie, every 6 weeks). **Cohort 5: ABI-009 + MRZ** ABI-009 will be administered at 60 mg/m^2 as a 30-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle. If ABI-009 is well tolerated at 60 mg/m^2 in the first 3 patients in the cohort, the dose may be increased to 75 mg/m^2. Three dose reduction levels will be allowed for toxicities: 45, 30, and 20 mg/m^2. MRZ will be administered at 0.8 mg/m^2 as a 10-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle. MRZ will be administered approximately 10 minutes after the end of the ABI-009 infusion. For Arm A, patients will continue to receive 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 discontinue combination agents may remain on study receiving ABI-009 in the absence of disease progression or toxicity. Patients will be enrolled sequentially from Cohort 1 through 5 in groups of 3 patients. After the enrollment of 3 patients in the previous cohort, enrollment in subsequent cohorts can start. If a patient is not eligible for enrollment into the next cohort due to prior exposure to therapy, he/she is allowed to be enrolled in a subsequent cohort if the patient meets all other inclusion criteria. If the drug supply to a cohort is delayed or limited, an eligible patient can be enrolled into the next cohort. **Arm B (ndGBM):** **Induction Treatment: ABI-009** Induction Treatment will start at least 3-8 weeks following surgical resection of ndGBM and after the surgical wound is fully healed. ABI-009 will be administered IV at 60 mg/m^2 as a 30-minute IV infusion every week for 4 weeks. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2. **Concomitant Treatment: ABI-009 + TMZ + RT** Concomitant Treatment will start 1 week after the completion of Induction Treatment and will last for 6 weeks (2 cycles). ABI-009 will be administered IV at 60 mg/m^2 as a 30-minute IV infusion on Days 8 and 15 of every 21-day cycle. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2.

	Temozolomide will be administered at 75 mg/m^2 PO daily for 6 weeks. Focal RT will be given daily at 30x 200 cGy, 5 days/week for a total dose of 60 Gy (or equivalent regimens as per RTOG guidelines). **Adjuvant Treatment: ABI-009 + TMZ** Adjuvant Treatment will start 4 weeks after the completion of Concomitant Treatment and will last for 24 weeks. ABI-009 will be administered IV at 60 mg/m^2 as a 30-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle for 6 cycles. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2. Temozolomide will be administered at 150 mg/m^2 PO daily on Days 1-5 of every 28-day cycle for 6 cycles. In the absence of toxicity, TMZ may be administered at 200 mg/m^2/day starting in Cycle 2.
KEY EFFICACY ASSESSMENTS	All patients with measurable tumor per RANO 2010 criteria (see Appendix 2. Response Assessment for Neuro-Oncology (RANO)) at baseline who received at least 2 doses of ABI-009 and had a follow-up MRI will be evaluated for efficacy. **Arm A (recurrent high-grade glioma):** Tumor response, including complete response (CR), partial response (PR), stable disease (SD), or PD, will be assessed with MRI using the RANO 2010 criteria, including: • Radiographic Response Rate • PFS, PFS at 6 months, PFS at 12 months Overall Survival will be recorded, and OS at 12 months will be calculated. For Cohorts 1 and 4, MRI will be done every 6 weeks; for Cohorts 2, 3 and 5, MRI is every 8 weeks. **Arm B (ndGBM):** Tumor response will be assessed with MRI imaging on Day 1 and 4 weeks (±7 days) after the end of Concomitant Treatment and prior to the start of Adjuvant Treatment, and then every 8 weeks (±7 days) during Adjuvant Treatment until disease progression. For both Arms A and B, the primary endpoint of ORR will be determined by a local radiologist(s). After disease progression, patients will be followed for survival every 12 weeks, or more frequently as needed, until death, withdrawal of consent, or the study closes, whichever is the earliest.

	The primary endpoint is ORR by independent radiologic review and is defined as the proportion of patients who achieve a confirmed PR or CR per RANO 2010 criteria. PFS at 6 months, PFS at 12 months, median PFS, OS at 12 months, and median OS will be summarized using Kaplan-Meier (KM) analysis. Quartiles with 95% CIs will be summarized.
KEY SAFETY ASSESSMENTS	All patients will be evaluated for safety analysis if they receive at least 1 dose of ABI-009. 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 investigational product (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, following NCI-CTCAE v5.0. Physical examination, vital sign, KPS, and laboratory assessments will be monitored frequently as needed throughout the treatment cycles (eg, serum chemistry at Day 1 of every cycle, hematology at every treatment visit). All serious AEs (SAEs) (regardless of relationship to IP) will be followed until resolution. Laboratory analysis will be performed as per study schedule. The treated population (Full Analysis Set) will be the analysis population for all safety analyses. Adverse events will be grouped by their system organ class and preferred term. Summary tables will include the number and percentage of patients with AEs, SAEs, fatal AEs and other AEs of interest.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AED	anti-epileptic drug
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
ANC	absolute neutrophil count
AST	aspartate transaminase (SGOT)
AUC	area under the time-concentration curve
β-hCG	beta human chorionic gonadotropin
BBB	blood-brain barrier
BCNU	carmustine
BEV	bevacizumab
BSA	body surface area
BTZ	bortezomib
C_{max}	maximum plasma drug concentration
CBC	complete blood count
CCNU	lomustine
CI	confidence interval
CNS	central nervous system
CR	complete response
CT	computed tomography
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiography
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EIAED	enzyme-inducing anti-epileptic drug
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration

GBM	glioblastoma
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
HGG	high-grade glioma
HIV	human Immunodeficiency Virus
HUVEC	human umbilical vein endothelial cells
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IND	investigational new drug
INR	international normalised ratio
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
KM	Kaplan-Meier
KPS	Karnofsky Performance Status
mg	milligram
mL	milliliter
MRI	magnetic resonance imaging
MRZ	marizomib
MTD	maximum-tolerated dose
mTOR	mammalian target of rapamycin
nab	nanoparticle albumin-bound
ndGBM	newly diagnosed glioblastoma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival

PO	orally
PR	partial response
PT	prothrombin time
PTEN	protein tyrosine phosphatase
PTT	partial thromboplastin time
RANO	Response Assessment in Neuro-Oncology Criteria
rGBM	recurrent glioblastoma
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	serious adverse event
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
T2-FLAIR	T2-weighted-Fluid-Attenuated Inversion Recovery
TBL	total bilirubin level
TMZ	temozolomide
TTFields	alternating electric fields therapy
ULN	upper limit of normal
WHO	World Health Organization

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 combination agent 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 4 weeks of the last dose of ABI-009 or combination agent, whichever is later.
Follow-up Period	The 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 RANO 2010 criteria at baseline who received at least 2 doses of ABI-009 and had a follow-up MRI (or CT) (modified treated population).
Safety Analysis Set	All enrolled patients who receive at least 1 dose of ABI-009 (treated population).
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 RANO 2010 criteria. 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 RANO or death due to any cause, whichever comes first.

1. INTRODUCTION

1.1. Glioma and Glioblastoma

Gliomas start in the glial cells of the brain or the spine and comprise about 30% of all brain and central nervous system tumors, and 80% of all malignant brain tumors (Goodenberger, 2012). High-grade gliomas (HGG) are either World Health Organization (WHO) grade 3 or grade 4 tumors and tend to grow rapidly and spread faster than tumors of a lower grade. The most common grade 3 tumor is anaplastic astrocytoma and the most common grade 4 tumor is glioblastoma (GBM). Other HGGs include anaplastic oligodendroglioma and pleiomorphic xanthoastrocytoma (Bouffet, 2009; Louis, 2016).

Glioblastoma remains a deadly disease with currently limited treatment options. The median survival is only 15 months from initial diagnosis for patients with newly diagnosed GBM (ndGBM), with a 2-year survival rate of 27% and 5-year survival rate less than 5% (Stupp, 2005; Khosla, 2016). For ndGBM, currently the standard-of-care treatment strategy is surgical resection followed by radiotherapy (RT) with concomitant and adjuvant temozolomide (TMZ). Additional treatment options are to insert a carmustine (BCNU) wafer at surgery or adding electrical fields at the time of adjuvant TMZ. Alternating electric fields therapy (TTFields) is another treatment option that has been approved by the Food and Drug Administration (FDA) to use in combination with TMZ adjuvant treatment (National Comprehensive Cancer Network, 2016).

After first-line treatment, almost all GBM patients will relapse within 9 months of initial treatment (Stupp, 2012). For patients with recurrent GBM (rGBM), the median survival is only about 7 months (Gallego, 2015). An effective treatment strategy is yet to be established for rGBM patients. There are currently 3 FDA approved treatment options for rGBM: carmustine wafer, TTFields, and bevacizumab (BEV) (National Comprehensive Cancer Network, 2016). Bevacizumab has only gained accelerated approval based on overall response rate (ORR) and progression-free survival (PFS) in 2 phase 2 studies but has not shown a clear improvement in overall survival (OS) (Genentech, 2016). When used in randomized controlled trials as a treatment in patients with rGBM, BEV alone resulted in median OS of 7 to 9 months, similar to historical data reported with chemotherapies (Friedman, 2009; Kreisl, 2009; Taal, 2014; Field, 2015)**.** Therefore, there is a clear need for novel treatment options for this devastating disease.

1.2. mTOR

mTOR is a serine/threonine-specific protein kinase, downstream of the phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B) pathway, and a key regulator of cell survival, proliferation, stress, and metabolism. Additionally, mTOR is involved in regulating angiogenesis by controlling endothelial and smooth muscle cell proliferation via the hypoxia-inducible factor-1α and vascular endothelial growth factor (Corradetti, 2006). Sirolimus and its analogs (rapalogs), including everolimus and temsirolimus, 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, an oral therapeutic, is an efficacious mTOR inhibitor, it has poor solubility, low oral bioavailability, and dose-limiting toxicity (DLT) (O'Donnell, 2008; Yuan, 2009).

Consistent with its role in cell proliferation, the mTOR pathway is frequently over activated in multiple human malignancies including GBM and is thus considered to be an attractive target for anticancer therapy. Activation of PI3k/Akt pathway has been frequently found in GBM patients and is associated with reduced survival (Chakravarti, 2004). PI3K/Akt/mTOR pathway activation can occur by ligand binding to the extracellular domain of receptor tyrosine kinases such as epidermal growth factor receptor (EGFR), which is amplified or mutated in 40% to 60% of GBM (Hurtt, 1992). Furthermore, alterations in the PTEN tumor suppressor gene, including PTEN mutations/deletions which occur in 30% to 40% of GBM patients, can also result in pathway activation (Wang, 1997). In in vitro experiments, glioma cell lines were among the most sensitive to the effect of temsirolimus. In vivo studies demonstrated activity of temsirolimus against subcutaneous and orthotopic GBM models in nude mice. Preclinical studies have shown that everolimus and temsirolimus have poor brain penetration, limiting their potential use for the treatment of GBM (EMEA, 2007; O'Reilly, 2010).

In a phase 2 study in 100 patients with newly diagnosed ndGBM, the combination of oral everolimus at 70 mg 1x weekly during and after conventional TMZ-based chemoradiotherapy resulted in moderate toxicity, with 57% of patients having at least 1 grade 3+ adverse event (AE) and 23% of patients having a grade 4 AE, with the most common events being thrombocytopenia (18%) and neutropenia (16%) (Ma, 2015). Grade 3 or 4 nonhematologic events were observed in 45 patients, and 21 patients had at least 1 grade 4 nonhematologic AE. The most common grades 3–4 nonhematologic events were fatigue (11%) and hypercholesterolemia (9%). Twenty-two patients terminated therapy early because of an AE. One patient died due to neutropenia and sepsis. Combined everolimus/chemoradiotherapy was not associated with prolonged survival compared with historical controls. Patients in this study had a 12-month OS rate of 64%, a median OS of 15.8 months (95% CI: 13.0, 20.3), and a median PFS of 6.4 months (95% CI: 5.4, 9.0).

In a phase 2 study of temsirolimus in 43 patients with rGBM (Chang, 2005), temsirolimus was administered at 250 mg weekly to patients on enzyme-inducing anti-epileptic drugs (EIAEDs) and at 250 mg and later 170 mg weekly to patients not on EIAEDs. Overall, temsirolimus was well tolerated, with no grade 4 hematological toxicities and no toxic death. The major toxicities observed were elevation in lipid profiles, lymphopenia, and stomatitis. There was no evidence of efficacy with temsirolimus as a single agent, with 1 patient progression-free at 6 months. Of the patients assessable for response, there were 2 partial responses and 20 with stabile disease (SD). The median time to progression was 9 weeks.

In a separate phase 2 study of temsirolimus in 65 patients with rGBM (Galanis, 2005), temsirolimus administered at 250 mg weekly was well tolerated. The incidence of grade 3 or higher nonhematologic toxicity was 51%, and consisted mostly of hypercholesterolemia (11%), hypertriglyceridemia (8%), and hyperglycemia (8%). Grade 3 hematologic toxicity was observed in 11% of patients. There was no objective response with temsirolimus as a single agent but 36% of patients showed evidence of improvement in neuroimaging. Progression-free survival at 6 months was 7.8% and median OS was 4.4 months.

1.3. ABI-009

ABI-009 (*nab*-sirolimus) is a nanoparticle form of human albumin-bound sirolimus with a mean particle size of approximately 100 nm developed with a proprietary nanoparticle albumin-bound

(*nab*®) technology. ABI-009 is freely dispersible in saline and is suitable for intravenous (IV) administration and has produced both a favorable safety profile and evidence of efficacy in patients with metastatic solid tumors (Gonzalez-Angulo, 2013). 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, making it an ideal candidate for drug delivery (Kremer, 2002; Kratz, 2008). Importantly, albumin has been shown to be able to penetrate the blood-brain barrier (BBB) and highly accumulate in GBM. Intravenous administration of 5-aminofluorescein-labeled albumin prior to surgery resulted in the fluorescent visualization of malignant gliomas, which facilitated the complete resection of fluorescent tumor tissue (Kremer, 2009). In an orthotopic mouse GBM xenograft model, albumin-linked aldoxorubicin but not doxorubicin significantly delayed tumor growth and prolonged survival. In a phase 2 study of patients with rGBM, aldoxorubicin treatment resulted in 3 partial response (PR), 7 SD, and 11 progressive disease (PD) according to magnetic resonance imaging (MRI) among 21 patients (Groves, 2016). In a biodistribution study in rats, radiolabeled ABI-009 showed significant brain uptake at 5 days (Aadi internal data). Therefore, albumin may facilitate the efficient delivery of *nab*-sirolimus into GBM tumors, making it a useful treatment option for GBM.

1.3.1. ABI-009 Preclinical Pharmacology, Pharmacokinetics, and Toxicity

Preclinical primary pharmacology studies in vivo demonstrated significant antitumor activity of ABI-009 as a single agent administered IV at 40 mg/kg, 3 x weekly for 4 weeks, across different tumor xenograft models in nude mice, including breast, colorectal, multiple myeloma, 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). In addition, recent preclinical study has demonstrated that combination of ABI-009 with the Akt inhibitor perifosine induced synergistic antitumor activity in multiple myeloma (Cirstea, 2010).

Preclinical pharmacokinetic (PK) studies in rats showed that intravenously administered ABI-009 exhibited linear PK with respect to dose and large volume of distribution, 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 literature of sirolimus (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 GLP repeat-dose toxicity study in male and female rats, ABI-009 administered IV was well tolerated at doses up to 90 mg/kg (equivalent to 540 mg/m^2 human dose) when delivered every four days for 3 cycles. Nonclinical toxicology studies of ABI-009 showed no new or unexpected toxicity compared to what is already known for sirolimus and other rapalogs (Novartis Pharmaceuticals Corporation, 2014; Wyeth Pharmaceuticals Inc., 2015; Wyeth Pharmaceuticals Inc., 2017). Refer to the Investigators' Brochure of ABI-009 for more detailed preclinical safety information.

1.3.2. 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 administered intravenously per week for 3 weeks, followed by a week of rest (28-day cycle, qw3/4). Two dose-limiting toxicities of grade 3 AST increase and grade 4 thrombocytopenia occurred in the 150 mg/m^2 cohort, and 2 DLTs of grade 3 suicidal ideation and grade 2 hypophosphatemia occurred in the 125 mg/m^2 cohort. The maximum tolerated dose (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 confirmed SD: 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 AEs requiring a week dose delay.

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

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. Marizomib

The proteasome is a central cellular structure for the turnover of proteins. Cancer cells often exhibit enhanced proteasome activity and inhibition of proteasome activity may preferentially affect the viability of cancer cells, including high grade glioma (Crawford, 2011; Bota, 2016). Marizomib (MRZ), also known as Salinosporamide A (NPI-0052), is an irreversible inhibitor of the 20S proteasome (Chauhan, 2005; Groll, 2006). MRZ is currently in development for the treatment of newly diagnosed and recurrent glioblastoma, as well as other cancers by Celgene Corporation.

