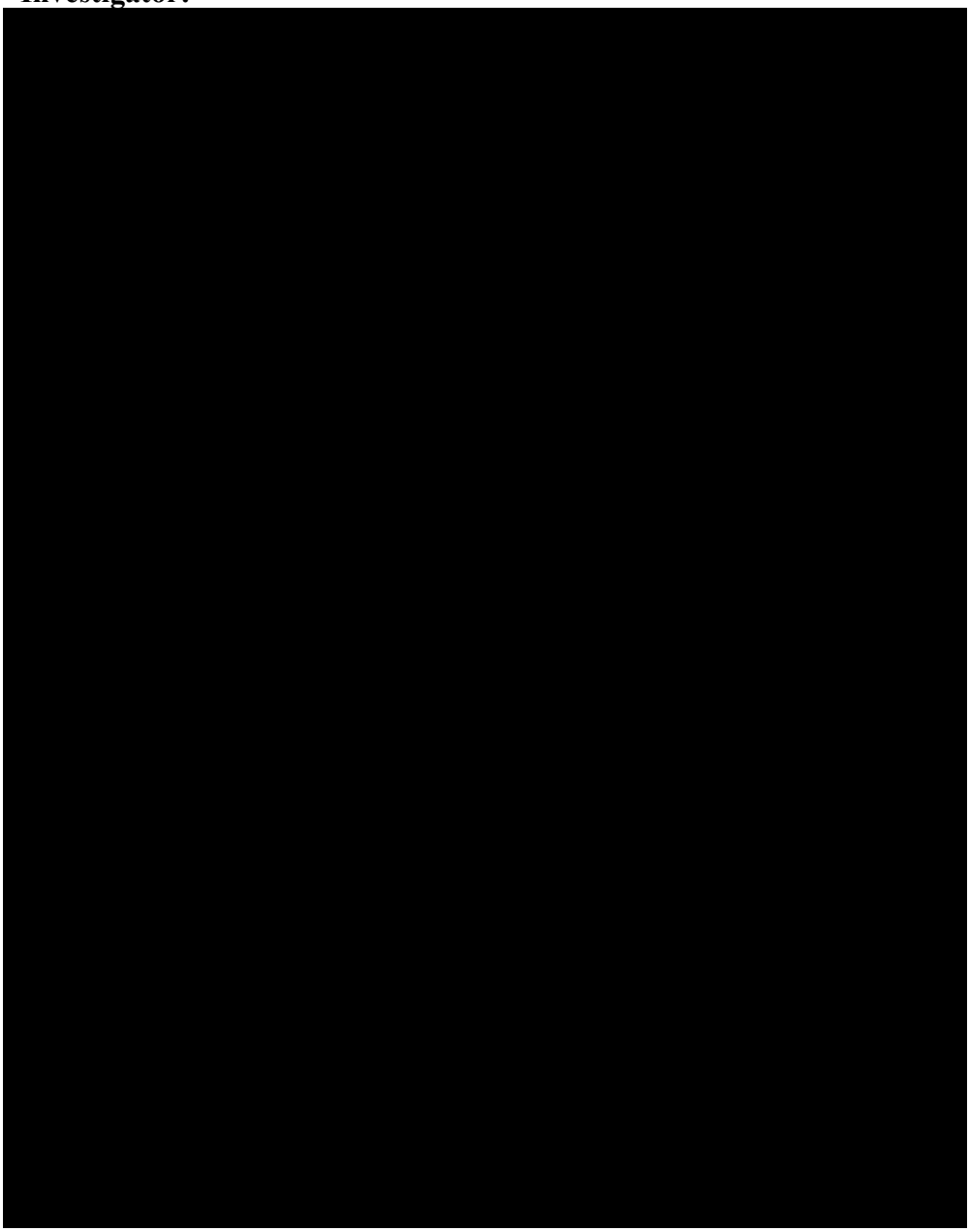
Radiation Therapy Oncology Group (RTOG) FOUNDATION COLLABORATION WITH ABBVIE INC.

RTOG 3508/AbbVie M13-813
(EudraCT 2015-001166-26)

AMENDMENT 9

A Randomized, Placebo Controlled Phase 3 Study of ABT-414 with Concurrent Chemoradiation and Adjuvant Temozolomide in Subjects with Newly Diagnosed Glioblastoma (GBM) with Epidermal Growth Factor Receptor (*EGFR*) Amplification (Intellance1)

Investigator:



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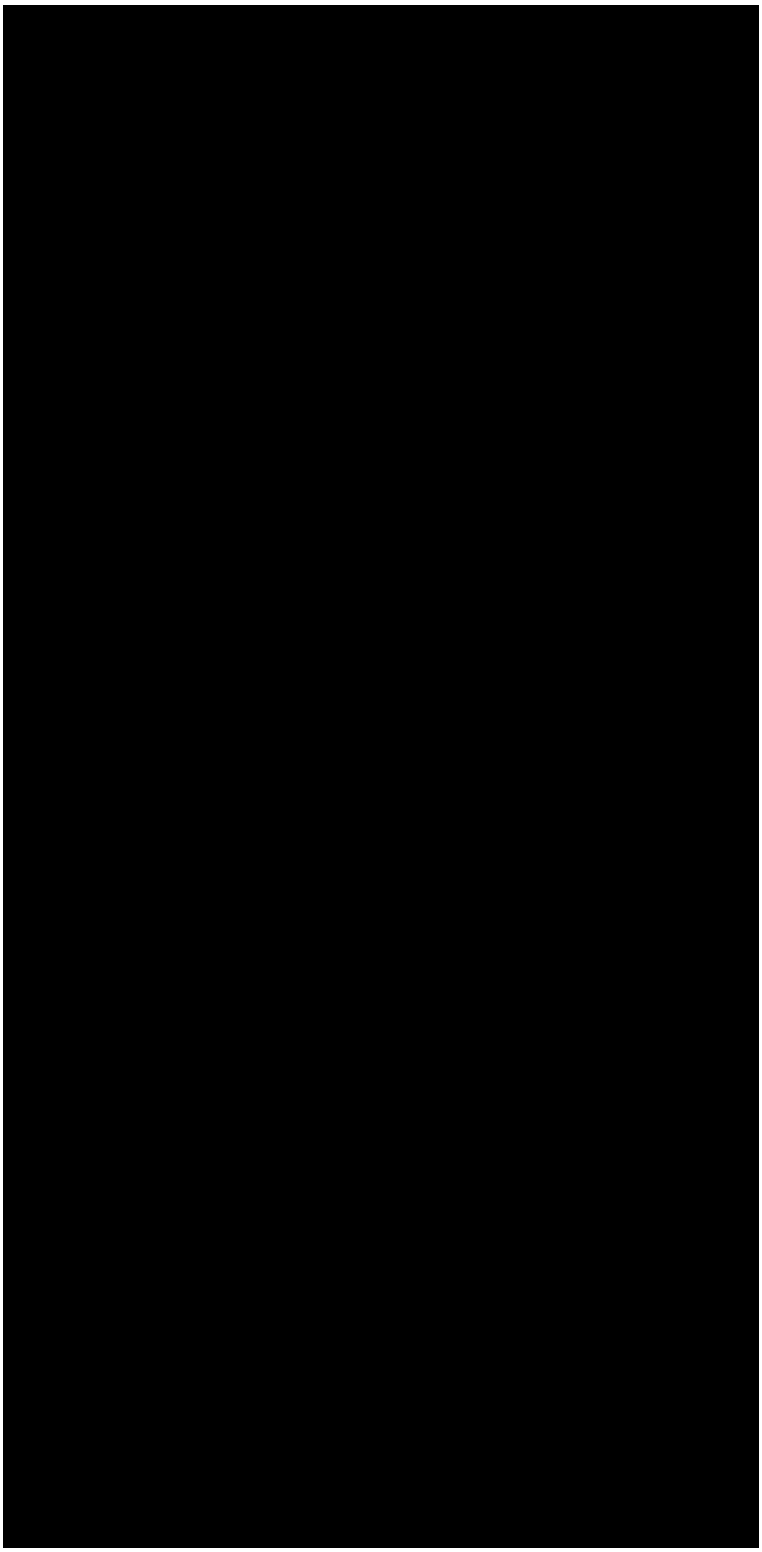

Sponsor:	**AbbVie Inc. (AbbVie)**
AbbVie IND AbbVie Investigational Product:	ABT-414
Date:	26 May 2019

Development Phase:	3
Study Design:	This is a randomized Phase 3 of ABT-414 in combination with radiation therapy and Temozolomide (TMZ) in subjects with newly diagnosed Glioblastoma with *EGFR* amplification.

Medical Monitors/Emergency Contact:

[redacted]

Should in case of subject safety concerns or medical emergencies the Medical Monitors are both unavailable, please call the following central back-up number:

Phone: [redacted]

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

Protocol Agent

Agent	Supply	IND #	EudraCT #	IND Sponsor
ABT-414	AbbVie	115,080	2015-001166-26	AbbVie
Temozolomide	Commercial	N/A		N/A

Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	30 April 2015
Amendment 1	01 July 2015
Amendment 2 (VHP Amendment)	10 September 2015
Amendment 3	08 March 2016
Amendment 4	07 December 2016
Amendment 5	13 January 2017
Amendment 6	06 December 2017
Amendment 7	29 May 2018
Amendment 8	29 November 2018

The purpose of this Amendment is to:

- Add brief summary of results for the protocol-specified interim efficacy analysis in the Introduction
- Provide modified study procedures and instructions for study drug dosing in Appendix X for those subjects currently receiving ABT-414 who choose to continue ABT-414. No additional efficacy data will be collected, and procedures have been minimized to include those necessary for study drug dosing, safety monitoring and collection of safety data related to adverse events and serious adverse events.
  Rationale: *The interim efficacy analysis results overall indicated no survival benefit for adding ABT-414 to standard RT/TMZ therapy in newly diagnosed GBM patients. However, given that no new clinically significant safety risks were identified, the RTOG Steering Committee and AbbVie believe it is appropriate to allow subjects who are currently receiving ABT-414 to continue ABT-414 treatment if the investigator and subject believe it is in the subject's best interest.*

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SCHEMA

SCREENING REQUIREMENTS

Central Pathology Review for confirmation of histology and adequacy of tissue for *MGMT* and *EGFR* analysis. Testing for *EGFR* amplification, *MGMT* promoter methylation, and *EGFRvIII* must be complete before Randomization. Only subjects with *EGFR* amplified tumors and available results for *MGMT* and *EGFRvIII* testing will be eligible. See protocol for details.

↓

RANDOMIZATION REQUIREMENTS

STRATIFY

MGMT methylation status: methylated vs. Unmethylated*
RPA class: III vs. IV vs. V
Region of the world: US/Canada vs. Other
EGFRvIII mutation status: mutated vs. Other

RANDOMIZE

↓ ↓

Arm A	**Arm B**
RT: ~60 Gy in ~30 fractions over 42 days (d) (up to 49 d)**	RT: ~ 60 Gy in ~30 fractions over 42 d (up to 49 d)**
+	+
Temozolomide: Daily for 42 d (up to 49 d)**	Temozolomide: Daily for 42 d (up to 49 d)**
+	+
Blinded ABT-414: D1 of Weeks 1, 3 and 5	Blinded Placebo: D1 of Weeks 1, 3 and 5
Approximately 28 d after completion of chemoradiation	Approximately 28 d after completion of chemoradiation
Temozolomide: D1-5 of 28-d cycle x 6 cycles**	Temozolomide: D1-5 of 28-d cycle x 6 cycles**
+	+
Blinded ABT-414: D1 and D15 of q 28-d cycle x 12 cycles	Blinded Placebo: D1 and D15 of q 28-d cycle x 12 cycles

* A test result of "insufficient tissue" indeterminate or invalid for *MGMT* is exclusionary (unless a valid *MGMT* result is available from another approved local or central testing lab, as described in the protocol), and the subject will not be able to be continue to randomization.

** Per local prescribing information or local institutional guidelines. See Section 5.2 for alternative radiation therapy options.

1.0 INTRODUCTION AND BACKGROUND

Study RTOG 3508/M13-813 is a clinical study of ABT-414 for subjects with newly diagnosed glioblastoma (GBM). ABT-414 is an antibody drug conjugate (ADC) designed for the treatment of tumors harboring amplified genomic *EGFR*. This is a Phase 3 randomized double-blind, placebo-controlled trial comparing the efficacy and safety of ABT-414 versus placebo, each as concurrent treatment with standard-of-care therapy of radiation/temozolomide (TMZ) plus adjuvant TMZ and followed by ABT-414/placebo monotherapy.

In addition there is an ABT-414 sub-study in subjects with hepatic impairment outlined in Appendix IX. The revised schedule of procedures is provided in Appendix IX, Table 3H. The objective of the sub-study is to assess the pharmacokinetics, safety and tolerability of ABT-414 in subjects with mild and moderate hepatic impairment.

Glioblastoma (GBM)

GBM is the most common and most aggressive type of primary brain tumor in adults, affecting 8,000 to 10,000 people per year in North America alone.[1] The median survival time from diagnosis is 3 months without any treatment. With treatment, patients can expect an average survival of 1 to 2 years. The survival depends greatly on many patient and tumor specific factors, including tumor stage, age, resectability, and genetic characteristics as well as performance status. Treatments may include surgical resection of the tumor, chemotherapy, radiation therapy, and immunotherapy. Despite advances in treatments, the prognosis of patients with GBM remains poor.

The current standard-of-care therapy for newly diagnosed glioblastoma following surgical debulking is radiation therapy (RT) in combination with temozolomide (TMZ), followed by 6 months of further TMZ monotherapy.[2] The standard of care is based on the results from a definitive Phase 3 trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada (NCIC) that demonstrated a survival benefit for patients treated with TMZ in addition to surgery and radiation.[3] In this study, patients in the radiation therapy plus concomitant and adjuvant TMZ arm had a longer median survival time (14.6 versus 12.1 months) and a greater 2-year survival rate (27% versus 10%) than patients in the radiation therapy alone arm.

Despite these improvements afforded by the addition of TMZ, the vast majority of patients will have their tumor recur after aggressive primary therapy. At the time of recurrence, the prognosis is quite dismal, with median survival times measured in months and response rates commonly

reported to be in the single digits. Treatment to prevent tumor re-growth is direly needed in order to make the most significant impact on the prognosis of those with this devastating disease.

One of the unique molecular characteristics of GBM tumors is the aberrant signaling, expression, mutation, and gene amplification of the epidermal growth factor receptor, or *EGFR*. The *EGFR* has been hypothesized to play a critical role in the development of GBM and thus has an extremely high rate of overexpression (nearing 60% or more), amplification (approximating 40 – 50%), and mutations (approximately 25% overall have been reported to harbor the constitutively active *EGFR* variant III (*EGFRvIII*) mutation). This makes the *EGFR* an attractive target for drug therapy. Unfortunately, *EGFR* signaling inhibitors have not been successful to date, likely due to the multiple signaling bypass pathways as well as the underlying and reactive mutational resistance mechanisms, and limited brain penetration of tyrosine kinase inhibitors at routine dosing used in other solid tumors. Other methods to exploit the *EGFR*, such as using the receptor as a target for selective chemotherapy or immunotherapy delivery, remain attractive. ABT-414 binds specifically to activated wild-type *EGFR* and *EGFRvIII* mutant GBM and, as an antibody drug conjugate, is constructed to deliver a potent toxin that circumvents most signaling resistance mechanisms and does not depend on inhibition of *EGFR* signaling.

ABT-414: An Antibody Drug Conjugate that Targets Amplified *EGFR*

ABT-414 is an antibody drug conjugate (ADC) designed for the treatment of tumors harboring amplified genomic *EGFR*. Antibody drug conjugates are a rapidly growing class of cancer drugs that combine the targeting properties of monoclonal antibodies (mAbs) with the anti-tumor effects of potent cytotoxic drugs. Significant advancements in linker stability and toxin potency are primarily responsible for the resurgence in ADC development. A recent example of a clinically relevant, advanced ADC is brentuximab vedotin (Adcetris®), an anti-CD30 ADC which received US Food and Drug Administration approval in 2011 for Hodgkin's lymphoma and anaplastic large cell lymphoma due to a high percentage of tumor responses in these largely chemotherapy refractory populations. The distinct clinical advantage to ADCs is their ability to deliver toxic payloads directly to a tumor, bypassing many downstream resistance mechanisms related to intracellular signaling.

ABT-414 is a newer generation antibody-drug conjugate, consisting of: 1) a veneered "humanized" recombinant IgG1κ antibody that has binding properties specific to a unique epitope of human *EGFR* with 2) non-cleavable maleimido-caproyl linkers each attached to 3) a potent antimicrotubule agent, monomethylauristatin F (MMAF). The antibody binds to the *EGFR* epitope (even in the absence of *EGFRvIII* mutation), is internalized, and then intracellular enzymes release the toxin leading to inhibition of microtubule function, the disruption of critical

cellular processes and cell death. Importantly, ABT-414 binds to an epitope that is available predominantly on tumor cells with the *EGFR*de2-7 (*EGFRvIII*) deletion mutant or on tumor cells with *activated* wild-type EGF receptors. The epitope is largely inaccessible when *EGFR* is expressed at normal physiological levels; thus, ABT-414 has limited binding to non-activated, wild-type *EGFR* expressed on normal tissues. These properties, therefore, favor limited effects of the toxin on normal tissues while maintaining a high degree of activity on *EGFR*-amplified tumor cells. Nonclinical studies to date have confirmed that ABT-414 has potency greater than what is observed with clinically available agents in a variety of human xenograft animal models, with at least an equivalent toxicity profile.

Clinical Data of ABT-414 in GBM

Study M12-356 is a Phase 1, open-label study designed to assess the safety and pharmacokinetics of ABT-414 as monotherapy, in combination with TMZ, or in combination with RT and TMZ in subjects with newly diagnosed or recurrent GBM. In this study, ABT-414 is given every 2 weeks by intravenous (IV) infusion, with treatment arms as follows:

- Arm A (ABT-414/RT/TMZ): Subjects with *newly diagnosed* GBM who start ABT-414 along with concomitant radiotherapy and TMZ and later continue ABT-414 along with adjuvant TMZ.
- Arm B (ABT-414/TMZ): Subjects who start ABT-414 with TMZ alone (without radiotherapy). Arm B subjects can be either *newly diagnosed* subjects, who are starting concomitant ABT-414/TMZ treatment after completion of initial concomitant radiotherapy and TMZ, or GBM subjects with *recurrent* disease, arising during or after adjuvant TMZ treatment.
- Arm C (ABT-414 monotherapy): Subjects with *recurrent* GBM only, who receive ABT-414 monotherapy.

As of January, 2016, 47 *newly diagnosed* GBM subjects in Arm A have received ABT-414 at dose levels ranging from 0.5 to 3.2 mg/kg in combination with radiation and TMZ. An objective response rate attributable to ABT-414 treatment alone cannot be accurately assessed in the newly diagnosed setting because of concomitant RT/TMZ, pseudoprogression, and/or minimal residual disease post-operatively. Although recurrence-free survival data are immature given the relatively brief follow-up to date on these subjects, the maximum tolerated dose (MTD) (2.4 mg/kg), as well as the recommended Phase 2 dose (2.0 mg/kg) in Arm A have been identified. As of the same cutoff date, 28 subjects with *recurrent, measurable* disease were enrolled either in Arm B (concomitant ABT-414 and TMZ) or Arm C (ABT-414 monotherapy). Of these, 18 subjects had *EGFR*-amplified tumors, and 6 (33%) subjects thus far have

demonstrated confirmed, objective responses as measured using Response Assessment in Neuro-oncology (RANO) criteria. Objective responses in the subjects with *EGFR*-amplified disease were seen at doses ranging from 1.0 – 1.5 mg/kg, with onset as early as 2 months after treatment initiation but with maximum response thus far seen as late 6 months into treatment. Importantly, these responses were observed in both Arms B and C, including one of the 2 complete responses (CR)s observed after ABT-414 monotherapy treatment. None of the subjects with tumors negative for *EGFR* amplification has experienced a confirmed objective response. The MTD and recommended phase 2 dose in Arms B and C was 1.25 mg/kg.

The dose-limiting toxicities (DLTs) observed after ABT-414 exposure have been limited to manifestations from the formation of corneal deposits related to cys-mcMMAF, a syndrome hereafter referred to as microcystic keratopathy. This is thought to be a result of damage directly to the transient amplifying cells of the limbus, cells that differentiate and give rise to the corneal epithelium. However, with the exception of these ocular adverse events, as described in detail below, adverse events reported were usually Grade 1 or 2, infrequent, and more likely related to the underlying cancer, concomitant chemotherapy or chemoradiotherapy. DLTs for all groups in both studies were comprised of a variety of different preferred terms for eye-related signs (including keratitis, corneal cysts, corneal deposits, ocular hyperemia) and symptoms (most commonly vision blurred, photophobia, dry eye, eye pain, foreign body sensation in eyes, and lacrimation increased). Similar findings have been reported for other ADCs utilizing the cys-mcMMAF toxin.[4] Given that the cornea regenerates every 3 – 4 weeks, to date, all cases of microcystic keratopathy have resolved without long-term sequelae after drug discontinuation. Both the incidence and severity of eye toxicity appear to be dose-related. While ABT-414 dose reduction for subjects with high-grade toxicities generally reduces symptom severity and allows for continued dosing, the overall incidence rate remains very high at the recommended Phase 2 doses proposed for further clinical studies.

The microcystic keratopathy noted in Study M12-356 is similarly described with other chemotherapy agents, including high-dose cytarabine. Prophylactic steroid eye drops are routinely used to control these symptoms. Thus, prophylactic steroid ophthalmologic solution was administered to subjects in Study M12-356 once ocular toxicities were observed. One subject in Study M12-356 who had stopped ABT-414 treatment due to a Grade 3 eye toxicity at the 1.0 mg/kg level without steroid ocular prophylaxis was able to tolerate the same 1.0 mg/kg dose level when ABT-414 was restarted along with steroid prophylaxis. Based on this and other experiences, ocular steroid prophylaxis is indicated for all subjects receiving ABT-414 treatment at dose levels of 1.0 mg/kg and above.

The dose of ABT-414 in combination with adjuvant TMZ is 1.25 mg/kg, based on the tolerability of ABT-414 in Arm B of Study M12-356. At this dose (and with steroid prophylaxis) during maintenance TMZ cycles, 2/10 subjects had ocular DLTs, but only 1 was attributable to ABT-414. To date, approximately 6 subjects have been treated at the recommended Phase 2 dose as part of an expanded safety cohort. Of these, although eye toxicity of any grade is very common, only approximately 20% have reported severe ocular adverse events (Grade 3 or greater).

The results from Arm A of Study M12-356, in which all subjects received ABT-414 combined with concomitant RT/TMZ, demonstrate that higher doses of ABT-414 with this combination can be tolerated. The recommended Phase 2 dose was declared at 2.0 mg/kg every other week, with no observed Grade 3 or higher toxicities observed. Higher doses were associated with at least 1 dose-limiting toxicity event and were not well tolerated.

As previously mentioned, the ocular manifestations of microcystic keratopathy to date have been reversible after withholding ABT-414, for 4 to 6 weeks. Subjects who restart ABT-414 at lower doses (~1.0 mg/kg) have less severe toxicities and can generally tolerate further therapy.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure (IB).[33]

INTELLANCE-2 Preliminary Results in Recurrent GBM

INTELLANCE-2 (Study M14-483) was a Phase 2, open-label, randomized study evaluating the efficacy and safety of Depatux-M (Depatuxizumab Mafodotin) alone or in combination with TMZ compared to lomustine (CCNU) or TMZ in subjects at first recurrence of GBM whose tumors were EGFR-amplified. Each subject was randomized in a 1:1:1 ratio to one of three study arms:

- Arm 1 (n = 88): Depatux-M 1.0 mg/kg IV q2 weeks in combination with TMZ 150 – 200 mg/m^2 on Days 1 – 5 of each 28-day cycle.
- Arm 2 (n = 86): Depatux-M monotherapy 1.0 mg/kg IV infusion q2 weeks.
- Arm 3 (n = 86): Control arm subjects were treated according to the timing of relapse in relation to their last cycle of TMZ (the same factor was used to stratify randomization):
    - Arm 3A: Subjects relapsing < 16 weeks after the first day of the last TMZ cycle were treated with lomustine 110 mg/m^2 on Day 1 of every 42-day treatment period.
    - Arm 3B: Subjects relapsing ≥ 16 weeks after the first day of the last TMZ cycle were treated with TMZ 150 – 200 mg/m^2 on Days 1 – 5 of each 28-day cycle.

The ABT-414/TMZ combination group (Arm 1) showed a 29% decrease in OS hazard rate compared to the control group treated with TMZ or lomustine (Arm 3), a result which nearly achieved statistical significance (HR = 0.71 [0.50 – 1.02], 2-sided p-value = 0.062) despite the limited sample size of the Phase 2 study. The estimated percentage of patients surviving at 1 year increased from 28% (Arm 3) to 40% (Arm 1). Of note, in the subgroup of subjects who relapsed ≥ 16 weeks after the last TMZ cycle, the estimated HR_{OS} for the TMZ/ABT-414 combination vs. TMZ monotherapy was 0.52 (0.27 – 1.0; p = 0.05), suggesting that adding ABT-414 to TMZ treatment provides additional benefit on OS.

A post hoc analysis controlling for additional prognostic factors (including MGMT methylation status and baseline tumor size) showed an estimated HR_{OS} = 0.55 (p = 0.001), suggesting that the primary analysis may have underestimated the benefit of ABT-414/TMZ combination therapy.

ABT-414 monotherapy (Arm 2) showed activity similar to the active chemotherapy controls (Arm 3) (HR = 1.04, 2-sided p-value = 0.835).

Importantly, safety analyses showed that toxicity associated with ABT-414 was consistent with what was seen in Phase 1 studies, and no new safety signals were identified for ABT-414. Ocular side effects were reported by 77% of subjects taking ABT-414 overall, with 28% reporting Grade 3/4 ocular events. 2.9% of subjects discontinued ABT-414 treatment due to ocular side effects. The incidence of adverse events known to be associated with TMZ (neutropenia and thrombocytopenia/decreased platelet count) in the ABT-414/TMZ combination group was similar to that of TMZ monotherapy.

Of note, the estimated HR_{OS} of 0.71 observed in recurrent GBM subjects in the INTELLANCE-2 study, if replicated in a larger study, would be considered clinically meaningful and is consistent with the underlying assumption in the current INTELLANCE-1 trial of a HR_{OS} = 0.75.

INTELLANCE-2 preliminary results were presented at SNO 2017 and a detailed discussion of the preclinical toxicology, metabolism, and pharmacology will be updated in the Investigator's Brochure (IB).[33]

Additional Safety Information

Preliminary safety data were available for 468 subjects who received at least 1 dose of ABT-414 in 4 open-label studies at the most recent IB update (version 6.0). The Phase 2 Study M14-483 (INTELLANCE-2) in recurrent GBM is the only trial for which safety data from a control arm (TMZ or lomustine monotherapy) is available. Adverse events reported for more than 20% of subjects receiving ABT-414 were fatigue (35.5%), vision blurred (26.7%), headache and keratitis

(25.0% for each), dry eye (24.2%) and corneal epithelial microcysts (22.1%). In addition to ocular side effects related to corneal epitheliopathy, treatment-emergent adverse events reported by ≥ 10% of subjects in the ABT-414 treatment groups and ≥ 5% more frequently than the lomustine/TMZ control group included headache, fatigue, constipation, and liver transaminase elevations (alanine aminotransferase and aspartate aminotransferase). The rate of constipation was mainly accounted for by the ABT-414/TMZ combination arm, for which the rate was similar to that of subjects receiving TMZ monotherapy.

In the ongoing blinded Study M13-813 (RTOG 3508) in newly diagnosed GBM, one subject receiving ABT-414 (unblinded) with radiation and TMZ in the chemoradiation phase and with TMZ in the adjuvant phase experienced Grade 5 (fatal) events of acute liver injury and cerebral edema after approximately 5 months of treatment. The subject had grade 4 GGT (> 33 × ULN) and grade 1 fatty liver at Screening. The investigator considered the event of fatal acute liver injury to be reasonably possibly related to ABT-414. The sponsor also assessed that there was a reasonable possibility that ABT-414 caused or contributed to the liver injury and subsequent death. The above-described case is the only event of fatal liver injury that has been reported in ABT-414 open-label or blinded studies, in which approximately 800 people have received ABT-414 to date.

Summary of Results from Pre-planned Interim Efficacy Analysis

An interim efficacy analysis based on a data cut of 30 April 2019 was performed by the RTOG Independent Data Monitoring Committee (IDMC), at which time 346 OS events had been observed out of 639 subjects included in the main part of the study. The primary analysis of OS based on the Intent-to-Treat (ITT) population showed no difference in OS between groups, with a median OS of 18.9 vs. 18.7 months for ABT-414 and placebo, respectively. The weighted ($\rho = 0$, $\gamma = 0.2$) stratified log-rank test p-value (1-sided) was 0.628, and the observed hazard ratio (HR) (95% CI) for OS was 1.01 (0.82, 1.25). The median PFS was 8.0 vs. 6.3 months for ABT-414 and placebo, respectively, with a stratified log-rank test p-value (1-sided) of 0.029. The observed hazard ratio (HR) (95% CI) for PFS was 0.84 (0.70, 1.02). Preliminary analysis of demographic and clinical characteristics did not reveal any factors predictive of OS benefit for the addition of ABT-414 to standard RT/TMZ therapy.

Overall, 99.4% and 97.8% of subjects experienced at least 1 adverse event, and 87.3% and 62.3% experienced a Grade 3 or higher AE in the ABT-414 and placebo arms, respectively. Overall, 94.7% and 36.1% of subjects experienced at least 1 ocular adverse event related to corneal epitheliopathy, 61.0% and 0.6% experienced a Grade 3 or higher AE related to corneal epitheliopathy, and 11.8% and 0% discontinued study drug (ABT-414 or placebo) in the

ABT-414 and placebo arms due to corneal epitheliopathy, respectively. The most common (> 10%) events related to corneal epitheliopathy included keratopathy, vision blurred, photophobia, dry eye, eye pain, keratitis, and punctate keratitis. Excluding events related to corneal epitheliopathy, events for which the incidence in the ABT-414 group was ≥ 5% greater than in the placebo group included thrombocytopenia, gamma-glutamyltransferase increased, aspartate aminotransferase increased, alanine aminotransferase increased, constipation, blood alkaline phosphatase increased, fatigue, and platelet count decreased. Excluding events related to corneal epitheliopathy, Grade 3 or higher events for which the incidence in the ABT-414 group was at least 5% and was ≥ 2% greater than in the placebo group included thrombocytopenia, gamma-glutamyltransferase increased, and alanine aminotransferase increased.