1.4.1. Clinical Experience with Marizomib

As of 10 Jul 2019, a total of 611 patients have received one or more doses of MRZ in 1 phase 3 study and 7 Phase 1 or Phase 1/2, dose-escalation, clinical studies evaluating MRZ as a single agent or in combination with other anticancer drugs.

Safety

In MRZ-108 (for completed Parts 1, 2, and 3) in recurrent glioblastoma (rGBM), at MRZ doses up to 0.8 mg/m^2 in the combination arm with BEV (n = 67), the most common treatment-emergent adverse events (TEAEs) were fatigue, nausea, vomiting, headache, hallucination, confusional state, hypertension, dizziness, fall, ataxia, diarrhea, dysphonia, and gait disturbance. The most common TEAEs reported in the 0.8 mg/m^2 monotherapy arm (n = 30) were fatigue, headache, hallucination, insomnia, nausea, vomiting, constipation, ataxia, hypokalemia, hyperglycemia, confusional state, diarrhea, dysarthria, platelet count decreased, and aphasia. The majority of Grade 3 and higher TEAEs occurred in the system organ classes (SOCs) of nervous system disorders, psychiatric disorders, and vascular disorders.

As expected, based on preclinical and earlier clinical studies, MRZ crosses the BBB leading to CNS AEs in more than 80% of patients in combination and in monotherapy including the special interest CNS AEs of hallucinations, ataxia, dizziness, dysarthria, fall, and gait disturbances. These CNS AEs are manageable with dose modification and supportive treatment as required. In addition, infusion site reactions were observed in 20% of patients in monotherapy and in 27% of patients in combination therapy at MRZ doses up to 0.8 mg/m^2; however, the incidence of events decreased over the course of the study with placement of central or peripherally inserted central catheter (PICC) lines as deemed necessary. Treatment-emergent AEs leading to permanent discontinuation of MRZ were observed in 3% of patients for monotherapy and in 12% of patients in combination therapy at MRZ doses up to 0.8 mg/m^2. The safety profile of this treatment in rGBM appears consistent with the individual agents and relatively safe in this population with limited treatment options.

In the ongoing Study MRZ-112 in ndGBM, available data with doses ranging from 0.55 mg/m^2 to 1.0 mg/m^2 of MRZ (n = 66) indicate that the safety profile is similar to the safety in the recurrent GBM study, with the most common TEAEs for the whole treatment period reported as fatigue, nausea, hallucination, vomiting, headache, confusional state, constipation, and gait disturbance. Grade $\geqslant$3 TEAEs occurred most frequently in the SOCs of nervous system disorders, general

disorders and administration site conditions, psychiatric disorders, and gastrointestinal disorders. Special interest CNS AEs occurred in 80.3% of patients and are similar to those observed in rGBM and manageable with the protocol outlined dose modifications and with supportive treatment. Infusion site reactions have occurred in 28.8% of patients. Treatment emergent AEs leading to permanent discontinuation of MRZ were observed in 21.2% of patients. Based on the available safety data in Study MRZ-112, MRZ in combination with TMZ/RT and followed by TMZ in patients with ndGBM, appears to be safe and tolerable at the studied doses and warrants continued clinical development in the first line setting.

In summary, toxicities associated with IV MRZ in both recurrent and newly diagnosed GBM have been manageable, with most AEs attenuated following dose reduction and reversible upon discontinuation of the drug. Refer to Marizomib Investigator's Brochure (Edition 13.0, dated Oct 4, 2019) for further information.

Efficacy

Study MRZ-108

Study MRZ-108 is a 4-part, open-label, combination study of MRZ and bevacizumab and of MRZ alone in patients with recurrent WHO Grade IV GBM. Part 1, Phase 1 of this study is a dose-escalation and dose-expansion study with MRZ in combination with BEV. Part 2, Phase 2 of this study evaluates MRZ used as a single agent. Part 3, Phase 2 of the study evaluates intrapatient dose escalation of MRZ in combination with BEV. Part 4, Phase 1 of the study was added to evaluate the feasibility of enterally administered MRZ.

In Parts 1, 2 and 3, 107 patients (36, 30, and 41 patients, respectively) with rGBM were enrolled and all 107 patients have discontinued treatment. Part 4 of the study is ongoing with 14 patients enrolled. No efficacy data is available.

Overall, the combination of MRZ + BEV has demonstrated encouraging clinical activity. The best overall Response Assessment in Neuro-Oncology (RANO) criteria response, as determined by the investigators, for the 67 patients in Parts 1 and 3 up to the 0.8 mg/m2 dose included: 2 complete responses (CR), 21 partial responses (PR), and 25 stable disease (SD) with an overall response rate (ORR) of 34.3%. The 6-month progression-free survival (PFS) rate was 29.8% and the median overall survival (OS) was 9.1 months (95% confidence interval [CI] 6.3 to 10.9 months).

Fifteen response-evaluable patients were enrolled to receive MRZ monotherapy in the first stage of MRZ-108 Part 2. One confirmed PR was observed in these 15 patients and the clinical study was expanded to enroll an additional 15 patients. None of the subsequently enrolled 15 patients had an objective response by RANO criteria. All 30 patients discontinued study treatment due to disease progression (28), patient decision (1), and for other reasons (1). While only 1 patient had a confirmed PR, 8 patients (26.7%) had SD (duration ranging from 0.7 to 9.5 months for 7 patients; 1 patient discontinued prior to progressive disease [PD]). Single agent activity with MRZ was also noted in 4 patients, including the 1 patient with a confirmed PR, and 3 patients with durable clinical stabilization. Two more patients were determined to have little or no tumor present upon subsequent surgery, supporting the observation of possible pseudoprogression with single-agent MRZ treatment; these 2 patients were assessed to have PD (per RANO criteria) prior to undergoing subsequent surgery.

Study MRZ-112

Study MRZ-112 is an ongoing Phase 1b study of MRZ in combination with TMZ/RT followed by TMZ in patients with ndGBM. During the dose escalation part of the study, patients are enrolled in parallel to the concomitant treatment arm (TMZ/RT + MRZ) and the adjuvant treatment arm (TMZ + MRZ). The study was amended to include a cohort of patients treated with the tumor treating fields device, Optune®, in combination with adjuvant MRZ and TMZ treatment.

Preliminary data from 10 Jul 2019 show a median OS of 14.5 months for patients enrolled in the concomitant treatment arm up to 0.8 mg/m2. The 9-month PFS and 12-month OS rates are 35.5% and 54.3%, respectively. In patients who started in the adjuvant treatment arm in doses up to 0.8 mg/m2 the median OS is 30.2 months. The 9-month PFS and 12-month OS rates are 45.5% and 72.7%, respectively. Refer to Marizomib Investigator's Brochure (Edition 13.0, dated Oct 4, 2019) for further information.

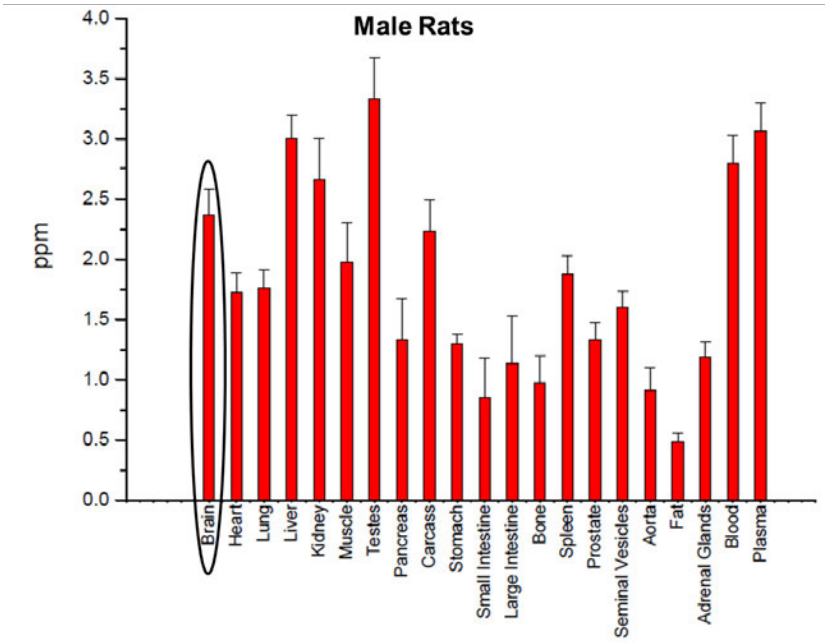
1.5. Rationale for Study Combinations

1.5.1. Rationale for Investigating ABI-009

Clinically, ABI-009 has unique characteristics amongst the available mTOR inhibitors. ABI-009 produced a fairly dose proportional increase of C_{max} and AUC across the dose range tested, and it significantly inhibited mTOR targets S6K and 4EBP1. The PK profile of sirolimus administered as ABI-009 is categorically different from those of the other oral or IV administered mTOR inhibitors. Intravenous infusion of ABI-009 from 45 to 150 mg/m^2 results in high C_{max} of sirolimus upon administration followed by a long half-life of approximately 60 hrs that allows once weekly dosing. Peak levels of sirolimus after ABI-009 are well above 1000 ng/mL range that may have significant tumor penetration effect. Oral mTOR inhibitors such as sirolimus or everolimus have poor absorption with a high inter- and intra-patient variability and a poor safety profile that requires low basal levels (low ng/mL level) to be maintained over the course of treatment. Temsirolimus on the other hand is a prodrug of sirolimus (sirolimus) and as a result, high levels of sirolimus are not achieved (<100 ng/mL) (Danesi, 2013). Clinically, administration of ABI-009 at 56 mg/m^2 IV weekly led to a much higher exposure to sirolimus (sirolimus) as compared with daily oral sirolimus at 5 mg/day (C_{max} 116-186 fold, AUC 9-16 fold, AUC/dose ~3-5 fold higher with ABI-009), temsirolimus weekly IV at 25 mg/week (C_{max} 44 fold, AUC 7 fold, AUC/dose 2 fold for ABI-009), and daily oral everolimus at 4-10 mg/day (C_{max} 47-65 fold, AUC 7-17 fold, AUC/dose ~5 fold higher with ABI-009) (Garrido-Laguna, 2010; Danesi, 2013; Gonzalez-Angulo, 2013). Unlike with other mTOR inhibitors, micromolar concentrations are reached and maintained for several hours with ABI-009 which could potentially circumvent acquired resistance to mTOR inhibitors via retroactivation of AKT by TORC2 (Banaszynski, 2005; Shor, 2008). The high exposure achieved with ABI-009 with acceptable safety profile could be highly relevant to the treatment of aggressive cancers.

As an albumin-bound nanoparticle, ABI-009 is potentially a suitable treatment option for disease indications in the brain, including epilepsy. In a biodistribution study in rats, radiolabeled ABI-009 showed significant brain uptake at 5 days (Aadi internal data). As shown in Figure 1, the radioactivity accumulation in the brain was comparable to all other major organs 5 days after a single IV dose of radiolabeled ABI-009.

Figure 1: Distribution of Radioactivity in Tissues in Male Rats



Further, in a recent PK/biodistribution study, female SD rats received a single IV dose of ABI-009 at 1.7, 9.5, and 17 mg/kg. The doses of 9.5 and 17 mg/kg corresponded with 56 and 100 mg/m^2 human doses, respectively. The sirolimus concentrations in blood and major organs at different time points between 2 to 120 hours were analyzed by LC-MS/MS. In the blood and well-perfused organs, there was a high initial peak of sirolimus concentration that dropped quickly with time between 2 hours and 24 hours. In contrast, sirolimus concentrations in the brain were relatively low at 2 hours but maintained at a steady level over time. After 5 days, sirolimus level in the brain was similar or higher compared with other organs, suggesting a preferential accumulation even when the blood levels were low (Figure 2). At all times and all doses, tissue levels of sirolimus in the brain were well above the threshold of 5-20 ng/mL (or ng/g) which is required for therapeutic activity. The brain was also the only tissue that showed a dose response for tissue levels after at 120 hours (5 days) after administration, suggesting that high ABI-009 doses may be desirable to achieve improved clinical benefits for the treatment of disease conditions in the brain. The tissue/blood ratios for all tissues except the brain remained fairly constant over 120 hours. In contrast, the brain/blood ratio increased over the same time period (Figure 3). In summary, results from this study clearly demonstrated substantial and prolonged drug distribution to the brain with ABI-009 IV administration.

Figure 2: Sirolimus Concentrations in Blood and Different Organs following ABI-009 IV Administration

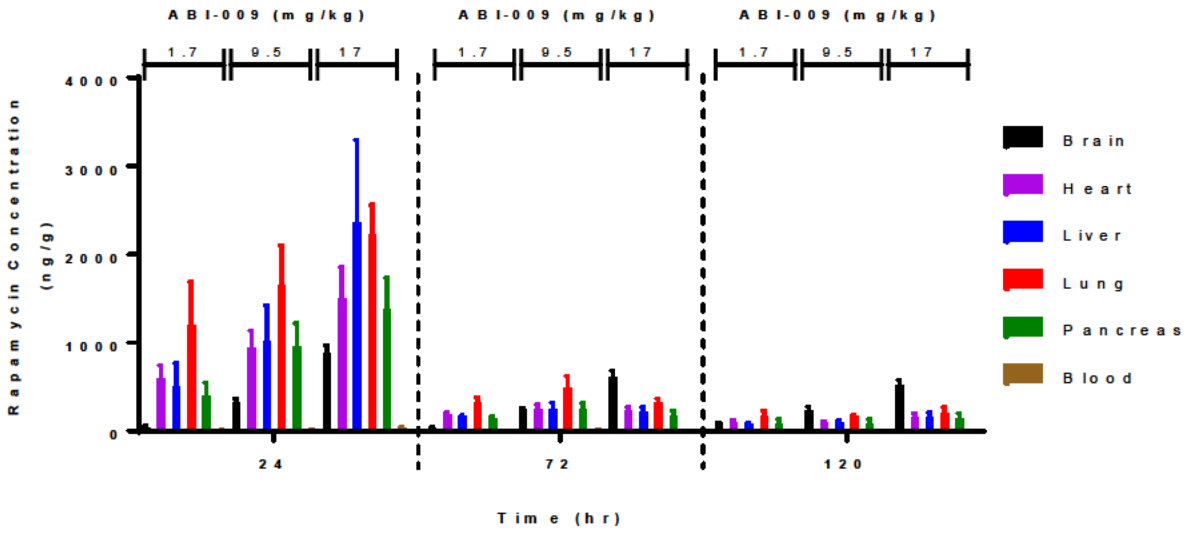
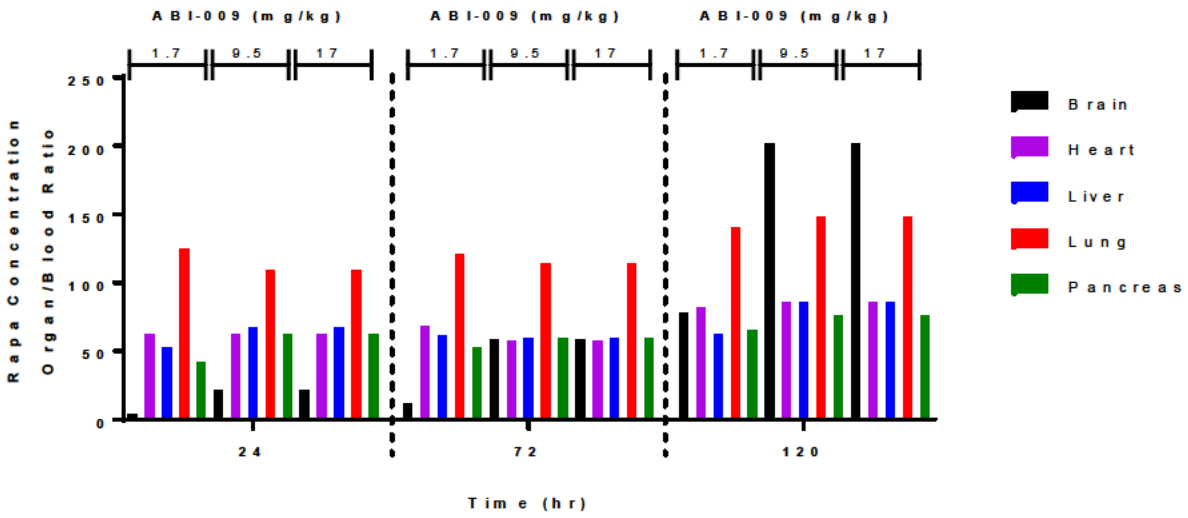


Figure 3: Tissue/blood Ratios of Sirolimus Concentrations in Different Organs following ABI-009 IV Administration



1.5.2. Rationale for Combination of ABI-009 plus Marizomib

Numerous clinical studies have shown that combination of proteasome inhibitors and mTOR inhibitors could be an effective treatment regimen for different cancer types. The combination of bortezomib (BTZ) and everolimus has been tested for the treatment of leukemia, lymphoma, multiple myeloma, and Waldenstrom macroglobulinemia (Wright, 2010; Ghobrial, 2015). Proteasome inhibition also holds potential for therapeutic activity in incurable brain tumors such as GBM. Bortezomib shows good activity against GBM cells in vitro (Bota, 2013), but BTZ does not cross the blood brain barrier (Foran, 2016). Considering this information plus the fact that

MRZ crosses the blood brain barrier, combination treatment with ABI-009 and MRZ may provide benefit to patients with high grade gliomas.