The interim efficacy analysis results overall indicate no survival benefit for adding ABT-414 to standard RT/TMZ therapy in newly diagnosed GBM patients. However, given that no new important safety risks were identified, the RTOG Steering Committee and AbbVie believe it is appropriate to allow subjects who are currently receiving ABT-414 to continue ABT-414 treatment if the investigator and subject believe it is in the subject's best interest. For those subjects who choose to continue ABT-414, study procedures have been modified as described in Appendix X. The appendix provides guidance for study drug administration and collection of safety data related to AEs and SAEs. No additional efficacy data will be collected.

1.1 Differences Statement

This is the first placebo-controlled study evaluating the efficacy of ABT-414 in the treatment of newly diagnosed GBM. In Study M12-356, the safety and tolerability of ABT-414 in newly diagnosed GBM subjects was evaluated in an open-label dose escalation study.

1.2 Benefits and Risks

ABT-414 is an ADC that has demonstrated initial evidence of clinical efficacy in *EGFR*-amplified GBM. ABT-414 also demonstrates a favorable *EGFR* binding ratio of tumor to normal tissue. These data together reflect an acceptable rationale and risk for treating *EGFR*-amplified GBM subjects with ABT-414 in the context of a clinical trial.

2.0 OBJECTIVES

2.1 Primary Objective

To determine whether the addition of ABT-414 to concomitant radiotherapy and TMZ plus adjuvant TMZ prolongs Overall Survival (OS) among subjects with newly diagnosed GBM harboring *EGFR* amplification.

2.2 Secondary Objectives

To determine whether the addition of ABT-414 to concomitant radiotherapy and TMZ plus adjuvant TMZ improves outcomes among subjects with newly diagnosed GBM harboring *EGFR* amplification for the following endpoints:

- PFS (assessed by IRC)
- OS for the MGMT unmethylated group
- OS for the MGMT methylated subgroup
- Time to deterioration in symptom severity score M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT)
- Time to deterioration in symptom interference score (MDASI-BT)
- Time to deterioration in neurocognitive functioning on the Hopkins Verbal Learning Test Revised (HVLT-R)
- OS for the EGFRvIII-mutated tumor subgroup
- PFS for EGFRvIII-mutated tumor subgroup

Safety:

- Assessment of comparative safety

2.3 Exploratory Objectives

To determine whether the addition of ABT-414 to concomitant radiotherapy and TMZ plus adjuvant TMZ improves outcomes among subjects with newly diagnosed GBM harboring *EGFR* amplification for the following endpoints:

- OS at 1 year
- OS at 2 years
- PFS at 1 year
- PFS at 2 years
- PFS for the MGMT unmethylated and methylated sub-groups

- OS for non-*EGFRvIII* subjects (comparison between arms)
- PFS for non-*EGFRvIII* subjects (comparison between arms)
- OS and PFS for Total *EGFR* expressions levels
- *EGFRvIII* status (as a prognostic factor independent of treatment assignment) overall and among molecular subgroups
- Change from baseline in HRQoL (EORTC QLQ-C30/BN20 scale scores)
- Change from baseline in symptom severity factor groupings (MDASI-BT neurologic, cognitive, treatment and symptom interference (activity-related, mood-related)
- Change from baseline in performance status (KPS)
- Median time KPS score was maintained at 70 or higher
- Time to deterioration in neurocognitive functioning on Controlled Oral Word Association (COWA-FAS)
- Change from baseline in neurocognitive functioning (HVLT-R and COWA-FAS)
- Change from baseline in Vision item on the MDASI-BT and EORTC BN20
- Change from baseline in health status (EQ-5D-5L and EQ-5D-VAS)
- Changes in *EGFR* molecular profile during therapy among subjects who undergo additional surgery as part of routine care
- Pharmacokinetics of ABT-414, total ABT-806, and unconjugated cys-mcMMAF
- Change from baseline in average daily (dexamethasone equivalent) corticosteroid dosing during treatment.

2.4 Biomarkers

Biospecimens (plasma, serum, tumor tissue) will be collected at designated time points throughout the study to conduct research with the intent of identifying biomarkers associated with subject outcome or to better characterize the disease. A portion of the tumor tissue will be used to confirm GBM diagnosis (central review of tumor histopathology), determination of *EGFR* amplification (required for study entry), *EGFRvIII* variant, and O6-methylguaninemethlytransferese (*MGMT*) methylation status (required for subject randomization).

2.5 Hepatic Impairment Sub-Study Objectives

This open-label, single arm sub-study, described in Appendix IX, will assess the pharmacokinetics, safety and tolerability of ABT-414 in subjects with newly diagnosed *EGFR*-amplified GBM who have mild or moderate hepatic impairment.

3.0 SUBJECT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact your local monitor/Clinical Research Associate.

See Appendix IX for subject selection and eligibility criteria for subjects with mild to moderate hepatic impairment.

Submission of tumor tissue is required for all subjects (see Section 4.2: Collection of Tumor Tissues). Investigators should check with their site Pathology department regarding release of biospecimens before approaching subjects about participation in the trial. (See details of tissue submissions in Study-Specific Laboratory Manual.) It is expected that approximately 40 – 50% of subjects tested will have *EGFR* amplification.

Screening Requirements

- Tumor tissue from surgery submitted for histological confirmation of GBM diagnosis by a central pathologist and for central biomarker testing for *EGFR* amplification, *EGFRvIII* mutation, and *MGMT* promoter methylation status. Results for each of these tests are required for study eligibility.
- If the subject has a valid result on an approved *MGMT* assay from screening for a different study, those results will be accepted for eligibility and stratification in this study (see Section 5.7 for details). Local *MGMT* testing also may be used for stratification purposes if approved by AbbVie or RTOG. If a valid central test result also is or becomes available prior to randomization, the central result will be entered for stratification.

Randomization Requirements

- A brain MRI scan with and without contrast, performed at any time after diagnostic surgery or biopsy but prior to randomization, is required to serve as a baseline scan for RANO tumor response assessments. The baseline MRI must include the image sequences (T1 with and without contrast, T2 FLAIR, etc.) required for making RANO assessments. The most recent scan done prior to randomization will be used as the baseline scan.
    - If a subject starts chemoradiation more than 28 days after surgery, the baseline MRI will be performed no more than 21 (and preferably fewer) days before the start of chemoradiation.
    - Although not required for eligibility, an MRI scan collected within ~72 hours after resection is strongly encouraged as the best way to accurately assess the extent of surgical resection; if other post-operative scans are obtained, submit and record results of scan(s).

- An intraoperative brain MRI scan may be used as the post-operative baseline scan if it includes the required imaging sequences.

- Randomization (requiring stratification based on *EGFRvIII*, *MGMT*, RPA results, and region of world) must be performed in Interactive Response Technology (IRT) before ABT-414/placebo is administered.
- Prophylactic steroid drops (open label) begin 48 hours prior to first dose of ABT-414/placebo.
- Chemoradiation (RT/TMZ + ABT-414/placebo) begins within 49 days (7 weeks) after biopsy/resection.
  - If a subject undergoes additional tumor resection(s) before randomization, the subject can be randomized if Chemoradiation starts within 49 days (7 weeks) of the latest resection and the subject meets all eligibility criteria. The latest resection must have been performed within 30 days after the initial biopsy/resection.

3.1 Inclusion Criteria

A subject cannot be considered eligible for this study unless ALL of the following conditions are met. ***Eligibility criteria for sub-study subjects with hepatic impairment are described in Appendix IX.***

Subjects may only be randomized if additional criteria below are met:

1. Histologically confirmed de novo Grade IV glioma (GBM, gliosarcoma or other subvariants) confirmed by central pathology tissue screening.
2. *EGFR* amplification in tumor tissue confirmed by central assessment.
3. *Inclusion criterion removed in Amendment 5.*
4. The subject must have recovered from the effects of surgery, post-operative infection, and other complications before enrollment including, suture/staple removal from brain surgery and sufficient wound healing before randomization.
5. ≥ 18 years of age.
6. Karnofsky performance status ≥ 70 at assessment ≤ 14 days prior to randomization.
7. Results for required stratification factors (*EGFRvIII* status, *MGMT* methylation status, Recursive Partitioning Analysis (RPA) class, and region of world) available prior to randomization.
8. Subject has adequate bone marrow, renal, and hepatic function ≤ 21 days prior to randomization as follows:

a) Absolute neutrophil count (ANC) ≥1,500/mm^3;

b) Platelets ≥ 100,000/mm^3;

c) Hemoglobin (Hgb) ≥ 9.0 g/dL (Note: The use of transfusion or other intervention to achieve Hgb ≥ 9.0 g/dL is acceptable.);

d) Renal function: calculated creatinine clearance ≥ 30 mL/min by the Cockcroft-Gault formula;

e) Hepatic function: Total bilirubin ≤ 1.5 times upper limit of normal (ULN), Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT) ≤ 3 times ULN. Subjects with Gilbert's syndrome documented in medical history may be enrolled if total bilirubin is < 3 times ULN.

9. Electrocardiogram (ECG) without evidence of acute cardiac ischemia ≤ 21 days prior to randomization.

10. Female subjects of childbearing potential (i.e., those who are not postmenopausal for at least 1 year or surgically sterile by bilateral salpingectomy, bilateral oophorectomy or hysterectomy) should practice at least one accepted method of birth control listed below during study entry, for the entire duration of the study and for at least 6 months after treatment with ABT-414 and TMZ treatment has ended. Male subjects should practice at least one of the accepted methods of birth control during study and for at least 6 months after ABT-414 and TMZ. If using a condom, practice at least one other method of birth control listed below during the study and for at least 6 months after ABT-414 and TMZ:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1;
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1;
- Bilateral tubal occlusion/ligation;
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable];
- A vasectomized male subject or a vasectomized partner of a female subject;
- Intrauterine device, IUD (females);
- Intrauterine hormone-releasing system, IUS (females);
- Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or cream) unless not deemed acceptable as highly effective contraception by local regulations.

11. Women of child-bearing potential must have a negative pregnancy test (urine or serum) within 7 days prior to randomization.
12. Must voluntarily sign and date informed consent form, for tumor tissue biomarker testing and for study participation, approved by an Independent Ethics Committee (IEC)/ Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

3.2 Exclusion Criteria

Subjects with one or more of the following conditions are NOT eligible for this study.

Eligibility criteria for sub-study subjects with hepatic impairment are described in Appendix IX.

1. Subject has multifocal GBM, defined as discrete sites of disease without contiguous T2/FLAIR abnormality that require distinct radiotherapy ports. Satellite lesions that are associated with a contiguous area of T2/FLAIR abnormality as the main lesion(s) and that are encompassed within the same radiotherapy port as the main lesion(s) are permitted.
2. ***Exclusion criterion removed in Amendment 5.***
3. Subject has recurrent GBM.
4. ***Exclusion criterion removed in Amendment 5.***
5. Subject has metastatic GBM.
6. Prior chemotherapy or radiosensitizers for cancers of the head and neck region; note that prior chemotherapy for a different cancer is allowable, except prior temozolomide.
7. Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation fields.
8. Any prior therapy for glioblastoma, except surgery (intra-operative techniques to guide resection are allowed as are experimental imaging techniques).
9. Prior invasive malignancy (except for non-melanomatous skin cancer; carcinoma in situ of the breast, oral cavity, or cervix) unless disease free for ≥ 2 years.
10. Prior, concomitant, or planned concomitant treatment with anti-neoplastic intent including but not limited to NovoTumor Treatment Fields (Novo TTF), *EGFR*-targeted therapy (including *EGFRvIII*-directed therapy), bevacizumab, Gliadel wafers or other intratumoral or intracavitary anti-neoplastic therapy, or other experimental therapeutics intended to

treat the tumor. Diagnostic or imaging studies; quality of life; biomarker or epidemiological studies; and operative guides to improve extent of resection are allowed.

11. Subject has had major immunologic reaction to an IgG-containing agent.
12. Subject has had LASIK (laser-assisted in situ keratomileusis) procedure within the last 1 year or cataract surgery within the last 3 months.
13. Subject has a history of hypersensitivity to TMZ or excipients, ABT-414 components or excipients, and dacarbazine (contraindication for TMZ).
14. Subject is unsuitable for receiving ocular steroids:
    - Subject has any active viral disease of the cornea or conjunctiva, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella; mycobacterial infection of the eye; fungal diseases of ocular structures; or any other contraindication for ocular steroid use.
    - Subject has a known or suspected hypersensitivity to any ocular steroid.
    - Subject has primary open angle glaucoma or a history of steroid-induced intraocular pressure elevation.
15. Subject is a lactating or pregnant female.
16. Severe, active co-morbidity, defined as follows:

    Severe hepatic impairment (Child-Pugh category C or higher [score of 10 or higher (Appendix VII)]); *Subjects with mild or moderate hepatic impairment (Child-Pugh score of 5 – 9) may be eligible for treatment, as described in Appendix IX.*

    - Unstable angina and/or congestive heart failure within the last 6 months;
    - Transmural myocardial infarction within the last 6 months;
    - Evidence of recent myocardial infarction or ischemia by the findings of S-T elevations of ≥ 2 mm using the analysis of an EKG performed within 21 days prior to enrollment;
    - New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 12 months prior to enrollment (Appendix IV);
    - History of stroke, cerebral vascular accident (CVA) or transient ischemic attack within 6 months;
    - Serious and inadequately controlled cardiac arrhythmia;
    - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of enrollment;
    - Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of enrollment;

- Subjects with clinically defined Acquired Immune-Deficiency Syndrome (AIDS)-defining illness. This is necessary to ensure subjects are likely to be able to receive the full TMZ regimen;
- Active connective tissue disorders, such as lupus or scleroderma, that in the opinion of the Investigator may put the subject at high risk for radiation toxicity;
- Any other major medical illnesses or psychiatric impairments that in the Investigator's opinion will prevent administration or completion of protocol therapy;

17. Subjects treated on any other therapeutic clinical protocols within 30 days prior to study entry or during participation in the study except intra-operative therapy to guide resection or experimental imaging without therapeutic intent.
18. Inability to undergo contrast-enhanced MRI scans.

4.0 STUDY OVERVIEW AND STUDY PROCEDURES

4.1 Study Overview

This is a Phase 3 randomized double-blind, placebo controlled trial comparing the efficacy and safety of ABT-414 versus placebo, each as concurrent treatment with standard-of-care therapy of radiation therapy/TMZ plus adjuvant TMZ and followed by ABT-414/placebo monotherapy, in subjects with newly diagnosed GBM.