The overall safety profile of MRZ shows limited overlapping toxicities with ABI-009, which mainly include general non-hematological toxicities (constipation, diarrhea, nausea, vomiting, and fatigue).

1.5.3. Rationale for Combination of ABI-009 plus Lomustine (CCNU)

Previous studies have shown that mTOR inhibition can sensitize cancer cells to alkylating chemotherapy (Tanaka, 2007; Cejka, 2008). In a study by Tanaka et al., sirolimus enhanced cytotoxicity induced by alkylating agent ACNU in human U251 malignant glioma cells (Tanaka, 2007), suggesting that the combination of ABI-009 and lomustine (CCNU) may provide improved anticancer activity.

1.5.4. Rationale for Combination of ABI-009 plus Temozolomide (± Radiotherapy)

Temozolomide is a standard treatment for ndGBM. In a recent in vitro study, the combination of the mTOR inhibitor temsirolimus with TMZ significantly increased growth inhibition and apoptosis in melanoma cells compared with either agent alone (Niessner, 2017). The improved antitumor activity is mediated by the downregulation of the anti-apoptotic protein Mcl-1 and the upregulation of the Wnt antagonist Dickkopf homologue 1 (DKK1). In a phase 1 study in patients with ndGBM (RTOG 0913), daily oral everolimus (10 mg) combined with both concurrent radiation and TMZ and adjuvant TMZ, was relatively well tolerated with an acceptable toxicity profile (Chinnaiyan, 2013). In a phase 2 study in patients with ndGBM (N057K), the combination of everolimus with conventional TMZ-based chemoradiotherapy resulted in OS rate at 12 months of 64%, median OS of 15.8 months, and median time to progression of 6.4 months (Ma, 2015). The combination had moderate toxicity but did not show an appreciable survival benefit compared with historical controls with conventional therapy. Based on preclinical and clinical study results, the novel mTOR inhibitor ABI-009 may potentially improve the activity of TMZ in ndGBM and rGBM settings.

Further, mTOR inhibitors have been shown to enhance the effects of radiation therapy. In a preclinical study with MCF7 breast cancer cells, sirolimus treatment led to significant suppression of homologous recombination (HR) and nonhomologous end joining (NHEJ), 2 major mechanisms required for repairing ionizing radiation-induced double-strand DNA break (Chen, 2011). In androgen receptor-positive prostate cancer cells, sirolimus and temsirolimus showed strong radiosensitization effects when used in combination with radiation (Schiewer, 2012). Increased phospho-mTOR and phospho-S6 proteins were also detected in irradiated human umbilical vein endothelial cells (HUVEC). The combination of everolimus and radiation resulted in a significant reduction in vasculature and blood flow in glioma xenografts in mice compared with mice treated with everolimus or radiation alone (Shinohara, 2005). Taken together, these study results support the induction treatment with ABI-009 prior to chemoradiation therapy, the approach used in Arm B of this study for the treatment of patients with ndGBM.

1.5.5. Justification for ABI-009 Dose Selections

In **Arm A (recurrent high-grade glioma), Cohort 1,** single agent ABI-009 will be administered IV as a 30-minute infusion at a dose of 100 mg/m^2 on Days 1 and 8 of every 21-day cycle, as 100 mg/m^2 was determined to be the MTD in a previous phase 1 study in patients with solid tumors (Gonzalez-Angulo, 2013).

In **Arm A, Cohort 2-5,** the combination cohorts, ABI-009 will be administered IV at 60 mg/m^2. At the discretion of the investigator, if ABI-009 is well tolerated (no DLTs, dose modifications, or dose delays) at 60 mg/m^2 in the first 3 patients in the cohort, the dose may be increased to 75 mg/m^2 for subsequent patients in the cohort. This dose is 40% lower than the MTD of 100 mg/m^2 potentially reducing the risk of overlapping toxicities with the combination drugs. The administration of ABI-009 at 56 mg/m^2 resulted in significantly higher exposure to sirolimus compared with weekly IV temsirolimus at 25 mg/week (C_{max} 44 fold higher, AUC 7 fold, AUC/dose 2 fold higher for ABI-009) and daily oral everolimus at 4-10 mg/day (C_{max} 47-65 fold higher, AUC 7-17 fold, AUC/dose ~5 fold higher for ABI-009) (Danesi, 2013; Gonzalez-Angulo, 2013).

For patients with recurrent disease, ABI-009 will be administered on Days 1, 8 and 15, of a 28-day cycle when combined with TMZ, or BEV, or MRZ, or on Days 1 and 8 of a 21-day cycle when combined with CCNU to align with established dosing regimens of the combination agents. It is hypothesized that lower doses of BEV may potentially improve chemotherapy delivery and ultimately patient outcome (Weathers, 2016). In a retrospective analysis, low dose intensity BEV (<5 mg/kg/week) was associated with improved PFS and OS with an inverse relationship seen between dose-intensity and OS when compared with normal dose intensity BEV at 10 mg/kg (Lorgis, 2012). Therefore, the BEV dose of 5 mg/kg is chosen for this study. Due to potential hematologic toxicities of ABI-009 and myelosuppression common with CCNU, the CCNU dose to be administered on Day 1 of each odd cycle will start at 90 mg/m^2 with a maximum dose of 160 mg per cycle (approximately 70% of the 130 mg/m^2 starting dose in patients with brain tumors) and will be discontinued for compromised bone marrow function.

In Arm B (ndGBM), single agent ABI-009 will be administered IV at 60 mg/m^2 once weekly for 4 weeks during induction treatment prior to standard RT + TMZ with the intent of eliminating any residual disease following surgery. ABI-009 will be administered IV at 60 mg/m^2 on Days 8 and 15 of a 21-day cycle, for 2 cycles, during concomitant RT + TMZ to provide a rest period before continuing with ABI-009 treatment. ABI-009 will then be administered IV at 60 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle with adjuvant TMZ. This dose is 40% lower than the MTD of 100 mg/m^2 potentially reducing the risk of overlapping toxicities with the combination therapy.

The use of induction period will allow us to evaluate single agent activity in newly diagnosed GBM and is a well-established approach. Several clinical trials have demonstrated the feasibility and safety of administering 1 to 4 cycles of chemotherapy prior to radiation therapy in patients with malignant gliomas (Recht, 1990; Watne, 1992; Gilbert, 2002; Chang, 2004), and that the delay to radiation does not appear to compromise patient outcome (Kirby, 1996; Fetell, 1997; Vinolas, 2002; Wick, 2002; Diaz, 2005). Much of the early work focused on chemotherapies in wide use at the time: alkylating agents such as BCNU, procarbazine, CCNU, and TMZ; platinums such as cisplatin and carboplatin, and other alkaloids such as vincristine, etoposide, and irinotecan. Some of the studies reported tumor response to chemotherapy prior to initiation of radiation therapy,

while others reported tumor response to the sequence of both chemotherapy and radiation therapy. A few studies demonstrated early evidence that agents were clearly inactive (Fetell, 1997; Hochberg, 2000; Balana, 2014).

1.5.6. Rationale for Performing the Study

Patients with HGG represent a population with a large unmet medical need. Based on the significance of mTOR pathway in GBM pathology, this study will evaluate the efficacy and safety of ABI-009 as a single agent and in combination with other therapeutic agents for the treatment of recurrent HGG. The best regimen among the combination arms may be further tested in additional clinical studies. This study will also evaluate the efficacy and safety of the addition of ABI-009 to the standard of care treatment for patients with ndGBM.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Arm A: Recurrent High-grade Glioma

Primary Objective

1. To evaluate the efficacy of IV ABI-009 as a single agent and as a combination of ABI-009 + TMZ, ABI-009 + BEV, ABI-009 + CCNU, and ABI-009 + MRZ in patients with recurrent HGG.

Secondary Objective

1. To evaluate the safety of ABI-009 as a single agent and in combination with TMZ, BEV, or CCNU, or MRZ in patients with recurrent HGG.

Arm B: Newly-diagnosed Glioblastoma

Primary Objectives

1. To evaluate the efficacy of the combination of ABI-009 and standard TMZ-based chemoradiotherapy.

Secondary Objectives

1. To evaluate the safety and efficacy of ABI-009 (Induction Treatment).
2. To evaluate the safety of the combination of ABI-009 + TMZ + RT (Concomitant Treatment).
3. To evaluate the safety of the combination of ABI-009 + TMZ (Adjuvant Treatment).

Exploratory Objective for Arms A and B

1. To evaluate tumor biomarkers related to mTOR pathway using pre-study archived tissue samples and if available, post-treatment tumor tissue samples.
2. To evaluate blood biomarkers and correlate to outcomes.

2.2. Endpoints

Primary Endpoint for Arms A and B

Objective ORR, according to RANO 2010 criteria

Secondary Endpoints for Arms A and B

PFS rate at 6 months, PFS rate at 12 months, median PFS, OS at 12 months, median OS, and AEs

Exploratory Endpoints for Arms A and B

- Assessment of pre-treatment archived tumor samples for the activity of mTOR pathway and correlation with activity/tolerability
- If available, tumor biomarkers post-progression
- To evaluate blood biomarkers and correlate to outcomes

3. OVERALL STUDY DESIGN

3.1. Study Design

This is a prospective, multi-cohort, non-randomized, open-label phase 2 study. **Arm A** (recurrent high-grade glioma) of the study will have 5 treatment cohorts, aiming to determine the efficacy and safety profile of ABI-009 as a single agent and in combination with TMZ, BEV, CCNU, and MRZ in patients with recurrent HGG, who have not previously received any mTOR inhibitors. Arm A of the study will use Simon's two-stage design. Up to 19 patients per cohort will be enrolled: initially 9 patients will be enrolled with a stopping rule that only if there are 2 or more positive responses will the study proceed to further enrollment of the next 10 patients. Patients will continue therapy until disease progression, unacceptable toxicity, until in the opinion of the investigator the patient is no longer benefiting from therapy, or at the discretion of the patient.

In **Cohort 1 of Arm A**, ABI-009 will be administered IV as a 30-minute infusion at 100 mg/m^2 on Days 1 and 8 of every 21-day cycle. Two dose reduction levels will be allowed: 75 mg/m^2 and 60 mg/m^2.

In **Cohort 2 of Arm A**, ABI-009 60 mg/m^2 is administered on Days 1, 8, and 15 of every 28-day cycle with oral TMZ 50 mg/m^2 daily.

In **Cohort 3 of Arm A**, ABI-009 60 mg/m^2 is administered on Days 1, 8, and 15 of every 28-day cycle with BEV 5 mg/m^2 on Days 1 and 15. Bevacizumab will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose, and 30 minutes afterward assuming tolerability).

In **Cohort 4 of Arm A,** ABI-009 60 mg/m^2 is administered on Days 1 and 8 of every 21-day cycle with oral CCNU 90 mg/m^2 on Day 1 of each odd cycle (ie, every 6 weeks).

In **Cohort 5 of Arm A**, ABI-009 60 mg/m^2 is administered on Days 1, 8, and 15 of every 28-day cycle with MRZ administered IV as a 10-minute infusion at 0.8 mg/m^2 on Days 1, 8, and 15 of every 28-day cycle.

For the combination cohorts, 2 dose reduction levels will be allowed for ABI-009: 45 mg/m^2 and 30 mg/m^2. At the discretion of the investigator, if ABI-009 is well tolerated (no DLTs, dose modifications, or dose delays) at 60 mg/m^2 in the first 3 patients in the cohort, the dose may be increased to 75 mg/m^2 for subsequent patients in the cohort. Intrapatient dose escalation is not allowed.

Arm B (ndGBM) of the study will examine the effect of the addition of ABI-009 to the standard of care treatment of TMZ+RT (Concomitant Treatment) and TMZ (Adjuvant Treatment) in patients with ndGBM who can have either non-measurable disease or enhancing tumors after surgery and have not previously received any local or systemic therapy. Up to 19 patients will be enrolled in Arm B.

Induction Treatment: ABI-009

Induction Treatment will start at least 3-8 weeks following surgical resection of ndGBM and after the surgical wound is fully healed.

- ABI-009 will be administered IV at 60 mg/m^2 as a 30-minute IV infusion every week for 4 weeks. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2.

Concomitant Treatment: ABI-009 + TMZ + RT

Concomitant Treatment will start 1 week after the completion of Induction Treatment and will last for 6 weeks.

- ABI-009 will be administered IV at 60 mg/m^2 as a 30-minute IV infusion on Days 8 and 15 of every 21-day cycle. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2.
- TMZ will be administered at 75 mg/m^2 PO daily for 6 weeks as part of routine therapy for GBM.
- Focal RT will be given daily at 30x 200 cGy, 5 days/week for a total dose of 60 Gy (or equivalent regimens as per RTOG guidelines) as part of routine therapy for GBM.

Adjuvant Treatment: ABI-009 + TMZ

Adjuvant Treatment will start 4 weeks after the completion of Concomitant Treatment (any time during the 4th week) and will last for 24 weeks.

- ABI-009 will be administered IV at 60 mg/m^2 as a 30-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle for 6 cycles. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2.
- TMZ will be administered at 150 mg/m^2 PO daily on Days 1-5 of every 28-day cycle for 6 cycles. In the absence of toxicity, TMZ may be administered at 200 mg/m^2/day starting in Cycle 2.

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

The Arm A of this study is expected to take approximately 32 months from first patient enrolled to last patient follow-up, including approximately 24 months of enrollment period, an estimated 6 months of treatment (or until unacceptable toxicity or disease progression) and an end of treatment visit within 4 weeks after last treatment.

The Arm B of this study is expected to take approximately 24 months from first patient enrolled to last patient follow-up, including approximately 16 months of enrollment period, up to 12 months of treatment (or until unacceptable toxicity or disease progression) and an end of treatment visit within 4 weeks after last treatment.

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

approximately every 12 weeks (±3 weeks), until death, withdrawal of consent, or the study closes, whichever is the earliest. This evaluation may be made by record review and/or telephone contact.

4. STUDY POPULATION

4.1. Study Population

The study population include patients with progressive HGG following prior therapy, who have not been previously treated with mTOR inhibitors; or patients with ndGBM who can have either non-measurable disease or enhancing tumors after surgery. Use of the Optune device is not allowed in Stage 1 of the study. Usage of Optune may be considered in Stage 2 of the study after review of the safety data.

Arm A (recurrent high-grade glioma): Patients at least 18 years of age with histologic evidence of high grade glioma and radiographic evidence of recurrence or disease progression (defined as either a greater than 25% increase in the largest bi-dimensional product of enhancement, a new enhancing lesion, or a significant increase in T2 FLAIR) following prior therapy. Patients must have previously failed a treatment regimen, including radiation and/or chemotherapy.

Arm B (ndGBM): Patients at least 18 years of age with histologic evidence of ndGBM. Patients must have surgery and can have either non-measurable disease or enhancing tumors after surgery detected by MRI, and have not previously received any local or systemic therapy for their GBM.

4.2. Number of Patients

Arm A: up to 95 response-evaluable patients will be enrolled (up to 19 per cohort; 5 cohorts).

Arm B: up to 19 response-evaluable patients will be enrolled.