The study comprises a Screening Period of up to 7 weeks from surgery/biopsy; a 6-week concomitant Chemoradiation Phase; an Adjuvant Phase beginning approximately 4 weeks after completion of chemoradiation, and a Follow-Up Phase. The Adjuvant Phase is comprised of 28-day cycles, with subjects receiving concomitant TMZ and study drug (ABT-414/placebo) for the first 6 cycles, and study drug (ABT-414/placebo) monotherapy for the following 6 cycles. Subsequent cycles will start approximately 28 days from the start of the previous cycle, and the cycle schedule will not be affected by delays or interruptions in TMZ or ABT-414/placebo dosing. Adjuvant treatment will be discontinued once disease progression has been determined. A Final Study Drug Visit will be performed upon discontinuation of study drug (ABT-414/placebo) for any reason, followed by 35-Day and 49 Day Follow-Up Visit (± 3 days). If subjects are unable to attend the 49 Day Follow-Up Visit, a phone call should be performed to obtain adverse event and concomitant medication information. In the Follow-Up Phase, subjects who complete adjuvant treatment or discontinue study drug prior to disease progression will continue to undergo MR imaging and assessment of neurocognitive functioning and PRO approximately every 8 weeks up to and including at the time of disease progression, starting 8 weeks after the last scheduled PRO assessments in the Adjuvant Phase. After disease progression, overall survival will continue to be assessed quarterly.

A sample of pre-treatment tumor tissues will be collected and sent to central laboratories to confirm the diagnosis of GBM (required to enroll in the trial) and test for *EGFR* amplification (required to enroll in the trial), *MGMT* promoter methylation (a stratification factor), *EGFRvIII* mutation (a stratification factor) and other biomarkers prior to starting chemoradiation. If a subject has a repeat surgery before initiating treatment then the tissue from either biopsy/resection may be used for histologic and *EGFR* amplification, *EGFRvIII* mutation and *MGMT* promoter methylation testing. If molecular results are discordant between multiple specimens from the same patient, then the results that permit eligibility will be used, unless EGFR amplification results differ at 2 distinct sites of sampling. Any question should be directed to the Medical Monitor(s). Remaining sample tissue will be retained for other

exploratory molecular analysis where allowed by local regulations. If local regulations do not allow tissue shipment or storage, the tissue will be immediately returned or destroyed after eligibility testing.

Screening procedures must be completed prior to Day 1 of the Chemoradiation Phase, which must start within 7 weeks after surgery. Screening procedures will include signing of a main study consent form, medical history, Karnofsky Performance Scale (KPS) assessment and recursive partitioning analysis (RPA) classification (referenced in Appendix VI), baseline ECG, physical, ophthalmologic and neurological examinations, laboratory test (chemistry, hematology, urinalysis and coagulation) (≤ 21 days from treatment start), and serum or urine pregnancy test if applicable (≤ 7 days from treatment start). Subjects will also complete neurocognitive testing and PRO measures. Subjects must have a baseline brain MRI prior to the start of chemoradiation. If a subject starts chemoradiation more than 28 days after surgery, the baseline brain MRI will be obtained no more than 21 (but preferably fewer) days prior to Day 1 Week 1 of the Chemoradiation Phase. The timing of the MRI should allow sufficient time to revise the radiation therapy plan *if needed* due to a significant change in tumor since surgery. Safety-related evaluations will be conducted 14 or fewer days prior to Day 1 of the Chemoradiation Phase. Subjects who screen positive for *EGFR* amplification in the tumor tissue may enter the study if all inclusion/exclusion criteria are met.

Upon study entry, subjects will be stratified according to the following 4 factors:

- Region of the world (United States/Canada or other country);
- RPA classes (III, IV or V);
- *MGMT* methylation (methylated or unmethylated);
- *EGFRvIII* status (mutated or other).

If a subject has a repeat surgery prior to randomization, the extent of surgical resection *after* the repeat surgery (biopsy-only vs. partial/total resection) will be used for determining RPA class (see Appendix VI).

A test result of "insufficient tissue", invalid or indeterminate for *MGMT* is exclusionary (unless a valid *MGMT* result is available from another approved local or central testing lab using approved methodology, as described in the protocol), and the subject will not be able to continue to randomization. *EGFRvIII* status of other is defined as wild type, indeterminate due to test failure, or insufficient tissue.

Subjects will be randomized within each stratum on a 1:1 ratio to receive:

- Arm A: ABT-414 during the Chemoradiation and Adjuvant Phases.
- Arm B: Placebo during the Chemoradiation and Adjuvant Phases.

During the Chemoradiation Phase, all subjects will undergo fractionated focal RT, with one treatment of approximately 2 gray (Gy) given daily 5 days per week for a total of approximately 60 Gy over approximately 6 weeks (and no more than 7 weeks). TMZ will be administered continuously from Day 1 of radiotherapy to the last day of radiation (including weekends and holidays) at a daily oral dose of 75 mg/m^2 for a maximum of 49 days. Subjects in Arm A will receive blinded ABT-414 at 2.0 mg/kg IV infusion over 30 – 40 minutes once every 2 weeks (Day 1 of Weeks 1, 3, and 5 of the 6-week regimen). Subjects in Arm B will receive blinded placebo IV infusion over 30 – 40 minutes once every 2 weeks (Day 1 of Weeks 1, 3, and 5 of the 6-week regimen). Treatment in the Chemoradiation Phase must begin ≤ 7 weeks after surgery/biopsy.

The start of the first cycle during the Adjuvant Therapy Phase will be scheduled approximately 28 days after the last day of radiotherapy. During the Adjuvant Therapy Phase, all subjects will receive oral TMZ 150 – 200 mg/m^2 once daily on Days 1 – 5 of each 28-day cycle for 6 cycles unless there is disease progression, unacceptable toxicity, or other reasons to discontinue. Subjects in Arm A will receive blinded ABT-414 1.25 mg/kg by intravenous infusion on Day 1 and Day 15 of each 28-day cycle for 12 cycles. Subjects in Arm B will receive blinded placebo IV infusion on Day 1 and Day 15 of each 28-day cycle for 12 cycles.

If after completing 12 cycles of adjuvant treatment, the subject is tolerating study drug (ABT-414 or placebo) and the Investigator believes the subject is continuing to benefit from ongoing study drug treatment, the Investigator may extend the Adjuvant Phase after consultation with the Neuro-Medical Oncology Chair or AbbVie Medical Monitor, as long as disease progression has not been determined.

Occurrence of disease progression to calculate PFS will be determined by the Investigator, based on local evaluation of images and other clinical information using the Response Assessment in Neuro-oncology (RANO) criteria (Appendix I). Post-baseline scans will be obtained ≤ 14 days before Day 1 of each odd-numbered cycle (Cycles 1, 3, 5, etc.) of the Adjuvant Phase and ≤ 14 days before each visit (approximately every 8 weeks) of the Follow-Up Phase. MR images will also be reviewed centrally by an independent blinded reviewer for radiographic evidence of disease progression. When study drug (ABT-414/placebo) is discontinued for any reason, a Final Study Drug Visit will be conducted. All subjects will have a 35-Day and 49-Day Follow-Up Visit (± 3 days) after the last dose of ABT-414/placebo. The 49-Day Follow-Up

Visit will focus on evaluation of ongoing adverse events. Overall survival will be assessed quarterly after study discontinuation.

Neurocognitive testing and patient-reported outcomes will be assessed approximately every 8 weeks during the Adjuvant and Follow-Up Phases, and then at disease progression.

Table 1. Study Activities – Chemoradiation Phase	**Screening[a]**		**Chemoradiation Phase[b]**						
Activity	**Screening 1**	**Screening 2**	**Day 1 Wk 1 (Fraction 1 of RT)**	**Day 1 of Wk 2**	**Day 1 of Wk 3**	**Day 1 of Wk 4**	**Day 1 of Wk 5**	**Day 1 of Wk 6**	**Day 1 of Wk 7**
Informed Consent	X								
Medical and Oncologic History		X							
Physical Exam (Including Weight and Karnofsky Performance Status)[c]		X	X		X		X		
Vital Signs		X	X		X		X		
Ophthalmology Exam		X				X[d]		X[d]	
ECG[e]		X							
Serum Pregnancy Test		X	X[f]						
Chemistry		X	X	X	X	X	X	X	X
Hematology		X	X	X	X	X	X	X	X
Urinalysis		X							
Coagulation		X							
MRI With and Without Contrast		X[k]							
Submit Tissue Sample for Confirmation of GBM, testing of *EGFR* amplification, *EGFRvIII* and *MGMT*	X								
Adverse Event Assessment/Concomitant Medications/Supportive Care			X		X		X		
Radiation Therapy[g]			X						
Temozolomide Administration			X[h]						
ABT-414 or Placebo Administration			X		X		X		
Prophylactic Eye Drop Administration			X[i]		X[i]		X[i]		
Randomization			X						
EORTC-QLQ-C30/BN20		X[j]							
MDASI-BT		X[j]							
NEI VFQ-25		X[j]							

Table 1. Study Activities – Chemoradiation Phase	**Screening[a]**		**Chemoradiation Phase[b]**						
Activity	**Screening 1**	**Screening 2**	**Day 1 Wk 1 (Fraction 1 of RT)**	**Day 1 of Wk 2**	**Day 1 of Wk 3**	**Day 1 of Wk 4**	**Day 1 of Wk 5**	**Day 1 of Wk 6**	**Day 1 of Wk 7**
Neurocognitive Function (HVLT-R, COWA-FAS)		X[j]							
EQ-5D-5L and EQ-5D-VAS		X[j]							

Wk = Week; F/U = Follow-up; RT= Radiation Therapy; KPS = Karnofsky Performance Status; EORTC-QLQ-C30/BN20 = EORTC Quality of Life Questionnaire, Cancer and Brain modules; MDASI-BT = MD Anderson Symptom Index for Brain Tumors; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire – 25;
HVLT-R = Hopkins Verbal Learning Test-Revised; COWA = Controlled Oral Word Association (FAS form); EQ-5D-5L = EuroQoL 5 Dimensions; VAS = Visual analog scale

a. Screening procedures may be conducted before or after results of *EGFR* amplification are received.

b. Chemoradiation Phase will be approximately 6 weeks (up to 7 weeks) of treatment with RT, TMZ, and ABT-414.

c. Height will be assessed at Screening only. Weight will be collected at all visits. Complete physical examination will be performed at Screening only. Symptom directed physical examination will be performed at all other designated visits as clinically indicated.

d. Ophthalmology exams are to be performed 7 to 14 days after the 2nd and 3rd infusions of ABT-414/placebo and must be completed prior to the next infusion of ABT-414/placebo.

e. ECG will be performed at screening, final visit and when clinically indicated.

f. For female subjects of childbearing potential, a serum pregnancy test will be performed within 21 days before Day 1 of chemoradiation. A urine or serum pregnancy test will be done on Day 1 Week 1 if a serum pregnancy test was performed more than 7 days before Day 1.

g. During Chemoradiation Phase, radiation therapy will begin on Day 1, Week 1 (Fraction 1). 60 Gy will be administered in ~30 fractions over 6 weeks (up to 49 days) per the local prescribing information or local institutional guidelines.

h. During Chemoradiation Phase, temozolomide (75 mg/m^2) will be given once per day, continuously (including weekends), from Day 1, Week 1 until completion of radiotherapy (up to 49 days).

i. Prophylactic eye drops will be administered for 7 days, from 2 days before until 4 days after, each dose of study drug (ABT-414 or placebo), as described in Section 5.5.

j. Baseline measure can be done at any time during Screening, up to and including Day 1 of Chemoradiation Phase, but preferably after *EGFR* amplification has been confirmed. The assessments will be translated into the local languages.

k. A brain MRI scan with and without contrast, performed at any time after diagnostic biopsy/resection but prior to randomization, is required to serve as a baseline scan for RANO tumor response assessments. If a subject starts chemoradiation more than 28 days after surgery, the baseline MRI is to be performed no more than 21 (but preferably fewer) days prior to Day 1 Week 1 of Chemoradiation Phase and should allow sufficient time to revise the radiation therapy plan if needed due to a significant change in tumor since surgery.

Table 2. Study Activities – Adjuvant Phase	**Adjuvant Phase – 28-Day Cycles[a]**										
Activity	**Day 1 of Every Cycle (1, 2, 3 etc.)**	**Day 1 of Odd-Numbered Cycles (1, 3, 5, etc.)**	**Day 1 of Cycle 2**	**Day 15 of Every Cycle[b]**	**Day 22 of Every Cycle[c]**	**Final Study Drug Visit[d]**	**35-Day F/U[e]**	**49-Day F/U**	**Follow-Up Phase (Every 8 Weeks Until Disease Progression)[f]**	**At Progression**	**Survival**
Physical Exam (Including Weight and Karnofsky Performance Status)[g]	X			X		X[d]	X		X		
Vital Signs	X			X		X	X				
Ophthalmology Exam[h]		X	X				X[i]				
ECG						X					
Chemistry	X					X	X				
Hematology	X				X	X	X				
MRI and Clinical Disease Progression Assessment		X[j]				X[d,k]			X[j]		
Adverse Event Assessment/Concomitant Medications/Supportive Care	X			X		X	X	X[r]			
Temozolomide Administration	X[l]										
ABT-414 or Placebo Administration	X[m]			X[m]							
Prophylactic Eye Drop Administration	X[n]			X[n]							
NEI VFQ-25[o]		X					X				
EORTC-QLQ-C30/BN20[o]		X							X	X[p]	
MDASI-BT[o]		X							X	X[p]	
Neurocognitive Function (HVLT-R, COWA)[o]		X							X	X[p]	
EQ-5D-5L and EQ-5D-VAS[o]		X							X	X[p]	
Treatment Satisfaction Question		X							X	X[p]	

Table 2. Study Activities – Adjuvant Phase	**Adjuvant Phase – 28-Day Cycles[a]**										
Activity	**Day 1 of Every Cycle (1, 2, 3 etc.)**	**Day 1 of Odd-Numbered Cycles (1, 3, 5, etc.)**	**Day 1 of Cycle 2**	**Day 15 of Every Cycle[b]**	**Day 22 of Every Cycle[c]**	**Final Study Drug Visit[d]**	**35-Day F/U[e]**	**49-Day F/U**	**Follow-Up Phase (Every 8 Weeks Until Disease Progression)[f]**	**At Progression**	**Survival**
Survival Assessment[q]											X

Wk = Week; F/U = Follow-up; RT = Radiation Therapy; KPS = Karnofsky Performance Status; EORTC-QLQ-C30/BN20 = EORTC Quality of Life Questionnaire, Cancer and Brain modules; MDASI-BT = MD Anderson Symptom Index for Brain Tumors; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire – 25;
HVLT-R = Hopkins Verbal Learning Test-Revised; COWA = Controlled Oral Word Association (FAS form); EQ-5D-5L = EuroQoL 5 Dimensions; VAS = Visual Analog Scale

a. Assessments in the Adjuvant Phase will be based on 28-day treatment cycles, with the first cycle starting approximately 4 weeks after completion of radiation therapy. Subjects will receive concomitant TMZ and study drug (placebo or ABT-414) for the first 6 cycles,and study drug monotherapy for an additional 6 cycles or until disease progression or study drug discontinuation. Subjects demonstrating continued benefit and no unacceptable toxicity from adjuvant TMZ can continue adjuvant TMZ to a maximum of 12 cycles at the discretion of the Investigator if this is considered an acceptable standard of care per local regulations. For subjects demonstrating continued benefit and no unacceptable toxicity with ABT-414/placebo after 12 cycles, the Adjuvant Phase may be extended at the discretion of the Investigator in discussion with the Neuro-Medical Oncology Chair or AbbVie Medical Monitor, with continued ABT-414/placebo treatment until disease progression is confirmed.

b. Day 15 visit will not be performed after discontinuation of study drug (ABT-414/placebo) treatment.

c. As per TMZ prescribing information, during the 28-day cycle of TMZ, a blood count for ANC and platelets should be performed 21 days (± 2 days) after the start of each TMZ cycle. If the ANC falls below 1,500/μL or if the platelet count falls below 100,000/mm^3, then blood counts should be performed weekly until recovery to these levels before TMZ dosing. A certified local lab may be used instead of central lab; if so, ANC and platelet results should be reported in the eCRF. Day 22 testing may be omitted for cycles in which TMZ is not administered or if local prescribing information allows for a different testing schedule for ANC and platelets.

d. Final Study Drug Visit to be performed approximately 14 days after last dose of ABT-414/placebo. The physical examination and MR imaging from the first visit of the Follow-Up Phase will be used for the Final Study Drug Visit if these visits coincide (e.g., if the subject completes 12 cycles of Adjuvant Phase).

e. To be performed 35 days (± 3 days) after the last dose of study drug (placebo or ABT-414). If the Final Study Drug Visit is more than 35 days after the last dose of study drug, then 35-day safety follow-up procedures will not be performed.

f. Visits in Follow-Up Phase to occur every 8 weeks, beginning 8 weeks after Day 1 of the last odd-numbered cycle in the Adjuvant Phase.

g. Height will be assessed at Screening only. Weight will be collected at all visits. Complete physical examination will be performed at Screening only. Symptom directed physical examination will be performed at all other designated visits as clinically indicated.

h. Ophthalmology exam to be performed prior to ABT-414/placebo dosing on Day 1 (or up to 7 days prior to Day 1) of Cycle 1, Cycle 2, and every odd-numbered cycle thereafter (Cycles 3, 5, 7, etc.). Ophthalmology exam for Cycle 1 Day 1 may be omitted if the subject had no corneal microcysts or ocular adverse events during or after the Chemoradiation Phase. Ophthalmology exams may be discontinued if the subject has been on Level 1 eye drops with no ocular toxicity for 2 consecutive eye exams.

i. Ophthalmology exam at Day 35 Follow-Up Visit to be done only if subject had corneal microcysts or other ocular findings related to ABT-414 or ocular steroids on previous exam and repeated at least every 8 weeks until satisfactory resolution of eye toxicities.

j. MRI to be performed ≤ 14 days before the start of each odd-numbered cycle or follow-up visit, starting at Cycle 1. If the subject discontinues study drug prior to disease progression, MRIs should continue to be obtained approximately every 8 weeks until disease progression is confirmed.

k. MRI to be performed, if not performed within last 3 weeks, if subject withdraws from study prior to disease progression.
l. TMZ will be administered once daily on Days 1 through 5 of each 28-day cycle for 6 cycles per the local prescribing information.
m. ABT-414 or placebo infusion will be administered on Day 1 and Day 15 of each 28-day cycle for 12 cycles. For subjects demonstrating continued benefit and no unacceptable toxicity with ABT-414/placebo after 12 cycles, the Adjuvant Phase may be extended at the discretion of the Investigator in discussion with the Neuro-Medical Oncology Chair or AbbVie Medical Monitor, with continued ABT-414/placebo treatment until disease progression is confirmed.
n. Prophylactic eye drops will be administered daily for 7 days with each dose of ABT-414/placebo, from 2 days before until 4 days after each dose of study drug (ABT-414 or placebo), as described in Section 5.5.
o. These assessments should be completed prior to study drug administration and any other study procedures being performed at these visits, and prior to discussing with the subject whether disease progression has occurred.
p. To be assessed at the time of disease progression (as soon as possible), regardless of the study phase in which disease progression occurred, or upon study withdrawal for any other reason.
q. Survival will be assessed quarterly after treatment discontinuation until death.
r. If the subject is unable to return to the site for the Day 49 Follow Up Visit, a phone call may be conducted to obtain AE and concomitant medication information.

Table 3. Blood Samples for Biomarker and Pharmacokinetic Schedule of Assessments*

Chemoradiation Phase					
Activity	**Day 1 Wk 1 (Fraction 1 of RT)**	**Day 1 of Wk 2**	**Day 1 of Wk 3**	**Day 1 of Wk 4**	**Day 1 of Wk 5**
Plasma Markers	0 hour (pre-dose)				
Serum Markers	0 hour (pre-dose)				
PK – ABT-414 and Total ABT-806 Assays	0 hour (pre-dose) & within 30 min post-dose	Anytime from 4 days before (preferred) to 1 day after the scheduled visits	0 hour (pre-dose) & within 30 min post-dose	Anytime from 4 days before (preferred) to 1 day after the scheduled visits	0 hour (pre-dose) & within 30 min post-dose
PK – CysmcMMAF assay	0 hour (pre-dose) & within 30 min post-dose	Anytime from 4 days before (preferred) to 1 day after the scheduled visits	within 30 min post-dose	Anytime from 4 days before (preferred) to 1 day after the scheduled visits	within 30 min post-dose
PK – Antidrug Antibody	0 hour (pre-dose)		0 hour (pre-dose)		0 hour (pre-dose)
Pharmacogenomic sample	0 hour (pre-dose)				
Adjuvant Phase (28-Day Cycles) and Post-Progression					
Activity	**Day 1 of Cycle 1**	**Day 1 of Cycles 2 – 12 (Every Cycle)**	**Day 1 of Cycle 14 and Every Other Cycle (14, 16, 18, etc.) while ABT-414/Placebo Treatment is Ongoing**	**Final Study Drug Visit**	**Post-Progression****
Plasma Markers	0 hour (pre-dose)			0 hour (pre-dose)	
Serum Markers				0 hour (pre-dose)	
Relapse Biopsy collection					yes
PK – ABT-414 and Total ABT-806 Assays	0 hour (pre-dose) & within 30 min post-dose on Day 1 of Cycle 1	0 hour (pre-dose)	0 hour (pre-dose)		
PK – Antidrug Antibody	0 hour (pre-dose)	0 hour (pre-dose)	0 hour (pre-dose)		

* For subjects in the hepatic sub-study the Biomarker and Pharmacokinetic Schedule of Assessments can be found in Appendix IX. Additional blood for PK can be collected at the discretion of the investigator in discussion with the Sponsor.

** For subjects who undergo tumor surgery (biopsy or resection) for medically directed reasons at any time during treatment or post-progression, a portion of the tumor tissue can be submitted for biomarker-related research.

4.2 Study Procedures

The study procedures outlined in Table 1 and Table 2 are discussed in detail in this section with the exception of the monitoring of treatment compliance (Section 5.10) and the collection of adverse event information (Section 7.0). All study data will be recorded on electronic case report forms (eCRFs), with the exception of pregnancy reporting forms and the neurocognitive function tests.

Procedures performed at Screening will serve as baseline, unless repeated prior to dosing; in which case the latter will serve as baseline. Unless otherwise noted, subsequent study procedures should be performed within 3 days prior to the scheduled study visit date when possible. Subjects who are not randomized will be considered a screen failure and will not be included in any intent-to-treat analyses.

Informed Consent

The informed consent for tissue and other pre-screening and for activities in the main study may be used separately or combined as a single informed consent document where allowed by local regulation and the IEC/IRB.

The IEC/IRB-approved informed consent must be signed and dated by each subject or the subject's legally acceptable representative prior to the submission of tumor tissue for screening, undergoing any study procedures or before any prohibited medications are withheld from the subject in order to participate in this study. Separate informed consent documents will also be required for the optional substudies in this protocol: for the collection of pharmacogenetic samples and the collection of tumor tissue post-treatment after disease progression, Section 15.3.

Tumor tissue testing will be conducted to confirm GBM diagnosis (central review of tumor histopathology), determination of *EGFR* amplification, *EGFRvIII* mutation and *MGMT* methylation status are all required for subject randomization. All clinical screening procedures should proceed simultaneously while tissue testing results are pending and should not be delayed until after EGFR amplification status is obtained.

For details on obtaining and documenting informed consents, Section 15.3.

Medical and Oncologic History

The following will be collected during the Screening Visit:

- Demographic information, including age, sex, and ethnicity. Ethnicity will include whether a subject is first generation Han Chinese.

- Complete medical history, including documentation of any clinically significant medical condition.
- History of tobacco and alcohol use.
- Detailed oncologic history including:
  - Date of primary cancer diagnosis;
  - Histology at the time of study entry;
  - Date and extent of surgical resection;
  - Neurologic deficits, if any, at the time of enrollment;

At each visit, the subject's medical history will be reviewed, and any changes from baseline will be recorded in the source documents and on the adverse event eCRF. On Day 1, any changes observed from the Screening Visit will be recorded in the subject's medical history.

Physical Examination

A complete physical examination (PE), including body weight and height, will be performed at Screening. A symptom directed physical examination will be performed at all other designated visits as clinically indicated. Weight will be collected at all visits and a PE will be performed as clinically indicated as outlined in Table 1. Clinically significant changes from baseline will be documented in the source documentation and electronic case report forms (eCRFs) as adverse events.

ABT-414-Targeted Ophthalmologic Examinations (ABT-414-TOE)

The ABT-414 Targeted Ophthalmologic Examination (ABT-414 TOE) was designed for this study to systematically identify and grade objective findings of ABT-414-related eye toxicity and to assess for adverse effects potentially related to ocular steroid use. The ABT-414 TOE will be provided as study specific start up materials. Changes in the steroid potency of prophylactic eye drops to be used with ABT-414/placebo dosing will be based on corneal findings from the ABT-414-TOE assessments performed throughout the study, as described below in Table 4.

Subjects will undergo ophthalmologic examinations as follows:

Screening: prior to starting chemoradiation

- Any clinically significant abnormal findings at Screening ophthalmologic examination are to be documented as part of the subject's medical history.

Chemoradiation Phase: within 7 days to 14 days after the 2nd and 3rd infusions of ABT-414/placebo

Adjuvant Phase: within 7 days prior to ABT-414/placebo dosing on Day 1 of Cycle 1, Cycle 2, and all odd-numbered cycles thereafter (Cycles 3, 5, 7, etc.) and at the 35-DayFollow-Up Visit.

Additional eye exams may be performed as needed throughout the study, including additional exams if evidence of microcystic keratopathy persists after the 35-Day Follow-Up Visit to monitor reversibility. A subset of sites will be asked to provide ophthalmic photography (e.g., slit lamp, confocal microscopy, Heidelberg Retina Tomographer [HRT3], etc.) of corneal abnormalities.

Ophthalmologic exams may be discontinued for subjects who have no evidence of eye toxicity on 2 consecutive examinations after being decreased to Level 1 eye drops.

Qualified medical personnel will perform the ophthalmologic examination, which will include assessments of visual acuity, intra-ocular pressure, funduscopic examination (at Screening, 35 DayFollow-Up Visit only), and slit lamp examination according to standard procedures of the ophthalmologist. The corneas will be evaluated via slit lamp at every exam to identify potential pathological changes. Grading on the ABT-414-TOE findings for "microcysts/edema" and "superficial punctate keratopathy" will be used to inform potential changes in the level of prophylactic steroid eye drops to be used with ABT-414/placebo dosing, as described in Section 5.5. Grading for these two items is as follows:

Microcysts/Edema

0	=	None
+0.5 (Trace)	=	Trace, localized epithelial haze
+1 (Mild)	=	Dull glass appearance that may include fine individual microcystic changes
+2 (Moderate)	=	Dull glass appearance of epithelium with large number of vacuoles with or without stromal edema
+3 (Severe)	=	Epithelial bullae and/or whorl keratopathy, localized or diffuse, with or without stromal striae

Superficial Punctate Keratopathy

0	=	None
+0.5 (Trace)	=	Trace (1 – 5 puncta)
+1 (Mild)	=	Mild (6 – 20 puncta)
+2 (Moderate)	=	Moderate (> 20 puncta, but countable)
+3 (Severe)	=	Severe (too many puncta to count)

Table 4: Ophthalmology Examination Schedule

STUDY VISIT/PERIOD*	EXAM REQUIRED?	COMMENTS
Screening	Yes	Establishes baseline assessment for corneal exam and visual acuity
Chemoradiation Phase		
Day 1, Week 5 (≤ 7 days before Week 5 ABT-414/placebo dose)	Yes	Do not decrease Level of eye drops until after the subject has received at least 2 eye exams
Day 1, Week 7 (7 – 14 days after Week 5 ABT-414/placebo dose)	Yes	--
Recovery Period		
No ophthalmology exam required	No	As-needed basis only
Adjuvant Phase		
Day 1, Cycle 1**	No	Exam not required if the subject had no corneal microcysts or ocular adverse events during or after the Chemoradiation Phase
Day 1, Cycle 2*	Yes	--
Day 1 of Cycles 3, 5, 7, etc.*	Yes***	Continue while subject is taking study drug (ABT-414/placebo)
35-Day Follow-Up Visit	Yes	
Ophthalmology exams required as scheduled for subjects on Level 2 – 4 eye drops.		

* Additional eye exams may be performed as needed. For eye toxicity considered by the investigator to be related to ABT-414, ophthalmology exams will be repeated until symptoms related to eye toxicity have resolved.

** Scheduled ophthalmology exams may be done at any time, up to 7 days before the scheduled date, prior to the scheduled infusion of ABT-414/placebo.

*** Eye exams may be discontinued for subjects who have no findings of ocular toxicity on 2 consecutive scheduled exams while on Level 1 (non-steroid) drops.

Adverse Event Reporting of ABT-414-TOE Findings

ABT-414-TOE reports will be reviewed by the Investigator (or medically qualified delegate). Examination records should be retained in the subject's source file. With the exception of the corneal findings described below, decisions on which findings, if any, from the ophthalmologic

examination or ABT-414-TOE report to be reported as adverse events will be made according to the Investigator's judgment. *Adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.0 criteria*, as discussed in **Section 7.2 and *not* according to the ABT-TOE grading system**.

To ensure consistent reporting of microcystic keratopathy, which is characteristic of ABT-414 but for which there is no Medical Dictionary for Regulatory Activities (MedDRA) preferred term or CTCAE adverse event term, any abnormal finding on the "corneal epithelium" and/or "superficial punctate keratopathy" fields of the ABT-414-TOE will be recorded as an adverse event, using the term "microcystic keratopathy." These events will be graded as shown in Table 5, which is based on CTCAE criteria for "keratitis."

Table 5. Adverse Event Reporting in eCRF for Corneal Findings from the ABT-414-TOE

Corneal finding from ABT-414-TOE	Adverse Event Report for eCRF	
	Adverse Event Verbatim Term	**CTCAE Grade**
Microcysts/Edema OR Superficial punctate keratopathy	Microcystic keratopathy	1 – Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
		2 – Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL
		3 – Decline in vision (worse than 20/40 but better than 20/200); limiting self care ADL
		4 – Perforation or blindness (20/200 or worse) in the affected eye

Vital Signs

Vital sign determinations of sitting blood pressure, heart rate and body temperature will be measured at all visits, as outlined in Table 1. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes.

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed for all subjects as outlined in Table 1 and Table 2.

Each ECG will be printed and evaluated by an appropriately qualified physician (in consultation with a cardiologist if necessary) at the study site. A qualified physician will determine if any findings outside normal physiological variation are clinically significant, document the presence

or lack of findings and the clinical significance (if any) on the ECG report and then sign and date the ECG report.