4.3. Inclusion Criteria

Inclusion Criteria Common for Both Arms A and B

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

1. Understand and voluntarily sign and date an informed consent document prior to any study specific assessments/procedures.
2. Males and females of age ≥18 years at the time of signing the informed consent document.
3. Karnofsky Performance Status (KPS) score ≥70%.
4. No investigational agent within 4 weeks prior to the first dose of study drug.
5. All AEs resulting from prior therapy and surgery must have resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 grade ≤1 (except for laboratory parameters outlined below).
6. Adequate hematological, renal, and hepatic function (assessment performed within 14 days prior to study treatment):
    - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
    - Platelets ≥100 x 10^9/L
    - Hemoglobin ≥9 g/dL.
    - Serum creatinine ≤1.5 x upper limit of laboratory normal (ULN); Total serum bilirubin ≤1.5 x ULN, or ≤ 3 x ULN if Gilbert's disease is documented

- Aspartate Serine Transaminase (AST), Aspartate Leucine Transaminase (ALT), Alkaline Phosphatase (ALP) ≤2.5 x ULN
- Serum triglyceride <300 mg/dL; serum cholesterol <350 mg/dL

7. Patients must be without seizures for at least 14 days prior to enrollment, and patients who receive treatment with anti-epileptic drugs (AEDs) must be on stable doses for at least 14 days prior to enrollment. Patients must be off EIAEDs for at least 14 days prior to enrollment and cannot be on EIAEDs at any time during the study.
8. Steroid therapy for control of cerebral edema is allowed at the discretion of the Investigator. Patients should be on stable or decreasing dose of corticosteroids for at least 1 week prior to the first dose of study drug.
9. 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.
    - Male patients with partners of child-bearing potential must agree to take contraceptive measures for the duration of treatment and for 3 months after the last study treatment.
10. Willing and able to adhere to the study visit schedule and other protocol requirements.

Inclusion Criteria Specific for Arm A

1. All patients must have histologic evidence of high grade glioma (WHO grade 3 or grade 4) and radiographic evidence of recurrence or disease progression (defined as either a greater than 25% increase in the largest bi-dimensional product of enhancement, a new enhancing lesion, or a significant increase in T2 FLAIR). Patients must have at least 1 measurable lesion by RANO criteria (≥10 mm in 2 perpendicular diameters).
2. Patients must have previously failed a treatment regimen, including radiation and/or chemotherapy.
3. No prior treatment with mTOR inhibitors.
4. No prior treatment with TMZ for the treatment of recurrent glioma for patients entering the ABI-009 + TMZ cohort.
5. No prior treatment with BEV or any other anti-angiogenic agents, including sorafenib, sunitinib, axitinib, pazopanib, or cilengitide for the ABI-009 + BEV arm.
6. No prior treatment with CCNU for the ABI-009 + CCNU arm.
7. No prior treatment with MRZ or any other proteasome inhibitors, including bortezomib (BTZ), carfilzomib (CFZ), or ixazomib (IXZ), for patients entering the ABI-009 + MRZ cohort.
8. At least 4 weeks from surgical resection and at least 12 weeks from the end of radiotherapy prior to enrollment in this study, unless relapse is confirmed by tumor biopsy or new lesion outside of radiation field, or if there are two MRIs confirming progressive disease (PD) that are approximately 4 weeks apart.

Inclusion Criteria Specific for Arm B

1. Histologically confirmed ndGBM.
2. Patients must have had surgery and can have either non-measurable disease or a measurable post-contrast lesion after surgery detected by MRI.
3. No prior treatment with mTOR inhibitors, and no prior local or systemic therapy for GBM.

4.4. Exclusion Criteria

Exclusion Criteria Common for Both Arms A and B

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

1. Co-medication or concomitant therapy that may interfere with study results, including anti-coagulants and enzyme-Inducing anti-epileptic drugs (EIAEDs).
2. History of thrombotic or hemorrhagic stroke or myocardial infarction within 6 months.
3. Pregnant or breast feeding.
4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring IV antibiotics & psychiatric illness/social situations that would limit compliance with study requirements, or disorders associated with significant immunocompromised state.
5. Active gastrointestinal bleeding.
6. Uncontrolled hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥90 mm Hg.
7. Patients with history of intestinal perforations, fistula, hemorrhages and/or hemoptysis ≤6 months prior to first study treatment.
8. Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy.
9. Patients with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension.
10. Use of strong inhibitors and inducers of CYP3A4 (such as EIAEDs including carbamazepine, phenytoin, oxcarbazepine, topiramate, among others) 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.
11. Known other previous/current malignancy requiring treatment within ≤ 3 years except for limited disease treated with curative intent, such as in situ prostate cancer, intracapsular renal cancer, cervical carcinoma in situ, squamous or basal cell skin carcinoma, and superficial bladder carcinoma.
12. Any comorbid condition that restricts the use of study drug and confounds the ability to interpret data from the study as judged by the Investigator or Medical Monitor.
13. Known infection with human Immunodeficiency Virus (HIV), or active Hepatitis B or Hepatitis C.

5. TABLE OF EVENTS

All study assessments, including safety and response assessments, are described in Table 1, Table 2, and Table 3, and summarized by type of study visit in the following pages. All visit dates and procedures are relative to Day 1, defined as the first day of treatment administration, of each cycle.

Table 1: Schedule of Assessments for Arm A 21-day Cycles (Cohorts 1 and 4)

Assessment	Screening *	Cycle 1		Cycle 2 through Last Cycle		End of Treatment (EOT) Visit [j]	Follow-up Period [k]
		Day 1 *	Day 8	Day 1	Day 8		
Informed Consent	X						
Demographics	X						
Medical History	X						
Physical Examination	X	X		X		X	
Vital Signs, Weight, and Height [a]	X	X	X	X	X	X	
BSA Calculation [b]		X					
Prior/Concomitant Medication Evaluation [c]	X	X	X	X	X	X	
Prior/Concurrent Procedures Evaluation [c]	X	X	X	X	X	X	
KPS	X	X		X		X	
Pregnancy Test [d]	X					X	
Tumor Sample for Biomarkers [e]	X					X	
Adverse Events		Continuous starting from signing of Informed Consent until 28 days after last dose of IP					
ABI-009 Dosing (Cohorts 1 and 4) [f]		X	X	X	X		
CCNU Dosing (Cohort 4)		X		Odd cycles			
Survival Status							X
Local Laboratory Assessments							
Clinical Chemistry Panel	X	X		X		X	
CBC/Differential	X	X	X	X	X	X	
PT, PTT, INR	X						
HIV, HBV sAg, HBV cAb, HCV Ab	X						
Urinalysis	X						
Fasting Lipids [g]	X			X			
Sirolimus level [h]		X	X	X	X		
Blood collection for research		X		X		X	
Imaging and Efficacy Assessments							
MRI [i]	X			Every 6 weeks (±7 days) after C1 D1		X	

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

* Screening evaluations to be obtained ≤21 days prior to study treatment Day 1 unless specified otherwise. Day 1 evaluations can be omitted if screening evaluations are performed within 72 hours of Cycle 1 Day 1.

a. Height is only collected at baseline.

b. BSA calculated ONLY on C1/D1; to be recalculated only if the weight changes by >10% in subsequent cycles.

c. Prior: record all medications taken and procedures done ≤28 days prior to screening; Concomitant: any medications or procedures after the signing of informed consent. At the end of treatment visit, information on concomitant medications or procedures will be collected until 28 days after the last dose of IP.
d. For females of childbearing potential only. A serum β-hCG pregnancy test must be performed to assess patient eligibility at screening prior to first IP administration (negative results required for IP administration). Urine pregnancy test will be performed at EOT Visit (can be done locally) and as clinically indicated as per institutional guidelines.
e. It is mandatory for patients to provide surgical samples, if they are available and local regulations allow it. Ensure the surgical pathology report is submitted with tumor tissue sample. Archival or fresh tumor sample: formalin-fixed, paraffin-embedded (FFPE) tumor tissue (preferred) or unstained slides (20-30 slides) from biopsy will be collected (refer to Instruction Sheet for details). On-study tumor tissue collection, if available, is optional only for patients who provide additional consent, and will be collected upon disease progression and/or end of last dose of IP.
f. ABI-009 must be administered after all study specific assessments are done in a visit.
g. Fasting lipids at base line and Day 1 of every even number cycle starting with Cycle 2 (eg, C2, C4, C6, etc.).
h. On Cycle 1 Day 1, sirolimus levels are done immediately prior to the end of infusion (ie, at 30 mins post start of infusion) and analyzed by a central lab. Thereafter on subsequent treatment days in Cycles 1 and 2, only trough levels (predose) of sirolimus are done by local labs.
i. Screening MRI scans must be performed within 21 days prior to study day 1, preferably as close to the day of enrollment as possible. Tumor evaluation by MRI will be performed during screening; every 6 weeks (±7 days) until disease progression. EOT visit MRI should be performed only for those patients that discontinue treatment for a reason other than disease progression. If an initial observation of objective ORR (confirmed response [CR] or PR) is made, a confirmation scan should be done at 6 weeks after initial observation.
j. End of Treatment Visit must occur within 4 weeks after the last dose of ABI-009.
k. Follow-up for survival and initiation of anticancer therapy can be performed by telephone contact every 12 weeks (±3 weeks) or more frequently if needed, from EOT Visit. All patients that discontinue study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase for survival and anticancer therapy. This evaluation may be made by record review and/or telephone contact.

Table 2: Schedule of Assessments for Arm A 28-day Cycles (Cohorts 2, 3, and 5)

Assessment	Screening *	Cycle 1			Cycle 2 through Last Cycle			End of Treatment (EOT) Visit [k]	Follow-up Period [l]
		Day 1*	Day 8	Day 15	Day 1	Day 8	Day 15		
Informed Consent	X								
Demographics	X								
Medical History	X								
Physical Examination	X	X			X			X	
Vital Signs, Weight and Height [a]	X	X	X	X	X	X	X	X	
BSA Calculation [b]		X							
Prior/Concomitant Medication Evaluation [c]	X	X	X	X	X	X	X	X	
Prior/Concurrent Procedures Evaluation [c]	X	X	X	X	X	X	X	X	
KPS	X	X			X			X	
Pregnancy Test [d]	X							X	
Tumor Sample for Biomarkers [e]	X							X	
Adverse Events		Continuous starting from signing of Informed Consent until 28 days after last dose of IP							
ABI-009 Dosing (Cohort 2, 3 and 5) [f]		X	X	X	X	X	X		
TMZ Dosing (Cohort 2)		Daily			Daily				
BEV Dosing (Cohort 3) [f]		X		X	X		X		
MRZ Dosing (Cohort 5)		X	X	X	X	X	X		
Survival Status									X
Local Laboratory Assessments									
Clinical Chemistry Panel	X	X			X			X	
CBC/Differential	X	X	X	X	X	X	X	X	
PT, PTT, INR	X								
HIV, HBV sAg, HBV cAb, HCV Ab	X								
Urinalysis [g]	X	X		X	X		X		
Fasting Lipids [h]	X				X				
Sirolimus level [i]		X	X	X	X	X	X		
Blood collection for research		X			X			X	
Imaging and Efficacy Assessments									
MRI [j]	X	Every 8 weeks (±7 days) after C1 D1						X	

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

* Screening evaluations to be obtained ≤21 days prior to study treatment Day 1 unless specified otherwise. Day 1 evaluations can be omitted if screening evaluations are performed within 72 hours of Cycle 1 Day 1.

a. Height is only collected at baseline.
b. BSA calculated ONLY on C1D1; to be recalculated only if the weight changes by >10% in subsequent cycles.
c. Prior: record all medications taken and procedures done ≤ 28 days prior to screening; Concomitant: any medications or procedures after the signing of informed consent. At the end of treatment visit, information on concomitant medications or procedures will be collected until 28 days after the last dose of IP.
d. For females of childbearing potential only. A serum β-hCG pregnancy test must be performed to assess patient eligibility at screening prior to first IP administration (negative results required for IP administration). Urine pregnancy test will be performed at EOT Visit (can be done locally) and as clinically indicated as per institutional guidelines.
e. It is mandatory for patients to provide surgical samples, if they are available and local regulations allow it. Ensure the surgical pathology report is submitted with tumor tissue sample. Archival or fresh tumor sample: formalin-fixed, paraffin-embedded (FFPE) tumor tissue (preferred) or unstained slides (20-30 slides) from biopsy will be collected (refer to Instruction Sheet for details). On-study tumor tissue collection, if available, is optional only for patients who provide additional consent, and will be collected upon disease progression and/or end of last dose of IP.
f. ABI-009 and Bev must be administered after all study specific assessments are done in a visit.
g. For **Cohort 2** ABI-009 + TMZ and **Cohort 5** ABI-009 + MRZ, urinalysis is done at screening only. For **Cohort 3** ABI-009 + BEV, urinalysis is done at screening and with BEV treatment every 2 weeks. Monitor proteinuria by dipstick urine analysis with serial urinalyses during BEV therapy. Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. Suspend BEV for >2 grams of proteinuria/24 hours and resume when proteinuria is <2gm/24 hours. Discontinue BEV in patients with nephrotic syndrome.
h. Fasting lipids at base line and Day 1 of every even number cycle starting with Cycle 2 (eg, C2, C4, C6, etc.).
i. On Cycle 1 Day 1, sirolimus levels are done immediately prior to the end of infusion (ie, at 30 mins post start of infusion) and analyzed by a central lab. Thereafter on subsequent treatment days in Cycles 1 and 2, only trough levels (predose) of sirolimus are done by local labs.
j. Screening MRI scans must be performed within 21 days prior to study day 1, preferably as close to the day of enrollment as possible. Tumor evaluation by MRI will be performed during screening and every 8 weeks (±7 days) until disease progression. EOT visit MRI should be performed only for those patients that discontinue treatment for a reason other than disease progression. If an initial observation of objective ORR (CR or PR) is made, a confirmation scan should be done at 8 weeks after initial observation.
k. End of Treatment Visit must occur within 4 weeks after the last dose of ABI-009.
l. Follow-up for survival and initiation of anticancer therapy can be performed by telephone contact every 12 weeks (±3 weeks) or more frequently if needed, from EOT Visit. All patients that discontinue study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase for survival and anticancer therapy. This evaluation may be made by record review and/or telephone contact.

Table 3: Schedule of Assessments for Arm B

Assessment	Screening *	Induction Treatment [j]				Concomitant Treatment [j]			Adjuvant Treatment [j]			End of Treatment (EOT) Visit [k]	Follow-up Period [l]
		D1 *	D8	D15	D21	D1	D8	D15	D1	D8	D15		
Informed Consent	X												
Demographics	X												
Medical History	X												
Physical Examination	X	X				X			X			X	
Vital Signs, Weight, and Height [a]	X	X	X	X	X	X	X	X	X	X	X	X	
BSA Calculation [b]		X											
Prior/Concomitant Medication Evaluation [c]	X	X	X	X	X	X	X	X	X	X	X	X	
Prior/Concurrent Procedures Evaluation [c]	X	X	X	X	X	X	X	X	X	X	X	X	
KPS	X	X				X			X			X	
Pregnancy Test [d]	X											X	
Survival status													X
Tumor Sample for Biomarkers [e]	X											X	
Adverse Events		Continuous starting from signing of Informed Consent until 28 days after last dose of IP											
ABI-009 Dosing [f]		X	X	X	X		X	X	X	X	X		
TMZ Dosing						Daily for 6 weeks			Daily, Day 1-5 of 28-day cycle				
Radiotherapy						Daily (M-F) for 30 days							
Local Laboratory Assessments													
Clinical Chemistry Panel	X	X				X			X			X	
CBC/Differential	X	X	X	X	X	X	X	X	X	X	X	X	
PT, PTT, INR	X												
HIV, HBV sAg, HBV cAb, HCV Ab	X												
Urinalysis	X												
Fasting Lipids [g]	X					X			X				
Sirolimus level [h]		X	X	X	X	X	X	X					
Blood collection for research		X				X			X			X	
Imaging and Efficacy Assessments													
MRI [i]	X					D1			Prior to the start of and every 8 weeks during			X	

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

* Screening evaluations to be obtained ≤21 days prior to study treatment Day 1 unless specified otherwise. Day 1 evaluations can be omitted if screening evaluations are performed within 72 hours of Cycle 1 Day 1.

a. Height is only collected at baseline.

b. BSA calculated ONLY on C1/D1; to be recalculated only if the weight changes by > 10% in subsequent cycles.

c. Prior: record all medications taken and procedures done ≤ 28 days prior to screening; Concomitant: any medications or procedures after the signing of informed consent. At the end of treatment visit, information on concomitant medications or procedures will be collected until 28 days after the last dose of IP.

d. For females of childbearing potential only. A serum β-hCG pregnancy test must be performed to assess patient eligibility at screening prior to first IP administration (negative results required for IP administration). Urine pregnancy test will be performed at EOT Visit (can be done locally) and as clinically indicated as per institutional guidelines.

e. It is mandatory for patients to provide surgical samples, if they are available and local regulations allow it. Ensure the surgical pathology report is submitted with tumor tissue sample. Archival or fresh tumor sample: formalin-fixed, paraffin-embedded (FFPE) tumor tissue (preferred) or unstained slides (20-30 slides) from biopsy will be collected (refer to Instruction Sheet for details). On-study tumor tissue collection, if available, is optional only for patients who provide additional consent, and will be collected upon disease progression and/or end of last dose of IP.

f. ABI-009 dosing schedule: Induction Treatment: weekly for 4 weeks; Concomitant Treatment: 2 weeks out of 21-day cycle; Adjuvant Treatment: 3 weeks out of every 28-day cycle. ABI-009 must be administered after all study specific assessments are done in a visit. Adjuvant Treatment will start 4 weeks (any time during the 4th week) after the completion of Concomitant Treatment and will last for 24 weeks.

g. Fasting lipids at base line, Day 1 of the 1st cycle in Concomitant Treatment, and Day 1 of every odd numbered cycle in Adjuvant Treatment (C1, C3, and C5).

h. On Day 1 of the Induction Treatment, sirolimus levels are done immediately prior to the end of infusion (ie, at 30 mins post start of infusion) and analyzed by a central lab. Thereafter on subsequent treatment days on Week 2 to 4 during the Induction Treatment and on the 1st cycle (Week 1 to 3) during the Concomitant Treatment, only trough levels (predose) of sirolimus are done by local labs.

i. Screening MRI scans must be performed within 21 days prior to study day 1, preferably as close to the day of enrollment as possible. Tumor evaluation by MRI will be performed during screening, on Day 1 and 4 weeks (±7 days) after the end of Concomitant Treatment but prior to the start of Adjuvant Treatment, and then every 8 weeks (± 7 days) during Adjuvant Treatment until disease progression. EOT visit MRI should be performed only for those patients that discontinue treatment for a reason other than disease progression. If an initial observation of objective ORR (CR or PR) is made, a confirmation scan should be done at 8 weeks after initial observation.

j. Refer to treatment schema of Arm B. Induction Treatment: 4 weeks; Concomitant Treatment: 21-day cycle x2 (6 weeks); Adjuvant Treatment: 28-day cycle.

k. End of Treatment Visit must occur within 4 weeks after the last dose of ABI-009.

l. Follow-up for survival and initiation of anticancer therapy can be performed by telephone contact every 12 weeks (±3 weeks) or more frequently if needed, from EOT Visit. All patients that discontinue study drug and have not withdrawn full consent to participate in the study will continue in the follow-up phase for survival and anticancer therapy. This evaluation may be made by record review and/or telephone contact.