The ECG tracings will be retained as source documentation in the subject's records at the study site. The baseline (Screening) ECG will be used to document baseline status of the subject so that safety comparisons can be made if necessary. Repeat ECGs will be performed whenever clinically necessary.

Karnofsky Performance Status

Karnofsky Performance Status (KPS)[5] will be evaluated at the same time as the physical examinations. The status will be determined as:

100 – normal, no complaints, no signs of disease
90 – capable of normal activity, few symptoms or signs of disease
80 – normal activity with some difficulty, some symptoms or signs
70 – caring for self, not capable of normal activity or work
60 – requiring some help, can take care of most personal requirements
50 – requires help often, requires frequent medical care
40 – disabled, requires special care and help
30 – severely disabled, hospital admission indicated but no risk of death
20 – very ill, urgently requiring admission, requires supportive measures or treatment
10 – moribund, rapidly progressive fatal disease processes
0 – death

Pregnancy Test

For female subjects of childbearing potential, a serum pregnancy test will be performed ≤ 21 days before Day 1 of chemoradiation. A urine or serum pregnancy test will be done on Day 1 Week 1 if a serum pregnancy test was performed most recently more than 7 days before Day 1.

The test may be repeated at the discretion of the investigator at any time during the study. A lactating or pregnant female will not be eligible for participation in this study.

Clinical Laboratory Tests

All subjects will have the laboratory analyses performed as outlined in Table 6. Laboratory samples will be assessed using a certified central laboratory, and these data will be used for all

data analysis. The central laboratory for this study will provide instructions regarding the collection, processing, and shipping of samples.

Clinical chemistry, hematology, and urinalysis labs will be collected according to the schedule shown in Table 1 and Table 2 (± 3 days). Screening labs will be performed within 21 days prior to Day 1 of the Chemoradiation Phase, and results must be reviewed by the Investigator or designee prior to dosing on Day 1. Screening labs may be repeated if clinically indicated to confirm eligibility.

The Principal Investigator or designee as noted on the delegation of authority log will review, initial and date all laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the Investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in Section 7.

A certified local reference laboratory may perform laboratory testing as needed for immediate subject management. For laboratory results that are required per protocol to make study treatment decisions (e.g., to determine eligibility to continue TMZ), results from a certified local lab may be used if central results may not be available prior to dosing. However, the sample for central laboratory analysis should be drawn and sent as per the protocol schedule to be used in the data analysis. In the case of contradictory results, in which the local lab result supports eligibility or treatment decision that would be prohibited based on the central lab result, the local laboratory result must be recorded in the eCRF to be included in the data analysis. Other local laboratory values should not be captured in the eCRF. The appropriate documents will be collected for both the central and local laboratories, as needed.

For Day 22 hematology assessments during the Adjuvant Phase (performed when adjuvant TMZ treatment is ongoing) a certified local laboratory may be used alone without central testing. If a central laboratory result is not available for the Day 22 lab, the local lab results for platelet count and absolute neutrophil count (ANC) will be recorded in the eCRF.

Table 6. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands (if detected) Lymphocytes Monocytes Basophils (if detected) Eosinophils (if detected) Absolute platelet count Mean corpuscular volume (MCV) **Coagulation (screening Only)** Prothrombin time (PT) Activated PartialThromboplastin Time (aPTT) International normalized ratio (INR)	Blood urea nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase (ALP) Gamma-glutamyl transferase (GGT) Sodium Potassium Calcium Inorganic phosphorus Glucose Cholesterol Triglycerides Total protein Uric Acid Albumin Lactate dehydrogenase (LDH) Magnesium Chloride Bicarbonate	Specific gravity Ketones pH Protein Blood Glucose Microscopic examination if dipstick results are positive

For any laboratory test value outside the reference range that the Investigator considers to be clinically significant:

- The Investigator will follow the out-of-range value to a satisfactory clinical resolution.
- A laboratory test value that requires a subject to be discontinued or interrupted from any study treatment agent (ABT-414, TMZ or RT) or from the study, or requires a subject to receive treatment (medical intervention) will be recorded as an adverse event.

MRI and Clinical Assessment for Disease Progression

A brain MRI scan with and without contrast, performed at any time after diagnostic surgery or biopsy but prior to randomization, is required to serve as a baseline scan for RANO tumor response assessments. The most recent scan done prior to randomization will be used as the baseline scan. A baseline MRI must include the image sequences (T1 with and without contrast and T2 FLAIR) required for making RANO assessments. If a subject starts chemoradiation ≤ 28 days after surgery, the post-operative MRI scan (including an intraoperative or post-operative MRI scan) performed as part of standard care prior to Screening may be used as

the baseline scan for RANO assessments; if so, this scan must be included with the submission of scans for central imaging reviews. If the subject starts chemoradiation more than 28 days after surgery, then the baseline MRI must be performed within 21 (preferably fewer) days prior to Day 1 Week 1 of Chemoradiation and must allow sufficient time to revise the radiation therapy plan if needed due to a significant change in tumor since surgery.

Post-baseline MRIs with contrast will be obtained ≤ 14 days before Day 1 of each odd-numbered cycle (Cycles 1, 3, 5, etc.) of the Adjuvant Therapy Phase; approximately every 8 weeks of the Follow-Up Phase (≤ 14 days before each Follow-Up Visit), and at the Final Study Drug Visit (if the subject withdraws from the study prior to disease progression and has not had an MRI with contrast within the previous 3 weeks). At the discretion of the Investigator, MRI with contrast may be performed at additional times as clinically indicated or as needed to assess whether there has been progression of disease. If the subject discontinues study drug prior to disease progression, every effort should be made to acquire MRIs according to the same schedule while the subject is willing.

Scheduled tumor assessments are not affected by delays in therapy or drug holidays. Subjects will continue to be monitored by the same techniques as at baseline. Ideally, subjects should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes. The Standardized Brain Tumor Imaging Protocol should be used wherever technically feasible at the site.[6]

Changes in measurable lesions over the course of therapy and changes in systemic corticosteroid dose and clinical status will be assessed, and the assessment of disease progression will be determined by the Investigator using the updated Response Assessment in Neuro-Oncology (RANO) criteria[7] (Appendix I). MRI images will also be reviewed centrally by an independent blinded reviewer for radiographic evidence of disease progression.

Scan Submission Quality Assurance and Quality Control in Imaging

The designated central imaging vendor will track all scans of all subjects received from the sites and will request/query missing/incomplete scans. Scan submissions should include pre-study (pre-surgical and post-surgery) scans and all on-study scans. Furthermore, if the scans arrive in unacceptable quality or in a non-acceptable format, the site will be informed to provide substitute scans.

Scans may be uploaded by the participating centers via a central imaging platform. Please refer to the imaging guidelines/manual for more details regarding submission of images, qualification of sites, and imaging QA/QC level description.

Assignment of Subject Numbers

All screening activities must be completed and reviewed prior to randomization. Subjects who meet the eligibility criteria will proceed to randomization via the IRT system. Randomization may be registered in IRT up to 3 days prior to Day 1 Week 1 of chemoradiation.

Screening numbers will be unique 5-digit numbers and will begin with 10101 with the first 3 digits representing the investigative site, and the last 2 digits representing the subjects at that site. Randomized subjects will keep their screening number as their subject number. Subjects will be randomized on Day 1 as described in Section 5.9 and will receive a separate unique 6 digit randomization number that will be recorded automatically in the eCRF through the IRT system. This randomization number will be used only by the Sponsor for loading the treatment schedule into the database.

Systemic Corticosteroid Use

Systemic corticosteroid dates of use, dosing, and frequency will be recorded as concomitant medications beginning from 7 days prior to the start of chemoradiation and throughout the study.

Neurocognitive Function – Verbal Memory and Executive Function

Two brief, sensitive, repeatable, highly standardized, and objective tests will be used to assess neurocognitive changes across time; the Hopkins Verbal Learning Test-Revised (HVLT-R) and COWA-FAS verbal fluency test. The COWA test form used in this trial (which includes the letters F, A, and S in English and frequency-matched letters in other languages) is different than the two forms used as part of the Multilingual Aphasia Exam (MAE) which use C, F, and L or P, R, and W. Several previous studies of neurocognitive function in subjects with GBM or metastatic brain tumors have used the MAE COWA test as part of a multi-domain assessment called the Clinical Trial Battery (CTB).[8,9] The FAS and CFL forms of the COWA test may vary in difficulty, which could in turn influence subject performance.[10] The Trail Making Test (TMT), which is also included as part of the CTB will not be used in this study because treatment-related changes in visual acuity may confound the interpretation of neurocognitive outcomes measured by this assessment. Administration of the HVLT-R and COWA-FAS verbal fluency test is practical in terms of burden on the subject.[11,12] Neurocognitive function has been

demonstrated to predict tumor progression[13] and to independently predict survival for subjects with central nervous system tumors.[14-17]

The neurocognitive tests are administered by certified test administrators at each site, and the total time for the cognitive testing is approximately 30 minutes, as follows:

Cognitive Domain	Test	Administration Time (minutes)
Memory	Hopkins Verbal Learning Test-Revised[18]	5
Executive Function	FAS verbal fluency[10]	5

The healthcare professional (e.g., nurse, psychologist) at each study site who is responsible for test administration in this study must be trained and pre-certified. Training materials and testing forms are produced, distributed and collected by VeraSci (formerly NeuroCog Trials) (http://www.verascience.com). See the VeraScitesting materials for additional details regarding administration and scoring of these assessments.

Subjects will complete the neurocognitive testing as outlined in Table 1 and Table 2. Neurocognitive testing should be completed prior to study drug administration and any other study procedures being performed at these visits, and prior to discussing with the subject that their disease has progressed.

Health-Related Quality of Life (HRQoL)

Health-related quality of life will be assessed with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) version 3[20] and with the EORTC Brain Cancer module (QLQ-BN20) module.[21] The QLQ-C30 is 30-item patient self-report questionnaire composed of both multi-item and single scales, including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/HRQoL scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Subjects rate items on a four-point scale, with 1 as "not at all" and 4 as "very much." The QLQ-C30 was developed and validated for use in a cancer patient population, and its reliability and validity is highly consistent across different language-cultural groups.[20]

The QLQ-BN20 is a 20-item patient self-report questionnaire that was developed specifically as a module for subjects with brain cancer. It consists of four domain scores, including future uncertainty, visual disorder, motor dysfunction, and communication deficit, as well as seven individual symptom items (headache, seizures, drowsiness, hair loss, itching, difficulty

with bladder control, and weakness of both legs). Subjects rate items on a four-point scale, with 1 as "not at all" and 4 as "very much." A retrospective validation study has been conducted confirming its psychometric validity.[22]

Subjects will complete the EORTC QLQ-C30/BN20 as outlined in Table 1 and Table 2. These assessments should be completed prior to study drug administration and any other study procedures being performed at these visits, and prior to discussing with the subject that their disease has progressed.

MD Anderson Symptom Inventory – Brain Tumor

The MD Anderson Symptom Inventory brain tumor module (MDASI-BT) is a patient self-report or interviewer-administered measure used to assess the severity of multiple brain tumor-related symptoms and the impact of these symptoms on daily functioning in the last 24 hours.[23] It was developed and validated specifically for use in patients with primary brain tumors. The MDASI-BT consists of the core 13 symptom items (pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or tingling), and 6 interference items (general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life and 9 brain tumor-specific symptom items: weakness on one side of the body, difficulty understanding, difficulty speaking, seizures, difficulty concentrating, vision, change in appearance, change in bowel pattern (diarrhea or constipation), and irritability. MDASI-BT items are rated from 0 to 10, with 0 indicating that the symptom is either not present or does not interfere with the patient's activities and 10 indicating that the symptom is "as bad as you can imagine" or "interfered completely" with the patient's life. Symptoms can be grouped into measured domains including neurologic, cognitive, affective, constitutional, general, and gastrointestinal. The interference items can be grouped into activity- and mood-related interference domains.

Subjects will complete the MDASI-BT as outlined in Table 1 and Table 2. These assessments should be completed prior to study drug administration and any other study procedures being performed at these visits, and prior to discussing with the subject that their disease has progressed.

EuroQol 5 Dimensions (EQ-5D-5L) and EuroQol 5 Dimension Value Sets (EQ-5D-VAS)

The EuroQol 5 Dimensions (EQ-5D-5L) is a generic preference instrument that has been validated in numerous populations. The EQ-5D-5L has five dimensions: mobility, self-care,

usual activities, pain/discomfort and anxiety/depression. These dimensions are measured on a five level scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L also contains a visual analog scale (VAS) to assess the subject's overall health.[24]

Subjects will complete the EQ-5D-5L and EQ-5D-VAS as outlined in Table 1 and Table 2. These assessments should be completed prior to study drug administration and any other study procedures being performed at these visits, and prior to discussing with the subject that their disease has progressed.

NEI VFQ-25

Visual functioning will be assessed with the National Eye Institute Visual Functioning Questionnaire – 25-item version questionnaire (NEI-VFQ-25), a reliable and valid 25-item version of the 51-item National Eye Institute Visual Function Questionnaire (NEI-VFQ). The NEI-VFQ-25 evaluates visual function and limitations in daily activities related to impaired visual function as well as the impact of ocular disease on patients' lives. The NEI VFQ-25 is a patient self-report questionnaire consisting of 25 questions, with a total score and subscale scores ranging from 0 – 100. In this questionnaire, the score of 0 corresponds to the lowest and of 100 to the highest vision-related quality of life. There are 12 subscales, each consisting of one or more questions, including general health, general vision, ocular pain, near activities, distance activities, vision specific social functioning, vision specific mental health, vision specific role difficulties, vision specific dependency, driving, color vision and peripheral vision.

The NEI VFQ-25 will be assessed as outlined in Table 1 and Table 2.

Treatment Satisfaction Question

A single treatment satisfaction question will be used to assess the subject's treatment experience.

The following question asks about your treatment experience. Please choose the response that best describes how you feel about the study treatment.

1. Based on your experience in this study, would you choose to receive the study treatment again?

	(Circle One)
Definitely would	1
Probably would	2
Unsure	3
Probably would not	4
Definitely would not	5

Survival Assessment

Overall survival will be assessed quarterly after treatment discontinuation until death. This can be conducted remotely such as by phone or other means.

Blood Biomarker Sample Collection

The collection, processing and storage should be performed as described in the study-specific laboratory manual.

Collection for Plasma Markers

Approximately 12 mL of blood will be collected pre-dose at time points outlined in Table 3. The collection, processing and storage should be performed as described in the study-specific laboratory manual.

Blood Collection for Serum Markers

Approximately 5 mL of blood will be collected pre-dose as outlined in Table 3. The collection should be performed as described in the study-specific laboratory manual.

Collection of Tumor Tissue

Subjects must consent to provide a tissue sample. Tissue blocks should be submitted as described in the study-specific laboratory manual. Tissue blocks can be returned upon request. Collection and submission of the samples should be performed as described in the study-specific laboratory manual. If permission is granted to submit slides, instructions will be provided to the sites at that time.

Subjects should have at least 1 block of tumor tissue; submission of 2 blocks is strongly encouraged to maximize the chances of eligibility. The size of tumor on the submitted block(s) should be sufficient to represent at least 1 square centimeter of viable glioblastoma tumor when a

section is cut onto a slide. In **rare** circumstances, alternative forms of tissue submission may be considered on a case by case basis in discussion with the Neuro-Medical Oncology Chair and Study Neuro-Pathologist.