6. PROCEDURES

6.1. Screening Evaluations

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

The patient identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a patient is rescreened.

Before patients may be entered into the study, the Sponsor requires a copy of the site's written IRB/IEC approval of the protocol, informed consent form, and all other patient information and/or recruitment material, if applicable. A signed and dated Institutional Review Board (IRB) approved informed consent form (latest approved version) must be obtained from each patient prior to performing any study-specific procedures. All patients must personally sign and date the consent form before commencement of study-specific procedures. Adverse Events are to be collected for a patient once they have signed the informed consent. The patients' tumor samples will be tested to confirm diagnosis and for biomarker analyses after informed consent form has been signed.

Screening evaluations will be performed for all patients to determine study eligibility. These evaluations must be obtained ≤21 days prior to enrollment unless otherwise specified. Any questions regarding patient eligibility should be directed to Aadi or other Aadi-nominated representatives or designees for approval.

The following procedures are to be completed during the screening period, after signed informed consent has been obtained (within 21 days of treatment initiation), designated in the Schedule of Assessments tables.

- Demographics (date of birth, sex, race, and ethnicity)
- Medical and cancer history
- Physical examination as per standard of care
- Vital signs (e.g., blood pressure, pulse, respiration rate, temperature), height, and weight
- Prior/concomitant medication evaluation: all medications taken ≤28 days prior to screening
- Prior/concurrent procedures evaluation: all procedures done ≤28 days prior to screening
- Karnofsky performance status
- Pregnancy test (women of child-bearing potential, includes tubal ligations)
- Pre-treatment tumor sample (archived or fresh) along with pathology report (required from all patients, if they are available and local regulations allow it)

- Local Laboratory Assessments: chemistry, complete blood count (CBC), differential, coagulation, HIV, HBV sAg, HBV cAb, HCV Ab, urinalysis (a urine dipstick may be used), fasting lipids
- MRI, must be performed within 21 days prior to study day 1, preferably as close to the day of enrollment as possible

For screening and treatment visits, the laboratory assessments may evaluate different analytes (see Table 4 for analyte listing).

Table 4: 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
Glucose	Differential:			Sirolimus
BUN	-Neutrophils			
Creatinine	-Lymphocytes			
Total bilirubin	-Monocytes			
Alkaline phosphatase	-Eosinophils			
AST (SGOT)	-Basophils			
ALT (SGPT)				
Amylase				
Lipase				

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 the electronic case report form (eCRF).

6.2. Treatment Period

ABI-009 and combination agents that require infusion are to be administered after all other protocol-specified pre-dose assessments have been performed during each study visit that it is required.

6.2.1. Day 1 of Each Cycle Assessment

The following assessments will be performed on Day 1 of each cycle (±3 days), unless otherwise specified:

- Physical examination

- Vital signs (temperature, systolic and diastolic blood pressure, and pulse) and weight
- BSA calculation (Calculated ONLY on C1/D1; to be recalculated only if the weight changes by >10% in subsequent cycles
- Concomitant medication and procedures evaluation
- Karnofsky performance status
- Adverse Event assessment
- Clinical chemistry panel (including but not limited to sodium, potassium, chloride, glucose, alkaline phosphatase (ALP), AST/SGOT, ALT/SGPT, serum albumin)
- CBC/differential
- Fasting lipids:
  - Arm A: Day 1 of every even numbered cycle starting with Cycle 2;
  - Arm B: Day 1 of 1st cycle in Concomitant Treatment, and Day 1 of every odd numbered cycle in Adjuvant Treatment (C1, C3, and C5)
- Blood samples for sirolimus levels by central lab are taken on
  - Day 1 of Cycle 1 in Arm A
  - Day 1 of Induction Treatment in Arm B
  - Trough blood sirolimus level (predose) by local lab only for Cycle 2 Day 1 in Arm A, and only for Cycle 1 Day 1 during the Concomitant Treatment in Arm B
- Blood collection (for potential microRNA profiling, circulating tumor DNA profiling, and other biomarkers)

Day 1 evaluations for Cycle 1 may be omitted if screening evaluations are performed within 72 hours of Cycle 1 Day 1.

6.2.2. Subsequent Treatment Day Assessment

The following assessments will be performed on every subsequent treatment day of each cycle, unless otherwise specified:

- Vital signs and weight
- Concomitant medication and procedures evaluation
- Adverse Event assessment
- CBC/differential
- Trough whole blood sirolimus level (predose) by local lab
  - Arm A: only for the first 2 cycles
    Arm B: for Week 2 to 4 during Induction Treatment, and for the 1st cycle during Concomitant Treatment

6.2.3. Response Assessment

Tumor response will be assessed by neuro-imaging of brain or spine with MRI scan according to RANO 2010 criteria. The same modality must be used at screening and throughout the study.

MRI scans are to be performed at the following frequency:

- ≤21 days prior to C1D1 (screening), preferably as close to the day of enrollment as possible
- For Arm A, Cohorts 1 and 4: every 6 weeks after C1D1 (±7 days)

- For Arm A, Cohorts 2, 3, and 5: every 8 weeks after C1D1 (±7 days)
- For Arm B:
  - During Concomitant Treatment: Day 1 (±7 days)
  - 4 weeks after the end of Concomitant Treatment (±7 days) and prior to the start of Adjuvant Treatment
  - During Adjuvant Treatment: every 8 weeks after C1D1 (±7 days)
- End of Treatment Visit 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.

At the time of disease progression, if a biopsy is performed, a tumor sample will be collected if available. Ensure that the surgical pathology report is submitted with the tumor tissue sample.

6.3. End of Treatment Visit Assessment

The EOT Visit is a safety follow-up visit that is to be performed within 4 weeks after the last dose of ABI-009. All efforts should be made to conduct this visit. If it is not possible to conduct the EOT Visit, documentation of efforts to complete the visit should be provided.

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

- Physical examination
- Vital signs and weight
- Concomitant medication and procedures evaluation
- Karnofsky performance status
- Pregnancy test
- Adverse Event assessment
- Clinical chemistry panel
- CBC/differential
- Blood collection for potential microRNA profiling, circulating tumor DNA profiling, and other biomarkers
- MRI (performed only for those patients that discontinue treatment for a reason other than disease progression)

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

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

6.5. Correlative Studies

6.5.1. Sample Collection and Processing

Tumor Tissue

Prior to treatment: Available archival tumor tissue will be analyzed for mTOR pathway activation by immunohistochemistry. One FFPE block (preferred) or 20-30 unstained slides will be collected.

Post-treatment: If additional tumor tissue is obtained as part of clinical care, attempts will be made to collect a portion of the tissue for molecular analysis of mTOR pathway activation. Tumor tissue for profiling will only be collected from excess tissue after clinical reviewed pathology.

Blood Samples

For sirolimus at Cmax/peak level (central lab): Postdose blood sirolimus levels are taken on Day 1 of Cycle 1 in Arm A and Day 1 of Induction Treatment in Arm B immediately prior to the end of infusion (ie, at 30 mins post start of infusion).

For sirolimus trough levels (local lab): Blood samples will be taken immediately predose starting at week 2 for the first 2 cycles in Arm A; and on Week 2 to 4 during the Induction Treatment and on the 1st cycle (Week 1 to 3) during the Concomitant Treatment in Arm B.

For research correlative studies: Extra blood for research will be collected when blood is already being drawn for standard clinical care. Up to 20 mL of whole blood will be collected into anti-coagulant containing tubes on Day 1 of each cycle and at the end of treatment visit. Blood specimens will be labeled with the participant's de-identified study number and collection date and should be processed within 30 minutes of collection if possible. Details for processing specimens and storage are provided in a separate Laboratory Manual. Blood samples are collected for potential microRNA profiling, circulating tumor DNA profiling, and other biomarkers for tumor burden, changes to treatment, and correlative analyses with clinical efficacy.

6.5.2. Specimen Analysis

Analyses will be performed by the laboratory of Santosh Kesari, MD, Ph.D., in the John Wayne Cancer Institute or other provider as agreed upon with Aadi.

Molecular pathology analysis of tumor tissue may be performed as part of standard clinical care in a CLIA-certified laboratory. Results of any these clinical assays (such as EGFR, MGMT, IDH1, HER2, and other aberrations) will be collected for the study so that it may be associated with the participant's research data. Results should be obtained from analyses performed on tumor tissue collected prior to study treatment, and when available, analyses performed on tumor tissue collection post-study treatment.

Molecular phenotyping of tumor tissue may also include the following and/or other markers as scientifically appropriate: PTEN, mTOR, phosphor-mTOR, pAkt, p-S6, and p-4EBP1 by immunohistochemistry. Blood samples will be analyzed by local lab for sirolimus levels following weekly ABI-009 treatment.

Blood samples collected for future studies that may include analysis of kinase activation markers and signaling pathways, microRNA profiling, circulating tumor cells, cell free nucleic acids, and/or additional analyses performed according to new findings.

6.5.3. Specimen Banking

Patient samples collected for this study will be retained at the John Wayne Cancer Institute (Santosh Kesari Laboratory) for the analyses described above and for future cancer research.

Specimens will be stored indefinitely or until they are used up. Samples will be labeled with the patient's de-identified study number and collection date. The link between study number and medical record number will be viewed over a password secured encrypted server-client.

The study research coordinator will review the patient's medical record for demographic and clinical information pertaining to the patient's general medical history, diagnosis, and outcomes of any treatments received. Samples and data extracted from the patient's medical record will be coded with a de-identified study number, and the patient's name and identifying information will be removed. A log that links the patient's name and identifiers to the study number will be maintained in a secure database distinct from the secure database into which the patient's clinical information will be entered by study personnel.

Dissemination of specimens for research is at the discretion of the Principal Investigator. Potential research collaborators outside of JWCI who approach the Institute for clinical specimens will be required to complete an agreement (Material Transfer Agreement or recharge agreement) stating that the specimens will only be released for use in disclosed research, and any specimen left over from research will either be returned to the Institute or destroyed. Any data obtained from the use of clinical specimen will be the property of JWCI for publication and any licensing agreement will be strictly adhered to. These outside collaborators may include for-profit biotechnology corporations interested in collaborating with JWCI investigators in research diagnostic, prognostic assays and drug development.

The specimens and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the patient that there is the potential for financial gain by JWCI, the investigator or a collaborating researcher or entity.

If patients later decide they do not want their specimens collected to be used for future research, they may tell this to the Principal Investigator who will use his best efforts to stop any additional studies and to destroy the specimens. Samples stored in the Kesari lab will be destroyed; for samples that have been disseminated outside of the Kesari lab, the Principal Investigator will contact the recipient to notify them of the need to halt further research and destroy specimens.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Study Treatment Schedule

7.1.1. Arm A Treatments

Patients with recurrent HGG will enroll sequentially to Arm A from Cohort 1 through 5 in groups of 3 patients (Figure 4). After the enrollment of 3 patients in the previous cohort, enrollment in subsequent cohorts can start. Patient will be assigned to the cohort that is open at the time of enrollment and may not be enrolled in more than 1 cohort. Table 5 summarized treatment regimens per cohort. If a patient is not eligible for enrollment into the next cohort due to prior exposure to therapy, he/she is allowed to be enrolled in a subsequent cohort if the patient meets all other inclusion criteria. If the drug supply to a cohort is delayed or limited, an eligible patient can be enrolled into the next cohort.

Cohort 1: ABI-009

ABI-009 will be administered IV at 100 mg/m^2 as a 30-minute IV infusion on Days 1 and 8 of every 21-day cycle. Two dose reduction levels will be allowed: 75 mg/m^2 and 60 mg/m^2.

Cohort 2: ABI-009 + TMZ

ABI-009 will be administered IV at 60 mg/m^2 as a 30-minute infusion on Days 1, 8, and 15 of every 28-day cycle. If ABI-009 is well tolerated (no DLTs, dose modifications, or dose delays) at 60 mg/m^2 in the first 3 patients in the cohort, the dose may be increased to 75 mg/m^2 for subsequent patients in the cohort. Intrapatient dose escalation is not allowed. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2. TMZ will be administered PO at 50 mg/m^2 daily.

Cohort 3: ABI-009 + BEV

ABI-009 will be administered IV at 60 mg/m^2 as a 30-minute infusion on Days 1, 8, and 15 of every 28-day cycle. If ABI-009 is well tolerated (no DLTs, dose modifications, or dose delays) at 60 mg/m^2 in the first 3 patients in the cohort, the dose may be increased to 75 mg/m^2 for subsequent patients in the cohort. Intrapatient dose escalation is not allowed. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2.

Bevacizumab will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose and 30 minutes afterward assuming tolerability) at a fixed dose of 5 mg/kg on Days 1 and 15 of every 28-day cycle. Bevacizumab will be administered approximately 10 minutes after the end of the ABI-009.

Cohort 4: ABI-009 + CCNU

ABI-009 will be administered IV at 60 mg/m^2 as a 30-minute IV infusion on Days 1 and 8 of every 21-day cycle. If ABI-009 is well tolerated (no DLTs, dose modifications, or dose delays) at 60 mg/m^2 in the first 3 patients in the cohort, the dose may be increased to 75 mg/m^2 for subsequent patients in the cohort. Intrapatient dose escalation is not allowed. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2.

Lomustine (CCNU) will be administered PO at 90 mg/m^2 on Day 1 of each odd cycle.

Cohort 5: ABI-009 + MRZ

ABI-009 will be administered IV at 60 mg/m^2 as a 30-minute infusion on Days 1, 8, and 15 of every 28-day cycle. If ABI-009 is well tolerated at 60 mg/m^2 in the first 3 patients in the cohort, the dose may be increased to 75 mg/m^2. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2.

MRZ will be administered at 0.8 mg/m^2 as a 10-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle. MRZ will be administered approximately 10 minutes after the end of the ABI-009 infusion.

Figure 4: Overall Treatment Scheme

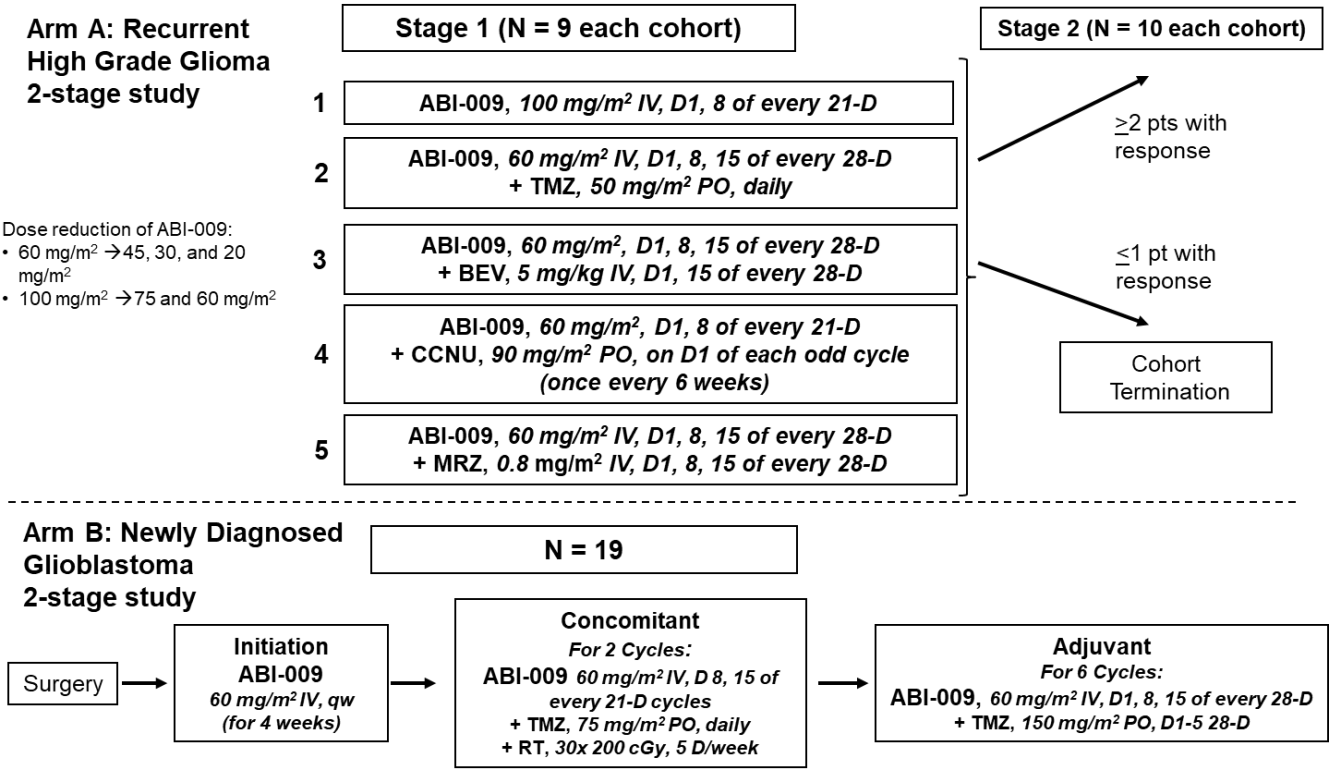


Table 5: Arm A Study Treatment Regimens Per Cohort

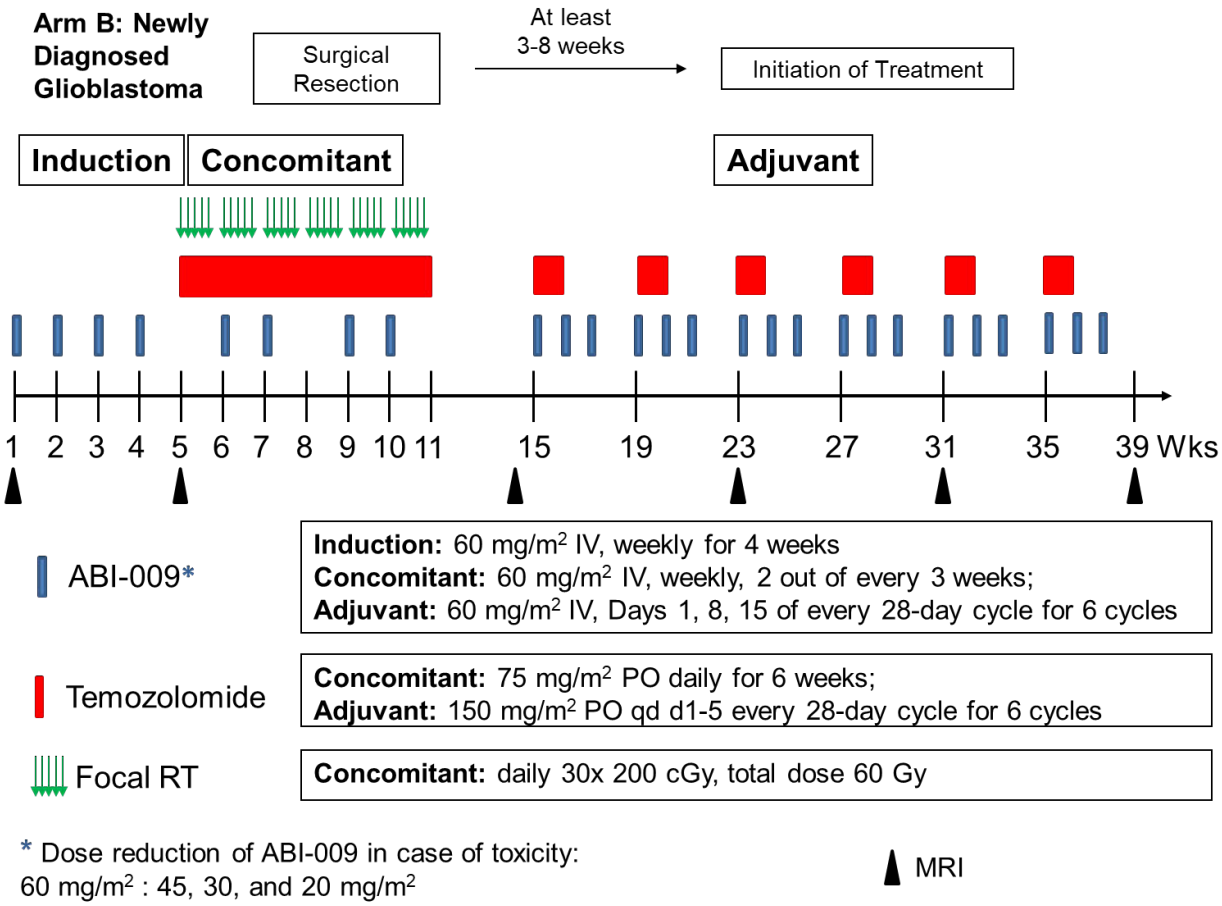
Cohort	Agent	Dose	Route	Schedule	Cycle length
Cohort 1	ABI-009	100 mg/m^2	IV	Days 1 and 8	21 days
Cohort 2	ABI-009	60 mg/m^2	IV	Days 1, 8, 15	28 days
	TMZ	50 mg/m^2	PO	daily	
Cohort 3	ABI-009	60 mg/m^2	IV	Days 1, 8, 15	28 days
	BEV	5 mg/kg	IV	Days 1 and 15	
Cohort 4	ABI-009	60 mg/m^2	IV	Days 1 and 8	21 days
	CCNU	90 mg/m^2	PO	Day 1 odd cycles	
Cohort 5	ABI-009	60 mg/m^2	IV	Days 1, 8, 15	28 days
	MRZ	0.8 mg/m^2	IV	Days 1, 8, 15	

For Arm A, patients will continue to receive 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.

7.1.2. Arm B Treatments

The treatment scheme for Arm B is presented in Figure 5.

Figure 5: Treatment Scheme for Arm B (Newly Diagnosed Glioblastoma)



Induction Treatment: ABI-009

Induction Treatment will start at least 3-8 weeks following surgical resection of ndGBM and after the surgical wound is fully healed.

- ABI-009 will be administered IV at 60 mg/m^2 as a 30-minute IV infusion every week for 4 weeks. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2.

Concomitant Treatment: ABI-009 + TMZ + RT

Concomitant Treatment will start 1 week after the completion of Induction Treatment and will last for 6 weeks.

- ABI-009 will be administered IV at 60 mg/m^2 as a 30-minute IV infusion on Days 8 and 15 of every 21-day cycle. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2.
- TMZ will be administered at 75 mg/m^2 PO daily for 6 weeks as part of routine therapy for GBM.
- Focal RT will be given daily at 30 x 200 cGy, 5 days/week for a total dose of 60 Gy (or equivalent regimens as per RTOG guidelines) as part of routine therapy for GBM.

Adjuvant Treatment: ABI-009 + TMZ

Adjuvant Treatment will start 4 weeks after the completion of Concomitant Treatment (any time during the 4th week) and will last for 24 weeks.

- ABI-009 will be administered IV at 60 mg/m^2 as a 30-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle for 6 cycles. Three dose reduction levels will be allowed: 45, 30, and 20 mg/m^2.
- TMZ will be administered at 150 mg/m^2 PO daily on Days 1-5 of every 28-day cycle for 6 cycles. In the absence of toxicity, TMZ may be administered at 200 mg/m^2/day starting in Cycle 2.

Enrollment to Arm B will be stopped, and the overall safety of adding ABI-009 to upfront standard of care (ie, surgery, RT, and temozolomide) will be re-assessed according to the following rules:

- If ≥2 of the first 6 patients are unable to start RT after induction treatment with ABI-009 at 60 mg/m^2, the dose and/or dosing frequency of ABI-009 will be reduced.
- If after dose and dosing frequency adjustment of the induction treatment with ABI-009, ≥2 of the next 6 patients in the study are unable to start RT after induction treatment with ABI-009, then induction treatment with ABI-009 will be eliminated, and subsequent patients in Arm B will be allowed to receive only concomitant and adjuvant treatment with ABI-009 as outlined in Figure 5.
- If ≥2 of the first 6 patients are unable to complete ≥75% of the planned RT due to toxicity related to ABI-009, the dose of ABI-009 will be reduced.
- If after dose reduction, ≥2 of the next 6 patients in the study are unable to complete ≥75% of the planned RT due to toxicity related to ABI-009, enrollment to Arm B will be stopped and the overall safety of adding ABI-009 to upfront standard of care will be re-assessed.

7.2. Definition of Dose-limiting Toxicity (DLT)

Toxicity grading is based on NCI-CTCAE v5.0, available at the website http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

A DLT is defined as 1 or more of the following that occurs within the first 28 days of treatment and is considered possibly, probably or definitely related to ABI-009, or the combination of ABI-009 with TMZ, BEV, or CCNU administration:

- Grade 4 neutropenia
- Grade 3 or higher febrile neutropenia;

- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding;
- Grade 3 non-hematologic toxicity (with exception of sub-optimally managed diarrhea, nausea and vomiting) that persists for >7 days*
- Grade 3 nausea, diarrhea, and vomiting lasting ≥5 days
- Grade 3 creatinine increase that persists ≥5 days* despite adherence to hydration guidelines;
- Any ≥grade 2 non-hematological toxicity requiring a dose delay of >2 weeks despite appropriate symptomatic therapy.

* verified by repeat assessment

Temozolomide dose reduction or interruption as described below will not necessarily constitute a DLT with respect to ABI-009 unless the AE, in particular myelotoxicity, is above and beyond that expected for TMZ with or without radiotherapy. The same rule applies for BEV and CCNU.

7.3. Dosing Delays and Dose Modifications Due to Toxicity

7.3.1. ABI-009 Schedule Adjustments for Toxicity

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 on Day 1 of each cycle, patients must meet the following hematological requirements:

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

Patients who experience a DLT at least possibly attributed to ABI-009 may continue treatment at the next lower dose level until disease progression or unacceptable toxicity. Once the dose has been reduced for a patient, it may not be escalated. Provisions are not made for dose levels below Dose Level -2; if Dose Level -2 is not acceptable for a particular patient, ABI-009 will be permanently discontinued for the patient.

Approval from the Medical Monitor is required to restart study treatment after interruption of a duration of one cycle (ie, 28 days for a 28-day cycle, 21 days for a 21-day cycle). Patients with ABI-009 discontinued due to dose limiting toxicities will be removed from the study (unless approved by Medical Monitor) and continue with safety follow-up. In combination cohorts, if ABI-009 is discontinued, the patient may continue to receive the combination agent as part of routine medical management but will be removed from the treatment portion of this study.

7.3.2. Dose Modification Guidelines for ABI-009

Doses will be reduced for hematologic and other toxicities. Dose modifications are permitted according to the criteria below. Dose reductions will occur sequentially, there should be no direct reduction by two dose levels. For planned ABI-009 dose of 100 mg/m^2, the reduced dose levels allowed are 75 mg/m^2 and 60 mg/m^2. For planned ABI-009 dose of 60 mg/m^2, the reduced dose levels allowed are 45, 30, and 20 mg/m^2. Dose adjustments are to be made according to the system showing the greatest degree of toxicity.

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

If the toxicity does not resolve to at least grade 1 in less than 14 days, withdrawal from treatment with the ABI-009 is recommended. However, if the investigator and Aadi Medical Monitor agree that further treatment would benefit the patient, treatment can continue with at least one dose level dose reduction, per Table 6.

Table 6: Dose Level Reduction Guidelines for ABI-009

Dose level	**ABI-009 Dose**	
0	Initial Dose: 100 mg/m^2	Initial Dose: 60 mg/m^2
-1 (first dose reduction)	75 mg/m^2	45 mg/m^2
-2 (second dose reduction)	60 mg/m^2	30 mg/m^2
-3 (third dose reduction)	NA	20 mg/m^2

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

ABI-009 dose modification guidelines are outlined in Table 7 for clinically significant toxicities that are deemed related. Adverse events considered for dose reduction should not include the events assessed by the investigator as exclusively related to underlying disease or other medical condition or concomitant treatment.

Table 7: Dose Modification Algorithms for Adverse Events Possibly Related to ABI-009

System/Organ	**Adverse Event**	**CTCAE Grade v5.0**	**Dose modification Algorithm**
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.
		Grade ≥3	Hold ABI-009 until resolution to Grade 1 or baseline and restart at the same dose for 1st occurrence for subsequent occurrences, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
Skin and Subcutaneous Tissue Disorders	Skin rash	Grade 2	Tolerable: Continue ABI 009 at full dose, monitor as clinically indicated
			Intolerable: Hold ABI-009 until resolution to Grade 1 or baseline and restart at the same dose for 1st occurrence; for subsequent occurrences, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.

System/Organ	Adverse Event	CTCAE Grade v5.0	Dose modification Algorithm
		Grade ≥3	Hold ABI-009 until resolution to Grade 1 or baseline; for subsequent events, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
Gastrointestinal Disorders	Diarrhea despite optimal medication	Grade 2	Hold ABI-009 until resolution to Grade 1 or baseline and restart at the same dose for 1st occurrences; for 2nd and subsequent events, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
		Grade ≥3	Hold ABI-009 until resolution to Grade 1 or baseline; for subsequent events, drug will be restarted at a reduced dose; provide supportive care as clinically indicated.
Metabolic disorders	Hyperlipemia (cholesterol, triglycerides)	Grade 3	If this is persistent for 2 months, reduce by 1 dose level at start of next cycle
		Grade 4	If this is persistent for 1 month, reduce by 1 dose level at start of next cycle
	Hyperglycemia	Grades 1 and 2	Start at home 2x/day glucose monitoring; initiate medical management
		Grade 3	Initiate medical management; If recurrent post ABI-009 despite adequate medical management, reduce by 1 dose level
		Grade 4	Initiate medical management, hold ABI-009 until grade 2 or less, restart 1 dose level lower
Hematologic toxicity	Thrombocytopenia, Neutropenia, Anemia	Grade 2	ABI-009 can be administered if meeting the following hematological requirements: ANC >1.5 x 10^9/L, platelets >100 x 10^9/L and hemoglobin ≥9 g/dL
		Grade ≥3	Hold ABI-009 immediately for the remainder of that cycle. Repeat blood collection within 3 days. ABI-009 can resume once meeting following requirements: ANC >1.5 x 10^9/L, platelet count >100 x 10^9/L and hemoglobin ≥9 g/dL. For 2nd and subsequent events, drug will be restarted at a reduced dose; G-CSF may be given as deemed indicated.
Respiratory events	Pneumonitis, bronchiolitis obliterans, and/or organizing pneumonia	Grade 2	Hold ABI-009 immediately for up to 3 weeks until resolved to ≤ grade 1, then reduce by 1 dose level. If it is still a Grade 2 after 3 weeks, discontinue treatment. If > Grade 2 recurs after resuming ABI-009 at a reduced dose level, discontinue treatment. For noninfectious pneumonitis, if cough is troublesome, prescribe corticosteroids.
		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

System/Organ	Adverse Event	CTCAE Grade v5.0	Dose modification Algorithm
			withdrawn from the study if they fail to recover to ≤ grade 1 within 3 weeks. For grade 4 noninfectious pneumonitis, discontinue ABI-009.

[a] 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.

7.3.3. Temozolomide Arm A Schedule Adjustment for Toxicity

Prior to TMZ administration on Day 1 of each cycle, or following TMZ interruption, patients must meet the following hematological requirements:

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

The treatment will be on hold up to 14 days until the patient has fulfilled these criteria. Temozolomide is administered at 50 mg/m^2 daily, with one dose reduction to 37.5 mg/m^2 allowed for toxicity (Table 8).