Relapse Tissue Collection

For all subjects in the study who undergo tumor surgery for medically directed reasons upon suspected disease progression or for other medical reasons during treatment, biopsy/resection material can be made available for biomarker analysis.

Blood Samples for ABT-414 and Total ABT-806 Drug Concentration Measurements

A single blood draw at the specified time points will allow for ABT-414 and Total ABT-806 pharmacokinetic analysis. Samples will be collected into appropriately labeled evacuated serum collection tubes without a gel separator at the time points specified in Table 3.

Pharmacokinetic (PK) samples should not be drawn from the same arm in which study drug (ABT-414 or placebo) is infused. Samples collected immediately after infusion should be collected after the full infusion procedure is complete.

Approximately 3.0 mL of blood will be collected to provide approximately 1.5 mL serum at each time point for both ABT-414 and Total ABT-806 determination (approximately 0.75 mL required for each assay).

The time that each serum sample is collected will be recorded to the nearest minute in the source documents and in the appropriate eCRFs. The date and start/end time of each ABT-414/placebo infusion shall also be recorded, in the appropriate eCRFs, to the nearest minute on days when pharmacokinetics sampling is performed.

ADA and Neutralizing ADA (nADA) Assays

Approximately 3.0 mL of blood for ADA/nADA analysis will be collected into appropriately labeled serum collection tubes at the time points specified in Table 3. It is important that serum, and not plasma, be harvested.

ADA/nADA samples should not be drawn from the same arm in which study drug is infused.

Approximately 3.0 mL of blood will be collected to provide approximately 1.5 mL serum at each time point for both ADA and nADA determination (approximately 0.75 mL required for each

assay). Samples for the nADA assay will be analyzed upon request. Pharmacokinetics and ADA samples collected may also be used for future assay development and validation activities.

The time that each serum sample is collected will be recorded to the nearest minute in the source documents and in the appropriate eCRFs.

Blood Samples for Unconjugated Cys-mcMMAF Assay

Blood samples for unconjugated Cys-mcMMAF for pharmacokinetic analysis will be collected in evacuated potassium edetic acid (ethylenediaminetetraacetic acid) K_2EDTA-containing collection tubes at the time points specified in Table 3. The time that each sample is collected will be recorded to the nearest minute in the source documents and in the appropriate eCRFs.

The collection, processing and storage should be performed as described in the study-specific laboratory manual.

Plasma concentration of unconjugated Cys-mcMMAF will be determined using validated methods under the supervision of Drug Analysis Department at AbbVie.

Blood Samples for Pharmacogenetic Analysis

One 4 mL whole blood sample for DNA isolation will be collected on Day 1 from each subject who consents to provide a sample for pharmacogenetic analysis. If the sample is not collected on Day 1, it may be collected at any time throughout the study.

Samples will be processed and shipped to AbbVie or a designated laboratory for deoxyribonucleic acid (DNA) extraction and long-term storage. Instructions for the preparation and shipment of pharmacogenetic samples will be provided in the study specific lab manual.

Abbvie will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on ABT-414 (or drugs of this class) continues but no longer than 20 years.

4.3 Definition of Disease Assessments

Progression Free Survival

Time to progression-free survival (PFS) will be defined as the number of days from the date of randomization to the date of earliest disease progression based on RANO criteria or to the date of death, if disease progression does not occur. All disease progression will be included regardless of whether the event occurred while subject was taking the study drug or had previously

discontinued the study drug. All events of death will be included for subjects who had not experienced disease progression. Subjects for whom neither death nor progression have been documented will be right-censored on the date of the last adequate assessment of disease. PFS will be analyzed by the Kaplan-Meier method.

The phenomenon of pseudoprogression should be considered when determining if there is disease progression, particularly during the first 3 months after radiotherapy. Pseudoprogression refers to the occurrence of "early delayed radiation reactions" that occur usually within the first 3 months post radiation treatment. These transient adverse signs and symptoms may spontaneously improve without therapy or with supportive care such as corticosteroids. Thus, care should be taken in making the diagnosis of tumor progression or recurrence (Appendix I).

Overall Survival

Overall survival (OS) will be defined as the number of days from the date of randomization to the date of death due to any cause. Subjects for whom death has not been documented will be right-censored at the last date the subject is documented to be alive. OS will be analyzed by the Kaplan-Meier method.

Karnofsky Performance Status

Changes from baseline will be summarized for each scheduled post-baseline visit and for the Final Study Drug Visit for Karnofsky performance status. The baseline will be defined as the last measurement collected before randomization. The post-baseline visit will include those occurring within 49 days of the last dose of study drug. The Final Study Drug Visit will be defined as the last post-baseline measurement collected within 49 days of the last dose of study drug (ABT-414, or placebo).

5.0 TREATMENT PLAN

Treatment must begin ≤ 7 weeks after brain tumor biopsy/resection.

5.1 Treatment Plan Overview

During the Chemoradiation Phase, all subjects will undergo focal RT, with one treatment given daily 5 days per week over approximately 6 weeks (and no more than 7 weeks). TMZ will be administered 75 mg/m^2 orally once daily continuously from Day 1 of radiotherapy to the last day of radiation for a maximum of 49 days. Subjects in Arm A will receive ABT-414 at 2.0 mg/kg IV infusion once every 2 weeks (on Day 1 of Weeks 1, 3, and 5) during this period. Subjects in Arm B will receive placebo IV infusion once every 2 weeks (on Day 1 of Weeks 1, 3, and 5) during this period. Treatment in the Chemoradiation Period must begin ≤ 49 days after surgery diagnosing GBM. Occasionally, a subject might require a staged or two-surgery approach; for such cases, subjects will still be considered eligible for this study if the latest surgery was performed within 30 days after the initial surgery/biopsy diagnosing GBM and if all screening procedures are completed and chemoradiation treatment begins ≤ 49 days after the latest surgery.

The start of the first cycle during the Adjuvant Phase will be scheduled approximately 28 days after the last day of chemoradiation. The AbbVie Medical Monitor or RTOG Neuro-Oncology should be notified if Adjuvant Phase treatment is to be started more than 42 days after the last day of chemoradiation. During the Adjuvant Phase, all subjects will receive oral TMZ 150 – 200 mg/m^2 once daily on Days 1 – 5 of each 28-day cycle for 6 cycles. Subjects in Arm A will receive ABT-414 at 1.25 mg/kg on Day 1 and Day 15 of each 28-day cycle for a total of 12 cycles. Subjects in Arm B will receive placebo IV infusion on Day 1 and Day 15 of each 28-day cycle for a total of 12 cycles. Adjuvant treatment will be discontinued upon determination of tumor progression as defined by RANO criteria, unacceptable toxicity, or refusal to continue study treatment.

<u>Duration of Adjuvant TMZ</u>

Subjects demonstrating continued benefit and no unacceptable toxicity from adjuvant TMZ can continue TMZ to a maximum of 12 cycles at the discretion of the Investigator if this is considered an acceptable standard of care per local regulations.

Subjects in Arm A will receive ABT-414 on Day 1 and Day 15 of each 28-day cycle. Subjects in Arm B will receive placebo IV infusion on Day 1 and Day 15 of each 28-day cycle. Subjects who discontinue TMZ for TMZ-related toxicity will continue ABT-414/placebo treatment. Subjects who discontinue ABT-414 or placebo due to ABT-414-related or placebo-related

toxicity prior to completion of the Adjuvant Therapy Phase will continue TMZ treatment as scheduled.

Duration of Adjuvant ABT-414 or Placebo

If after completing 12 cycles of adjuvant ABT-414/placebo, the subject is tolerating treatment and the Investigator believes the subject is continuing to benefit from ongoing study drug treatment, the Investigator may extend the Adjuvant Phase with ABT-414/placebo after consultation with the Neuro-Medical Oncology Chair or AbbVie Medical Monitor. The ABT-414/placebo will continue at the same dosing schedule, as long as disease progression has not been determined.

5.2 Radiation Therapy

Chemoradiation treatment must begin within 7 WEEKS after biopsy/resection.

The schema at the beginning of the protocol should be followed.

Within 3 months after site initiation, assessment of specific technology requirements is required for this study; please refer to the study-specific radiation manual for detailed instructions. Pneumocystis (*jirovecii*) pneumonia (PCP) prophylaxis should be per local regulation guidelines during the radiation phase (Section 5.8).

5.2.1 Treatment Technology

This protocol requires photon treatment. 3D-CRT and IMRT are allowed. Any of the methods of IMRT, including fixed gantry IMRT, helical tomotherapy, or volumetric arc therapy (VMAT) may be used, subject to protocol localization and dosimetry constraints. Computerized tomography (CT)-based treatment planning is necessary to assure accuracy in the selection of field arrangements. MRI-fusion for accurate target delineation is strongly recommended.

Treatment shall be delivered with megavoltage (MV) machines of a minimum energy of 6 MV photons. Selection of the appropriate photon energy(ies) should be based on optimizing the radiation dose distribution within the target volume and minimizing dose to non-target normal tissue. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Electron, particle, or implant boost is not permissible. IMRT delivery will require megavoltage radiation therapy machines of energy ≥ 6 MV.

Treatment may be performed using a **sequential boost** to the contrast-enhanced region of the target; otherwise treatment may be delivered **straight through** without sequential boost detailed

in Section 5.2.4. Any institution can choose any one technique, but once selected, should remain consistent through the completion of this protocol. Subject specific QA (Section 5.2.10) is highly recommended prior to start of treatment and is described in the study specific radiation manual.

5.2.2 Immobilization and Simulation

Immobilization

Proper immobilization is critical for this protocol. Subject setup reproducibility must be achieved using appropriate clinical devices.

Subjects shall be treated in a supine position and immobilized with a thermoplastic mask and headrest. Additional immobilization devices such as a bite block and/or knee-wedge are permitted. In rare instances, based on tumor location and patient anatomy, prone set-up is permissible.

Simulation Imaging

A planning CT scan of the cranial contents with 3.0 mm slice thickness or less will be required which will be fused with the pre- and post-operative MRI scans. Rigid registration is permitted, but deformable fusion is not permitted.

5.2.3 Imaging for Structure Definition, Image Registration/Fusion and Follow-Up

Rigid image registration must be used for the protocol. Deformable fusion is not allowed. Post-operative MRI with T2/fluid attenuated Inversion recovery (FLAIR) and contrast enhanced T1 sequences is required and must be obtained after surgical resection. Additionally, if a subject starts chemoradiation more than 28 days after surgery, the subject will have a brain MRI with T2/FLAIR and contrast enhanced T1 sequences included no more than 21 (but preferably fewer) days prior to Day 1 Week 1 of Chemoradiation Phase to be used as the baseline MRI scan for efficacy analyses; the timing of the MRI must allow sufficient time to revise the radiation therapy plan *if needed* due to a significant change in tumor since surgery. Radiotherapy planning is recommended to be completed as soon as reasonably feasible, but in all cases, chemo-radiotherapy MUST begin NO LATER than 7 weeks after initial biopsy or latest tumor resection.

The scans used for planning **MUST** be submitted as a complete series along with the treatment plan as well. If a pre-operative MRI scan is not available for fusion, fusion with only the post-operative MRI scan is permitted. It is recommended, not required, to obtain the pre-operative MRI scan to assist in treatment planning. Target volume delineation will be based on a contrast enhanced MRI scan obtained after surgery, ideally obtained within 72 hours after surgery although that timing is not mandatory. Pre-operative imaging should be used to guide

identification of target delineation, but critical structures are best contoured on the post-operative MRI and/or CT, as there is expected structural shift between the pre- and post-operative scans.

5.2.4 Definition of Target Volumes and Margins

Differences exist in methods utilized for GTV/CTV/PTV definitions; this protocol accommodates and permits two key philosophical concepts, labeled the "RTOG" and the "EORTC" approaches; each institution will be required to declare upfront which approach they will pursue, and will be required to adhere to that single approach during the conduct of this protocol.

The main "RTOG" approach describes a **sequential boost** or **cone-down** radiotherapy technique which is described below. However, this approach is less widely used in Europe. As such, the radiotherapy technique for sites wishing to follow the "EORTC" approach is also defined below as an alternative **straight through** or **single phase** technique, designed to reflect the broad overall tenets of radiotherapy practices for glioblastoma treatments in EORTC institutions. Although many individual variations on the themes exist, in this multi-institutional international study, these two concepts, as specifically defined within the protocol are permitted, and other variations, unless approved by one of the Radiation Oncology co-chairs, will be considered a major protocol violation. **As mentioned in Section 5.2.1, any institution can choose either of the two techniques, but once selected, must remain consistent through the completion of this protocol for all patients enrolled under this amendment or later by that institution (a site that used the RTOG approach prior to Amendment may switch to the EORTC approach, as long as that approach is maintained until the end of the study). An institution may not choose both techniques, and may not use different techniques for different patients, or different techniques for different physicians within the same institution. Additionally, if an institution starts a patient's treatment with a sequential boost approach using a certain fraction size (e.g., 1.8 GY per fraction), they are expected to complete the cone down with the same fraction size. Institutions must also send a composite plan showing the final accumulated dose distribution. The composite dose distribution will be used to score the plans for critical structure dose. Exceedingly rare exceptions on a case-by-case basis will only be permissible if approved in writing by a Radiation Oncology study chair.**

Note: All structures must be named for digital RT data submission as listed as in the table below. The structures marked as "Required" in the table must be contoured and submitted when applicable. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be

applied exactly as indicated, to ensure appropriate, timely, accurate, and reproducible QA process application to all cases.

Target Structured Labeling: Option 1: RTOG Approach – Sequential Boost

Standard Name	Description	Validation Required/Required When Applicable/Optional
GTV1	GTV to receive 45 or 46 Gy	Required
CTV1	CTV to receive 45 or 46 Gy	Required
PTV1	PTV to receive 45 or 46 Gy	Required
GTV2	GTV to receive 59.4 or 60 Gy	Required
CTV2	CTV to receive 59.4 or 60 Gy	Required
PTV2	PTV to receive 59.4 or 60 Gy	Required

Details Specifications

Target volumes will be based upon post-operative-enhanced MRI. Pre-operative imaging should be used for correlation and improved identification.

GTV1 – Either the T2 or the FLAIR abnormality on the post-operative MRI scan, inclusive of all contrast-enhancing T1 abnormality on the post-operative MRI and the surgical cavity. Areas of vascular infarction or compromise of normal brain should be excluded if they are deemed to not be part of the original pre-operative tumor volume, and a comparison of the pre- and post-operative scans will assist in this process.

CTV1 – Is defined as the GTV1 plus a margin of 2 cm, which may be reduced around natural barriers to tumor growth such as the skull, ventricles, falx, etc. to as low as 0 mm to "fixed" barriers, i.e., bone, and falx and as low as 3 – 5 mm to “non-rigid” barriers such as brain stem, ventricles, etc. If no surrounding edema is present (i.e., the FLAIR and/or T2 MR images do not demonstrate any significant abnormality), the CTV 1 in those instances should include the post-operative MRI enhancement and the surgical resection cavity plus a 2 cm margin, with reduction permitted as described above.