Table 8: Dose Level Reduction Guidelines for TMZ

Dose level	TMZ Dose
-1 (dose reduction)	37.5 mg/m^2
0	Initial Dose: 50 mg/m^2

Temozolomide dose modification guidelines are outlined in Table 9 for clinically significant toxicities that are deemed related. If TMZ is discontinued, patients may continue to receive ABI-009 and remain on the treatment portion of this study.

Table 9: Dose Modifications for Adverse Events Possibly Related to TMZ (Arm A)

Toxicity	Reduce TMZ by 1 Dose Level	Discontinue TMZ
Absolute Neutrophil Count	< 1.0 x 10^9/L	If dose reduction < 37.5 mg/m^2 required; or if same Grade 3 nonhematological toxicity (except alopecia, nausea, vomiting) recurs after dose reduction
Platelet Count	≥ 10 x 10^9/L and < 100 x 10^9/L	
Nonhematological Toxicity (except alopecia, nausea, vomiting)	Grade 3	Grade 4

7.3.4. Temozolomide Arm B Schedule Adjustment for Toxicity

If treatment cannot be administered on the planned visit date, TMZ may be administered ±3 days from the scheduled date. Prior to TMZ administration on Day 1 of each cycle, or following TMZ interruption, patients must meet the following hematological requirements:

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

The following TMZ modifications are provided as guidelines that may be used as appropriate or modified as per local institutional practice. During concomitant radiotherapy, TMZ is administered at 75 mg/m^2 PO daily. TMZ dosing should be interrupted or discontinued during concomitant phase according to the hematological and nonhematological toxicity criteria as noted in Table 10.

Table 10: Temozolomide Dose Modifications During Concomitant Treatment with Radiotherapy (Arm B)

Toxicity	TMZ Interruption	TMZ Discontinuation
Absolute Neutrophil Count	≥0.5 x 10^9/L and <1.5 x 10^9/L	<0.5 x 10^9/L
Platelet Count	≥10 x 10^9/L and <100 x 10^9/L	<10 x 10^9/L
Nonhematological Toxicity (except for alopecia, nausea, vomiting)	Grade 2	Grade 3 or 4

During adjuvant treatment, TMZ is administered at 150 mg/m^2/day on Day 1-5 of every 28-day cycle for 6 cycles. In the absence of toxicity, TMZ may be administered at 200 mg/m^2/day starting in Cycle 2. Dose reduction or discontinuation during Adjuvant Treatment should be applied according to Table 11 and Table 12. If TMZ is discontinued, patients may continue to receive ABI-009 and remain on the treatment portion of this study.

Table 11: Temozolomide Dose Levels for Adjuvant Treatment (Arm B)

Dose level	TMZ Dose (mg/m^2/day)	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose for Cycles 2+ in absence of toxicity

Table 12: Temozolomide Dose Modifications During Adjuvant Treatment (Arm B)

Toxicity	Reduce TMZ by 1 Dose Level	Discontinue TMZ
Absolute Neutrophil Count	<1.0 x 10^9/L	If dose reduction <100 mg/m^2 required; or if same grade 3 nonhematological toxicity (except alopecia, nausea, vomiting) recurs after dose reduction
Platelet Count	≥10 x 10^9/L and <100 x 10^9/L	
Nonhematological Toxicity (except alopecia, nausea, vomiting)	Grade 3	Grade 4

7.3.5. MRZ Schedule Adjustment for Toxicity

If treatment cannot be administered on the planned visit date, MZB may be administered +/- 3 days from the scheduled date. Prior to MRZ administration on Day 1 of each cycle, patients must meet the following hematological requirements:

- Creatinine ≤ 1.5 x ULN
- Hemoglobin ≥ 8 g/dL
- Platelet count ≥ 75 x 10^9/L

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

Patients who experience a DLT at least possibly attributed to MRZ may continue treatment at the next lower dose level (see Table 15 below) until disease progression or unacceptable toxicity. Once the dose has been reduced for a patient, it may not be escalated. Provisions are not made for dose levels below Dose Level -2; if Dose Level -2 is not acceptable for a particular patient, MRZ will be permanently discontinued for the patient.

Day 1 Dose Missed

If the dose held or missed was to be given on Day 1 of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the patient (i.e., D1-D8-D15-Rest, X-D1-D8-D15-Rest, etc.).

Day 8 Dose Missed

Cycle continues per protocol, with one dose not given (i.e., D1-D8-D15-Rest, D1-X-D15-R, D1-D8-D15-Rest, etc.). Day 15 is administered as per cycle calendar if counts and chemistries permit.

Day 15 Dose Missed

That week becomes the week of rest. Next dose (if counts and chemistries permit) becomes Day 1 of a new cycle (i.e., D1-D8-D15-Rest, D1-D8-X, D1-D8-D15-Rest, etc.).

Approval from the Medical Monitor is required to restart study treatment after interruption of a duration of one cycle.

7.3.6. Dose Reduction Guidelines for MRZ

In the event of clinically significant AE in any part of the study, treatment may be withheld, and supportive therapy administered as clinically indicated. If the toxicity or event is not grade 3/4 and resolves to baseline or grade 1 in less than or equal to 14 days of stopping therapy, then treatment may be restarted. Dose reduction (Table 13) of MRZ should be considered as clinically indicated.

Table 13: Dose Level Reduction Guidelines for MRZ

Dose level	MRZ Dose
0	Initial Dose: 0.8 mg/m^2
-1 (first dose reduction)	0.7 mg/m^2
-2 (second dose reduction)	0.55 mg/m^2

MRZ dose modification guidelines are outlined in Table 14 for clinically significant toxicities that are deemed related. If MRZ is discontinued, patients may continue to receive ABI-009 and remain on the treatment portion of this study.

Table 14: MRZ Dose Modification

Toxicity	MRZ Dose Modifications & Actions
Grade 2 Central Nervous System AEs or moderately severe Hallucinations* related to MRZ	Consider holding MRZ until toxicity resolves. When toxicity resolves, consider reinitiating with reduced dose of MRZ to be determined in discussion with the Medical Monitor, but usually to the level of the next lower dose cohort.
Grade 3 Central Nervous System AEs related to MRZ Other Grade 3 AEs related to MRZ Grade 4 Hematologic or Severe Hallucinations* related to MRZ	Hold MRZ until toxicity resolves. When toxicity resolves, may reinitiate with reduced dose of MRZ to be determined in discussion with the Medical Monitor, but usually to the level of the next lower dose cohort.
Grade 4 Nonhematological or Extremely Severe Hallucinations* related to MRZ	Generally discontinue all study treatment. Exceptions may be discussed with the Medical Monitor for approval if it is determined by the investigator that re-initiation at a lower dose may be appropriate based on clinical judgment.
AE related to MRZ that requires a dose delay > 14 days	Consider reinitiating with reduced dose of MRZ to be determined in discussion with the Medical Monitor, but usually to the level of the next lower dose cohort. Prior to initiation of subsequent cycles, reassessment of safety laboratory tests is required for liver functions tests (LFTs), serum creatinine, and complete blood count.

*Hallucinations are defined as follows:

Very mild: While resting or going to sleep, sees visions, smells odors or hears voices, sounds, or whispers in the absence of external stimulation, but no impairment in functioning.

Mild: While in a clear state of consciousness, hears a voice calling the individual's name, experiences non-verbal auditory hallucinations (e.g., sounds or whispers), formless visual hallucinations or has sensory experiences in the presence of a modality relevant stimulus (e.g., visual illusions) infrequently (e.g., 1-2 times per week) and with no functional impairment.

Moderate: Occasional verbal, visual, gustatory, olfactory or tactile hallucinations with no functional impairment OR non-verbal auditory hallucinations/visual illusions more than infrequently or with impairment.

Moderately Severe: Experiences daily hallucinations OR some areas of functioning are disrupted by hallucinations.

7.3.7. Bevacizumab Schedule Adjustment for Toxicity

If treatment cannot be administered on the planned visit date, BEV may be administered ±3 days from the scheduled date. Dose reduction or discontinuation of BEV should be applied according

to Table 15 and Table 16. If BEV is discontinued, patients may continue to receive ABI-009 and remain on the treatment portion of this study.

Table 15: Dose Level Guidelines for BEV

Dose level	BEV Dose (mg)	Schedule (28-day cycle)
-1	7.5	Day 1
0	5	Days 1 and 15

Table 16: Dose Modifications for Adverse Events Possibly Related to BEV

Adverse Event	Severity	Dose modification Algorithm
Gastrointestinal perforation	Any	Discontinue.
Fistulae	• Tracheoesophageal fistula, any grade • Fistula Grade 4 • Fistula formation involving any internal organ	Discontinue.
Wound healing complications	• Wound healing complications requiring medical intervention • Necrotizing fasciitis	Discontinue.
Hemorrhage	• Grade 3 or 4	Discontinue.
	• Recent history of hemoptysis of 1/2 teaspoon (2.5 mL) or more	Withhold if not controlled with medical management; resume at modified dose once controlled.
Hypertension	• Hypertensive crisis • Hypertensive encephalopathy	Discontinue.
	• Hypertension, severe	Withhold if not controlled with medical management; resume at modified dose once controlled.
Posterior reversible encephalopathy syndrome (PRES)	• Any	Discontinue.
Renal toxicity and proteinuria	• Nephrotic syndrome	Discontinue.
	• Proteinuria ≥2 g/24 hours in absence of nephrotic syndrome	Withhold until proteinuria less than 2 g/24 hours.
Infusion Reaction	• Severe infusion reaction	Discontinue.
	• Clinically significant	Interrupt infusion; resume at a decrease rate of infusion after symptoms resolve.
	• Mild, clinical insignificant	Decrease infusion rate.
Congestive heart failure	• Any	Discontinue.

7.3.8. Lomustine (CCNU) Schedule Adjustment for Toxicity

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

- Leukocytes ≥4.0 x 10^3/uL
- Platelet count ≥100 x 10^9/L

Table 17: Dose Level Guidelines for CCNU

Dose level	CCNU Dose (mg/m^2)	Schedule (21-day cycle)
0	90	Days 1 of each odd cycle (once every 6 weeks)

The treatment may be held until hematological requirements are met. If CCNU is not tolerated at 90 mg/m^2, there will be no further dose reduction and CCNU will be discontinued. If CCNU is discontinued, patients may continue to receive ABI-009 and remain on the treatment portion of this study.

7.3.9. 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.

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 ULN
- AND increased AST or ALT from the relevant baseline value as specified below:

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

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

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.

Criteria for Rechallenge with ABI-009 After Potential Hepatotoxicity

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

If signs or symptoms recur with rechallenge, then ABI-009 should be permanently discontinued. Patients who clearly meet the criteria for permanent discontinuation (as described in Section 7.3.1) should never be rechallenged.

7.3.10. Overdose

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

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

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

8. STUDY DRUG MANAGEMENT

8.1. Description of Study Drugs

8.1.1. ABI-009

8.1.1.1. Supply and Storage

ABI-009 is an investigational product (IP) that will be supplied by the Aadi Bioscience 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 designated study monitor for verification of proper study drug storage.

8.1.1.2. 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 and administered to the patient in the study site (see Pharmacy Manual). The Investigator will calculate the body surface area (BSA) of the patient in order to determine the total amount of ABI-009 to be administered.

8.1.1.3. Receipt and Return

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

8.1.2. Temozolomide

8.1.2.1. Supply, Storage, and Use

Temozolomide will be obtained at the local hospital pharmacy by Investigator/physician prescription for standard of care therapy and used according to TMZ Product label and standard institutional practices. Aadi Bioscience will not be sourcing or providing temozolomide. Temozolomide is supplied as capsules for oral use in child-resistant sachets and should be stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F). Patients will be instructed to take their dose as scheduled.

8.1.3. Marizomib

8.1.3.1. Supply and Storage

Marizomib is an investigational product that will be provided by Celgene in drug kits contain 1 single-use vial of lyophilized product (2 mg MRZ) along with 1 sing-use vial of 20 mL diluent. Each

vial will be labeled according to country-specific regulatory requirements for labeling of IPs. Vials should be stored **upright** in a refrigerator (2°-8°C; 36°-46°F). Reconstituted MRZ may be stored for up to 3 hours at 2-8°C (36°- 46°F), followed by 2 hours at room temperature (<25°C).

8.1.3.2. Preparation and Administration

MRZ will be reconstituted by appropriate study personnel and administered to the patient in the study site (see Pharmacy Manual). The Investigator will calculate the body surface area (BSA) of the patient in order to determine the total amount of MRZ to be administered.

8.1.3.3. Hydration

To mitigate the theoretical possibility of renal dysfunction, patients will receive approximately 250 ml normal saline administered over approximately 30 minutes before the MRZ infusion. After the MRZ infusion has been completed, additional fluid may be given at the investigator's discretion.

8.1.3.4. Receipt and Return

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

8.1.4. Bevacizumab

8.1.4.1. Supply and Storage

Bevacizumab will be obtained at the local hospital pharmacy by Investigator/physician prescription for standard of care therapy and used according to the bevacizumab Product label and standard institutional practices. Aadi Bioscience will not be sourcing or providing bevacizumab. Bevacizumab Injection is a clear to slightly opalescent, colorless to pale brown, sterile solution for intravenous infusion supplied as single-dose vials. Vial must be stored refrigerated at 2-8°C (36-46°F) and protect from light. Vials must not be frozen or shaken. Bevacizumab solution can be stored at 2-8°C (36-46°F) for up to 8 hours.

8.1.4.2. Preparation and Administration

Bevacizumab will be prepared and administered according to standard institutional practice. In general, the necessary amount of BEV is withdrawn from vials and diluted in a total volume of 100 mL of 0.9% Sodium Chloride Injection (never administered or mixed with dextrose solution). The first infusion is administered over 90 minutes. The second infusion can be administered over 60 minutes if the first infusion is tolerated. Subsequent infusions can be over 30 minutes of second infusion over 60 minutes is tolerated.

8.1.5. Lomustine (CCNU)

8.1.5.1. Supply, Storage, and Use

Lomustine will be obtained at the local hospital pharmacy by Investigator/physician prescription for standard of care therapy and used according to CCNU Product label and standard institutional practices. Aadi Bioscience will not be sourcing or providing lomustine. Lomustine is supplied as capsules in bottles for oral use and should be stored at 25°C (77°F) with excursions permitted to

15-30°C (59-86°F). Temperatures over 40°C (104°F) must be avoided. Patients will be instructed to take their dose as scheduled.

8.2. Drug Accountability, Disposal, and Compliance

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

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

8.2.1. ABI-009

Upon receipt of ABI-009 supplies, the Investigator or designee will conduct an inventory and sign both copies of the study drug receipt and forward one copy to the address indicated on the form. One copy of the receipt and the packing slip must be retained in the Investigator's regulatory file records.

Only completely unused ABI-009 vials should be retained by the site until a representative from Aadi or Aadi-designee 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.

A representative from Aadi or his/her designee will inspect the ABI-009 drug inventory, Drug Accountability Record form(s), and will arrange for the disposition of any remaining unused study drug. No study drug may be returned to Aadi without the representative from Aadi or other Aadi-designated personnel first inspecting the study drug inventory and accountability documentation.

8.2.2. Temozolomide

Temozolomide is managed as a prescribed medication and is administered according to standard institutional practices.

8.2.3. Marizomib

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

Only completely unused MRZ vials should be retained by the site until a representative from Aadi or Aadi-designee 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.

8.2.4. Bevacizumab

Bevacizumab is managed as a prescribed medication and is administered according to standard institutional practices.

8.2.5. Lomustine (CCNU)

Lomustine is managed as a prescribed medication and is administered according to standard institutional practices.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

All concomitant treatments, including blood and blood products, must be reported on the eCRF. Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. If a patient requires treatment with any of those listed in Section 9.2, the patients will be removed from study treatment.

Concomitant therapies are to be collected from enrollment through the EOT Visit. Therapy name including indication, dose, frequency, route, start date and stop date will be recorded on each patient's eCRF.

9.1. Permitted Medications and Procedures

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

Patients should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheas, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. WBC growth factors may be administered at the discretion of the investigator, consistent with institutional guidelines. MRZ has caused some hallucinations, therefore both the therapeutic and prophylactic use of anti-psychotics is allowed at the discretion of the investigator as necessary.

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

9.2. Prohibited Medications and Procedures

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

The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on treatment in this study.
- Antiretroviral drugs (patients with known HIV are ineligible for study participation).
- Herbal remedies (e.g., 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 affect sirolimus metabolism and/or increase toxicities, and thus may only be used under special circumstances (e.g., as a single use for a procedure) while treatment with study drug is interrupted. The list may be modified based on emerging data, but may include:

Strong CYP3A4 Inhibitor		Strong CYP3A4 Inducer		
clarithromycin indinavir itraconazole ketoconazole nefazodone	ritonavir saquinavir suboxone telithromycin	barbiturates carbamazepine efavirenz glucocorticoids modafinil	nevirapine oxcarbazepine phenobarbital phenytoin pioglitazone	rifabutin rifabutin St. John's Wort troglitazone

- Use of strong inhibitors and inducers of CYP3A4 within the 14 days prior to receiving the first dose of ABI-009 is prohibited as inhibitors and inducers of CYP3A4 may affect ABI-009 metabolism and/or increase toxicities.
- 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.

10. STATISTICAL CONSIDERATIONS

10.1. Study Populations

The Safety population (Full Analysis Dataset) will consist of all patients who have received at least one dose of ABI-009. The efficacy-evaluable population (Efficacy Analysis Dataset) will consist of all patients who received at least two cycles of ABI-009 and underwent a post-treatment disease assessment or who received at least one dose of ABI-009 and withdrew from the study prior to completion of 2 full cycles due to progressive disease, death or drug-related toxicity. A patient who is removed from the study because of disease progression, death or drug-related toxicity prior to the end of cycle 2 will be included in the efficacy-evaluable patient population.

The primary efficacy analysis will be performed in the Efficacy Analysis Dataset and the Full Analysis Dataset. Safety analyses will be performed in the Full Analysis Dataset.

10.2. Primary Endpoint

The primary endpoint is ORR by independent radiologic review and is defined as the proportion of patients who achieve a confirmed PR or CR per RANO 2010 criteria.

For Arm A, Cohort 2, 3, and 5, tumor response, including CR, PR, SD, or PD, will be assessed with MRI imaging every 8 weeks.

For Arm A, Cohorts 1 and 4, tumor response will be assessed with MRI imaging every 6 weeks.

For Arm B, tumor response will be assessed with MRI imaging on Day 1 and at the end of Week 6 during Concomitant Treatment, and then every 8 weeks (± 7 days) during Adjuvant Treatment until disease progression.

10.2.1. Power and Sample Size for Primary Endpoint

Simon's two-stage design (Simon, 1989) will be used for Arm A of this study. The null hypothesis that the true response rate is 15% will be tested against a one-sided alternative. In the first stage, 9 patients will be accrued. If there are 1 or fewer responses in these 9 patients, the study will be stopped. Otherwise, 10 additional patients will be accrued for a total of 19. The null hypothesis will be rejected if 6 or more responses are observed in 19 patients. This design yields a type I error rate of 0.0497 and power of 0.8132 when the true response rate is 40%. Arm B of the study will enroll 19 patients as an exploratory analysis to obtain a signal of efficacy.

10.3. Secondary Endpoints

Demographic and baseline measurement variables will be summarized. Compliance to the study schedule will be evaluated and any deviation from the schedule of treatment will be recorded. The percentage of patients failing to complete the study or discontinuing prematurely (as well as the times and reasons for discontinuation) will be displayed, along with the time and reason for discontinuation.

10.3.1. Secondary Efficacy Assessments

The analysis of PFS rate at 6 months, PFS rate at 12 months, median PFS, and median OS will be conducted on the Efficacy Analysis Dataset. A sensitivity analysis will also be conducted using the

Full Analysis Dataset. Progression-free survival at 6 months, PFS at 12 months, median PFS, OS at 12 months, and OS for patients will be summarized using KM methods.

Progression-free survival is defined as the time from the first dose date to the first observation of a disease progression or death due to any cause. If a patient has not progressed or died by the data cutoff date, the PFS time will be censored at the time of the last evaluable tumor assessment.

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

Secondary efficacy endpoints will consist of the following for both Arm A and Arm B:

- PFS at 6 months
- PFS at 12 months
- PFS
- OS at 12 months
- OS

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

10.4. Safety Assessments

All patients will be evaluated for safety analysis if they receive at least one dose of ABI-009. 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. Adverse events will be grouped by their system organ class and preferred term. Summary tables will include the number and percentage of patients with AEs, SAEs, fatal AEs and other AEs of interest.

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

10.5. Exploratory Endpoints

Exploratory studies will be performed in consenting patients to gain a more in-depth understanding of molecular profiling and mTOR pathway status in this patient population. Assessment of pre-treatment archived tumor samples and sirolimus levels following weekly ABI-009 treatment will be performed for molecular information, including but not limited to the activity of mTOR pathway, and correlation with activity/tolerability to ABI-009 treatment. These exploratory studies are not designed to meet statistical significance and data from these studies will be summarized using descriptive statistics, including number of patients (N), mean, standard deviation (SD), median, and coefficient of variation (CV). As necessary, more definitive statistical

methods can be applied to evaluate apparent trends. Subgroup analyses will be performed as appropriate.

A logistic regression model will be used to identify biomarkers for responders and non-responders. Cox models will be used to explore the association between these molecular phenotypes and duration of PFS and overall survival. Multiple adjustments will not be performed for this analysis and, therefore, these studies are considered exploratory.

Tissue sampling at additional time points is not required, but if additional tissue is obtained as part of clinical care during the treatment portion of the study or following progression and it is possible to obtain molecular information on that tissue, the information will be collected for the study. Possible effects of ABI-009 treatment on these markers (change from baseline) will be assessed if post-treatment tissue specimen(s) are available.

Blood samples are collected for potential microRNA profiling, circulating tumor DNA profiling, and other biomarkers for tumor burden, changes to treatment, and correlative analyses with clinical efficacy.

11. MONITORING, RECORDING AND REPORTING OF ADVERSE EVENTS

11.1. Adverse Events

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

Abuse, withdrawal, sensitivity or toxicity to the IP should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the appropriate CRF, see Section 7.3.10 for the definition of overdose. Any sequela of an accidental or intentional overdose of the IP should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

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

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

The investigator's clinical judgment is used to determine whether a patient is to be removed from treatment due to an AE. The investigator is responsible for ensuring that all AEs observed by the investigator or reported by the patient that occur after the first dose of IP through the EOT Visit are reported using the applicable eCRF (eg, AE Summary CRF).

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]
- Seriousness
- Assessment of relatedness to the study agents
- Assessment of relatedness to protocol-required procedures
- Action taken

The AE toxicity grading scale used will be the NCI-CTCAE v5.0.

11.2. Prior Experience

Expected events are those that have been previously identified as resulting from administration of the agent. An AE is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in this protocol, the current Investigator's Brochure, or the Product Label.

11.3. 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 (e.g., 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 (e.g., laboratory abnormality reported as grade 4 without manifestation of life threatening status), it will be left to the investigator's judgment to also report these abnormalities as SAEs. For any AE that applies to this situation, comprehensive documentation of the event's severity status must be recorded in the patient's medical record.

11.4. Maximum Intensity

The Investigator will evaluate all AEs and SAEs with regard to maximum intensity and relationship to study drug. Maximum intensity should be assigned using one of the severity grades as outlined in the NCI-CTCAE v5.0. If the AE is not specifically listed in CTCAE v5.0, the following grades will be used:

- Grade 1: mild
- Grade 2: moderate
- Grade 3: severe
- Grade 4: life-threatening or disabling
- Grade 5: death

11.5. Relatedness to Study Drug

The Investigator must attempt to determine if an AE or SAE is related to the use of study treatment based on clinical experience with known drugs, information contained within an Investigator's Brochure, or events listed in a Product Label. This relationship should be described as follows:

Unlikely The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication, a new condition which, based on the pathophysiology of the condition and the pharmacology of the study drug, would be unlikely to be related to use of the study drug.

Possible The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug *BUT* the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition and the pharmacology of the study drug, would be unlikely to be related to the use of the study drug *OR* the event could be the effect of a concomitant medication.

Probable The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug *AND* the event cannot have been reasonably explained by an intercurrent medical condition *OR* the event cannot be the effect of a concomitant medication.

Definite The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug.

Unknown Based on the evidence available, causality cannot be ascribed.

Relatedness should be assessed and provided for every AE and assigned to ABI-009, TMZ (± radiotherapy), BEV, and/or CCNU as appropriate. If more than one of the study agents may be considered as the cause, relatedness is to be reassessed and provided as additional information becomes available.

11.6. Adverse Event Reporting

Adverse events that are serious, unexpected, and at least possibly related to study participation will be reported to the Institutional Review Board and to the FDA within the timelines described below. All other AEs, such as those that are expected, or are unlikely or definitely not related to the study participation, are to be reported per the IRB's requirements and to FDA as part of regular data submission at the time of annual IND report. The Principal Investigator is obligated to provide progress and safety summaries to Aadi Bioscience, Inc, the IND-holder of ABI-009, for inclusion in its reports to Regulatory Authorities. Aadi Bioscience, Inc. will provide copies of IND safety reports in all studies with ABI-009 to the investigators for local reporting to their respective IRBs.

11.6.1. Reporting Procedures for Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of a SAE Report Form in addition to being recorded on the AE page/screen of the eCRF.

The **Principal Investigator** must be notified within 24 hours of learning of any SAE, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

Aadi Bioscience, Inc. must be notified 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 **FDA** must be notified within 7 calendar days of any unexpected fatal or life-threatening AE with possible relationship to study drug, and 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

The **IRB** must be notified within five (5) days of any promptly reportable information (PRI). The following events meet the definition of PRI:

- New or increased risk.
- Protocol deviation
    - that harmed a patient or placed patient at risk of harm, or
    - made without prior approval to eliminate an immediate hazard to a patient
- Audit, inspection, inquiry or written report by a federal agency
- Allegation of noncompliance or finding of noncompliance
- Breach of confidentiality
- Unresolved patient complaint
- Suspension or premature termination by the sponsor, investigator or institution
- Incarceration of a patient in a research study not approved to involve prisoners
- Adverse events or IND safety reports that require a change to the protocol or consent
- Information where the sponsor requires prompt reporting to the IRB.

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

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

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

11.7. Pregnancy and Breast-feeding Reporting

If a pregnancy occurs in a female patient while the patient is taking protocol-required therapies, the patient must discontinue study immediately and the pregnancy must be reported to Aadi immediately. The female patient should be advised to see an obstetrician-gynecologist for further evaluation and counseling. 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.

If a pregnancy occurs in a female partner of a male patient taking protocol-required therapies, the male should notify the Investigator immediately and the pregnant female partner should be advised to call her healthcare provider.

The investigator will follow the female until completion of the pregnancy and must notify Aadi Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form or approved equivalent form. If a lactation case occurs while the female patient is taking protocol-required therapies, report the lactation case to AADi immediately. 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.

11.8. Data and Safety Review

Safety monitoring during the study will be the responsibility of the Principal Investigator and will occur through frequent teleconferences and/or face-to-face meetings with other study staff.

Patients enrolled to the trial will be monitored for AEs by the Investigator and clinical co-investigators. Adverse events will be graded according to the NCI-CTCAE v5.0. Toxicity assessments are required prior to study treatment, at the beginning of each treatment cycle, following termination of study treatment, and may be performed at any additional time at the discretion of the treating physician.

All AEs will be evaluated for duration, intensity and relationship to (association with) the study treatment or other potential causes. All AEs except lab abnormalities will be recorded regardless of causality. Adverse events that are: 1) serious, 2) unexpected, and 3) at least possibly related to study participation will be reported to the Institutional Review Board within 5 business days and to the FDA within 15 calendar days (or 7 calendar days for deaths). All other AEs, such as those that are expected, or are unlikely, or definitely not related to the study participation, are to be reported annually to the IRB and FDA as part of regular data submission at the time of continuing review.

12. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

12.1. Discontinuation from Treatment and the Study

A patient may be removed from the study for a variety of reasons, including:

- Progressive disease according to the RANO criteria
- Initiation of treatment with an alternative anticancer therapy
- Patient withdraws consent to continue in the trial
- Patient develops an AE or intercurrent condition that precludes further participation or requires a prohibited treatment
- The investigator withdraws the patient in the patient's best interest
- The patient becomes pregnant
- The patient is lost to follow-up (defined as inability to contact the patient on at least 2 separate occasions over a period of 4 weeks)
- Administrative reasons (the patient is unable to return to the site, moves away from the investigational site, other social reasons)

Patients who withdraw in the absence of progressive disease will be followed for progression.

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 (eg, survival). Every effort should be made to collect survival data after patient withdraws from treatment.

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

12.2. Patient Replacement

Any patient who is enrolled but does not receive an infusion of ABI-009 will be replaced.

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

The investigator and/or sponsor can decide to withdraw a patient(s) from 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.

13. REGULATORY OBLIGATIONS

13.1. Ethical Considerations

This study will be conducted in accordance with current Regulatory Authorities regulations, ICH GCP guidelines, the principles of the Declaration of Helsinki, and local ethical and legal requirements.

13.2. Informed Consent

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

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

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

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

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

13.3. Institutional Review Board (IRB) Approval and Consent

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

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The

investigator is to notify the IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from Aadi, in accordance with local procedures.

The investigator is responsible for maintaining IRB approval throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to Aadi.

13.4. Confidentiality

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

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

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

13.5. 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.

13.6. 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.

14. DATA HANDLING AND RECORDKEEPING

14.1. Patient Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), patients who have provided written informed consent must also sign a patient authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to patient's medical information relevant to the study.

14.2. 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.

14.3. 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.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

14.4. 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 (Section 5), 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.

14.5. The investigator is responsible Sample Storage and Destruction

Any blood or tumor sample collected according to the Schedule of Assessments (Section 5) 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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator is responsible for assuring that all the required data will be collected and entered onto the case report forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

The Principal Investigational is responsible for Study Drug Accountability. Study drug ABI-009 for this study will be provided by Aadi Bioscience, Inc. The recipient will acknowledge receipt of the drug indicating shipment content and condition. Damaged supplies will be replaced. Accurate records of all study drug dispensed from and returned to the study site are to be maintained. The study site will not destroy or dispose of unopened vials of ABI-009, without written direction from Aadi Bioscience, Inc.

15.2. 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.

15.3. 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.

16. PUBLICATIONS

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

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Appendix 1. Karnofsky Performance Status

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most of his personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance
	30	Severely disabled; hospital admission is indicated although death not imminent
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

Appendix 2. Response Assessment for Neuro-Oncology (RANO)

Response and progression of tumors in the brain will be evaluated using the Response Assessment in Neuro-Oncology (RANO) Working Group criteria, which, in addition to radiographic scans, comprise elements of the neurological exam, KPS and steroid use. Response assessments are derived from baseline assessments (prior to study treatment) or Best Response.

Evaluable for Objective Response Only those patients who have measurable disease at baseline, have received at least one cycle of therapy and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 also will be considered evaluable.)

Measurable Disease	Bidimensionally measurable lesions with clearly defined margins by MRI or CT scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip.
Non-Measureable Disease	Either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal diameters less than 10 mm.
Number of Lesions	If there are multiple lesions, a minimum of the two largest lesions should be measured and the sum of the products of the perpendicular diameters of these lesions should be determined. However, given the heterogeneity of high-grade gliomas and the difficulty in measuring some lesions, a maximum of five of the largest lesions may be measured.

Objective Status for High Grade Gliomas

Unless progression is observed, objective status can only be determined when *all* measurable and non-measurable lesions are assessed using the same techniques as at baseline.

Complete Response (CR)

Requires all of the following:

- Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks;
- No new lesions;
- Stable or improved non-enhancing (T2/FLAIR) lesions;
- Patient must be off corticosteroids (or on physiologic replacement doses only); and
- Patient is stable or improved clinically.

Partial Response (PR)

Requires all of the following:

- Greater than or equal to 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained

for at least 4 weeks;
- No progression of non-measurable disease;
- No new lesions;
- Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. The corticosteroid dose at the time of the scan should be no greater than the dose at time of baseline scan; and
- Patient is stable or improved clinically.

Stable Disease (SD)

Requires all of the following:

- Does not qualify for CR, PR or progression; and
- Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuro-imaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Progression (PD)

Defined by <u>any</u> of the following:

- Greater than or equal to a 25% increase in the sum of products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids; or
- Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events; or
- Appearance of any new lesion; or
- Clear clinical deterioration not attributable to other causes apart from the tumor or changes in corticosteroid dose; or
- Failure to return for evaluation as a result of death or deteriorating condition, or clear progression of non-measurable disease.

Best Overall Response

Best response will be calculated from the sequence of objective status.

For patients who are having all disease sites assessed at every evaluation period, the best response will be defined as the best objective status. If the response does not persist at the next routinely-scheduled scan, the response will still be recorded based on the prior scan but will be designated as a non-sustained response. If the response is sustained, e.g. still present on the subsequent scan, it will be recorded as a sustained response, lasting until the time of tumor progression. Best response is unknown if the patient does not qualify for a best response or increasing disease and if all objective status determinations before progression are unknown.