GTV2 – Contrast enhancing T1 abnormality and the surgical cavity on the post-operative MRI scan. Areas of vascular infarction or compromise of normal brain should be excluded if they are deemed to not be part of the original pre-operative tumor volume, and a comparison of the pre- and post-operative scans will assist in this process. The exception to this is the polar tumor, e.g., temporal lobe, frontal lobe, or occipital lobe tip, where a gross total resection is achieved, and no post-operative "cavity" remains, consequential to the partial or total lobectomy. For these

uncommon patients, GTV2 will be defined as either the T2 or the FLAIR abnormality on the post-operative MRI scan, i.e., in these cases, GTV1 = GTV2.

CTV2 – Is defined as the GTV2 plus a margin of 2 cm. The CTV2 margin may be reduced around natural barriers to tumor growth such as the skull, ventricles, falx, etc. to as low as 0 mm to "fixed" barriers, i.e., bone, and falx and as low as 3 – 5 mm to "non-rigid" barriers such as brain stem, ventricles, etc.

PTV1 and PTV2 – In general the PTV is the CTV plus a geometric 5 – 7 mm expansion in all dimensions. This can be reduced to 4 mm if **daily volumetric (3D)** or **non-volumetric (2D) IGRT** is utilized. PTV may extend beyond bony margins and the skin surface.

Target Structure Labeling: Option 2: EORTC Approach – Single Phase

Standard Name	Description	Validation Required/Required When Applicable/Optional
GTV	GTV to receive 59.4 or 60 Gy	Required
CTV	CTV to receive 59.4 or 60 Gy	Required
PTV	PTV to receive 59.4 or 60 Gy	Required

Detailed Specifications

Target volumes will be based upon the post-operative-enhanced MRI. Pre-operative imaging should be used for correlation and improved identification.

GTV – Contrast enhancing T1 abnormality and the surgical cavity on the post-operative MRI scan. Areas of vascular infarction or compromise of normal brain should be excluded if they are deemed to not be part of the original pre-operative tumor volume, and a comparison of the pre- and post-operative scans will assist in the process. The exception to this is the polar tumor, e.g., temporal lobe, frontal lobe, or occipital lobe tip, where a gross total resection is achieved, and no post-operative "cavity" remains, consequential to the partial or total lobectomy. For these uncommon patients, GTV will be defined as either the T2 or the FLAIR abnormality on the post-operative MRI scan.

CTV – Is defined as the GTV plus a margin of 2 cm, which may be modified in two respects: 1) The CTV margin may be reduced around natural barriers to tumor growth such as the skull, ventricles, falx, etc., to as low as 0 mm to "fixed" barriers, i.e., bone, and falx and as low as 3 – 5 mm to "non-rigid" barriers such as brain stem, ventricles, etc., and 2) in all areas of persisting edema on FLAIR (preferred) or T2-weighted MRI images, the CTV will be expanded beyond 2 cm to include these regions.

PTV – In general the PTV is the CTV plus a geometric 5 mm expansion in all dimensions. This can be reduced to 4 mm if **daily volumetric (3D)** or **non-volumetric (2D) IGRT** is utilized. PTV may extend beyond bony margins and up to the skin surface.

5.2.5 Definition of Critical Structures and Margins

Note: For either "RTOG" or "EORTC" approaches, all structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structure does not conform to the standard Digital Imaging and Communications in Medicine (DICOM) name listed. Capital letters, spacing and use of underscored must be applied exactly as indicated.

All structures should be contoured on the planning CT, using the post-operative MRI for guidance. Due to variance in eye position between the CT and MRI, if possible, the lenses, retina, and optic nerves should be contoured using the CT dataset only.

Special consideration should be given to avoid doses greater than the prescription dose within the scalp as well as limiting exit dose through the oral cavity and mucosa.

Organs-at-Risk Structure Labeling: Option 1 and 2: RTOG and EORTC Approaches

Standard Name	Description	Validation Required/Required When Applicable/Optional
Lens_L	Left lens	Required
Lens_R	Right Lens	Required
Retina_L	Left retina	Required
Retina_R	Right retina	Required
OpticNrv_L	Left optic nerve	Required
OpticNrv_R	Right optic nerve	Required
OptNrv_PRV_L	Left optic nerve planning risk volume	Required
OptNrv_PRV_R	Right optic nerve planning risk volume	Required
OpticChiasm	Optic chiasm	Required
OptChiasm_PRV	Optic chiasm planning risk volume	Required
BrainStem	Brainstem	Required
SpinalCord	Spinal cord	Required
Brain	Whole brain parenchyma	Required
Glnd_Lacrimal_L	Left lacrimal gland	Required
Glnd_Lacrimal_R	Right lacrimal gland	Required
Cochlea_L	Left cochlea	Optional
Cochlea_R	Right cochlea	Optional

Detailed Specifications

Please refer to the organs at risk contouring guidelines and supplement published in Radiotherapy and Oncology: http://www.thegreenjournal.com/article/S0167-8140(15)00080-8/pdf.

Lens_L, Lens_R, Retina_L, Retina_R, OpticNrv_L, OpticNrv_R: Due to variance in eye position between the CT and MRI, if possible, the structures should be contoured using the CT dataset only. The retina is defined as the innermost of the three layers that form the wall of the eyeball. Please contour 5 mm posterior wall of the eye. Please refer to supplemental figure V:Va-Vg in the organs at risk contouring guidelines.

OptNrv_PRV_L: Left optic nerve should be expanded by a volumetric expansion of 3 mm.

OptNrv_PRV_R: Right optic nerve should be expanded by a volumetric expansion of 3 mm.

OpticChiasm: Located above the pituitary fossa, the optic chiasm includes both anterior and posterior limbs. It is best visualized on post-operative T2/FLAIR MRI Sequence, but should be confirmed on CT dataset due to potential variation in CT/MRI fusion.

OptChiasm_PRV: Optic chiasm should be expanded by a volumetric expansion of 3 mm.

BrainStem: Brainstem contour should include all three components: midbrain, pons, and medulla. The brainstem is bordered superiorly by the tentorial incisures and inferiorly by the foramen magnum. It can be visualized on post-operative MRI sequence, but should be confirmed on CT dataset due to potential variation in CT/MRI fusion.

SpinalCord: Spinal cord should be contoured, wherever possibly, on the CT dataset only.

Brain: Whole brain parenchyma includes all intracranial contents, inclusive of target volumes. Because some volumetric change could have occurred in the whole brain parenchyma due to evolving post-operative changes, it is recommended, whenever possible to contour the whole brain parenchyma using the CT dataset only.

Cochlea_L, Cochlea_R: Although not mandated, it is recommended that the left and right cochlea be contoured using the CT dataset on bone window.

Glnd_Lacrimal_L, Glnd_Lacrimal_R: The lacrimal gland is located supero-laterally to the extraconal portion of the orbit, medial to the zygomatic process of the frontal bone and is superior to the lateral rectus muscle and lateral to the superior rectus muscle. Please refer to supplementary figure V:Vd-Vh in the organs at risk contouring guidelines paper.

5.2.6 Dose Prescription

Note: The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priority table should be used during dose optimization. It is important to remember that ideal plans might not be achievable in all cases. Thus the Compliance Criteria table could be different than the information given here. Cases will be scored using the Compliance Criteria table.

Option 1: RTOG Approach – Sequential Boost

Target Standard Name	Dose (Gy)	Fraction Size (Gy)	# of Fractions	Dose Specification Technique
PTV1	44 – 46	2	23	≥ 95% of PTV receives 46 Gy
Optional:PTV1	45	1.8	25	≥ 95% of PTV receives 45 Gy
PTV2	60	2	30	95% of PTV should receive ≥ 60 Gy
Optional:PTV2	59.4	1.8	33	95% of PTV should receive ≥ 59.4 Gy

Option 2: EORTC Approach – Single Phase

Target Standard Name	Dose (Gy)	Fraction Size (Gy)	# of Fractions	Dose Specification Technique
PTV	60	2	30	95% of PTV should receive ≥ 60 Gy
Optional:PTV	59.4	1.8	33	95% of PTV should receive ≥ 59.4 Gy

5.2.7 Compliance Criteria

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results.

Normalization of Dose: 95% of the PTV ($D_{95\%}$) should be covered by 100% of the prescription dose.

Option 1: RTOG Approach – Sequential Boost

Target Volume Constraints and Compliance Criteria

Name of Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
PTV1	$D_{95\%}$(%)*	100% of prescribed dose (PD)	at least 95% of PD
PTV2	$D_{95\%}$(%)*	100% of prescribed dose (PD)	at least 95% of PD
	$D_{10\%}$(%)*	≤ 105% of PD	≤ 110% of PD
	$D_{0.03cc}$(%)*	≤ 106% of PD	≤ 112% of PD

* Dose is normalized to prescription dose (PD) in Gy.
Variation Acceptable ranges exclude those from Per Protocol.

Option 2: EORTC Approach – Single Phase

Target Volume Constraints and Compliance Criteria

Name of Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
PTV	$D_{95\%}$(%)*	100% of prescribed dose (PD)	at least 95% of PD
	$D_{10\%}$(%)*	≤ 105% of PD	≤ 110 of PD
	$D_{0.03cc}$(%)*	≤ 106% of PD	≤ 112% of PD

* Dose is normalized to prescription dose (PD) in Gy.

Variation Acceptable ranges exclude those from Per Protocol.

Normal Structure Constrains and Compliance Criteria for Both RTOG and EORTC Approaches

Name of Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
SpinalCord	$D_{0.03cc}$	≤ 50 Gy	
Brainstem	$D_{0.03cc}$	≤ 55 Gy	≤ 60 Gy
OpticChiasm_PRV	$D_{0.03cc}$	≤ 55 Gy	≤ 60 Gy
OptNrv_PRV_L or OptNrv_PRV_R	$D_{0.03cc}$	≤ 55 Gy	≤ 60 Gy
Retina_L or Retina_R	$D_{0.03cc}$	≤ 45 Gy	≤ 50 Gy
Brain	$D_{5\%}$	≤ 65 Gy	≤ 67 Gy
Lens_L or Lens_R	$D_{0.03cc}$	≤ 7 Gy	≤ 10 Gy
Glnd_Lacrimal_L or Glnd_Lacrimal_R	$D_{0.03cc}$	≤ 40 Gy	≤ 45 Gy
Cochlea_L or Cochlea_R	Mean dose	≤ 45 Gy	≤ 50 Gy

Note: A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plan falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

Exceptions:

1. SpinalCord does not have a Variation Acceptable; Deviation Unacceptable occurs when SpinalCord dose limit for Per Protocol is not met.
2. Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met for both OptNrv_PRV_L and OptNrv_PRV_L; or OptNrv_PRV_L if the subject does not have a serviceable vision in the right eye; or OptNrv_PRV_R if the subject does not have a serviceable vision in the left eye.
3. Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met for both Retina_L and Retina_R; or Retina_L if the subject does not have serviceable vision in the right eye; or Retina_R if the subject does not have serviceable vision in the left eye.

4. Exceeding the dose limits for Variation Acceptable for Lens_L or Lens_R will not be scored as Deviation Unacceptable.

Delivery Compliance Criteria

	Per Protocol	Variation Acceptable
Start date	≤ 7 weeks after surgery	None
Interruptions	≤ 4 days	5 – 7 days

5.2.8 Treatment Planning Priorities

Critical Structure and Target priorities must be listed in order of decreasing importance.

1. SpinalCord
2. BrainStem
3. OptChiasm_PRV
4. OptNrv_PRV_L and OptNrv_PRV_R
5. PTV1
6. PTV2 (If using the EORTC technique, PTV1 and PTV2 should be replaced by PTV)
7. Brain
8. Retina_L and Retina_R
9. Glnd_Lacrimal_L and Glnd_Lacrimal_R
10. Lens_L and Lens_R

In the event that an OAR with higher priority that PTV2 or PTV (depending on which approach is taken e.g., "RTOG" or "EORTC") is in immediate proximity to PTV2 or PTV such that dose to the OAR cannot be constrained within Unacceptable Deviation limits, then D95% for PTV2 or PTV should be lowered to Varian Acceptable range to ensure that the OAR with higher priority does not exceed Unacceptable Deviation limits. If this approach does not constrain the OAR with higher priority than PTV2 or PTV within Unacceptable Deviation limits, then D95% for PTV2 or PTV can be further lowered to below but as close as possible to Variation Acceptable range to ensure that the OAR with higher priority does not exceed Unacceptable Deviation limits; this will be scored as an Unacceptable Deviation for PTV2 or PTV.

5.2.9 Dose Calculations

Required algorithms
Acceptable choices of algorithm are listed at http://rpc.mdanderson.org/rpc/Services/Anthropomorphic_%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf. Any algorithm used for this study must be credentialed by IROC Houston.

Plan Review and Evaluation
Traditional DVHs and dose distribution displays will be used for plan review and evaluation DVHs will also be used for retrospective outcome analysis.

Dose matrix resolution
Dose matrix grid size must be 3 mm × 3 mm × 3 mm or smaller

5.2.10 Subject-Specific QA

For photon IMRT plans, subject specific QA is highly recommended. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 3% dose difference and 3 mm distance to agreement. For plans with highly modulated dose distributions a 5% dose difference and 3mm distance to agreement criterion may be used. The pass rate should be at least 90% measured for the entire plan.

Subject-specific QA data should be kept on record at each institution but will not be centrally collected or reviewed by RTOG.

5.2.11 Daily Treatment Locations/IGRT

Imaging should be performed at least once per week. Daily image-guided radiation therapy (IGRT) is optional for this protocol, and image-guidance is per individual institutional standards and the margins stated in Section 5.2.4. The RTOG defines IGRT as a computer assisted process. That is, image handling together with calculation of shift and rotations (if available) must be determined with computer assistance. Acceptable non-volumetric or two-dimensional IGRT systems include: 1) Orthogonal or near-orthogonal 2D imaging that is integrated with the functioning of the delivery device. These systems can use the treatment beam or special kV x-ray head(s) positioned at a known position in the treatment room. Acceptable volumetric or three-dimensional IGRT systems include: 1) A diagnostic quality CT scanner positioned with a known geometry in the treatment room. 2) Volumetric cone-beam devices that use either MV or kV x-ray beam. 3) Tomotherapy technology that uses a fan-beam imaging approach.

For this study, the cranium is used for image registration. It is important to include as much of the anatomy of this structure as possible to ensure correct alignment of the head. **Caution should be taken to avoid excess repeat imaging on a given treatment day to minimize subject dose outside the treatment region, and steps to control subject position to less than 3 mm should not be taken.**

5.2.12 Case Review

These reviews will be ongoing and performed remotely by the Radiation Oncology study chair or his/her designee.

Digital RT Data Submission to RTOG Using the TRIAD Portal

RTOG will provide sites with the American College of Radiology Imaging Network's image acquisition and management software, Transmission of Imaging and Data (TRIAD), via electronic installation. TRIAD-OA offers a web-based, software solution allowing institutions to submit DICOM data securely through electronic transmission. Internal to the site, TRIAD allows the site to "DICOM push" from the site's Treatment Planning System (TPS), thus eliminating the need to burn physical media. Once the institution has transferred the RT data onto a TRIAD workstation, the software will anonymize, encrypt, and submit the DICOM RT data via secure internet to the RTOG image archive. For more information please visit the TRIAD web site at https://triad.acr.org.

TRIAD technical assistance may be requested by e-mailing TRIAD-Support@acr.org. Please always include the institution name and trial number when requesting TRIAD technical assistance.

Summary of Dosimetry Digital Data Submission Item	**Due**
Preliminary Dosimetry Information	Within 1 week of start of RT

Digital data submission includes the following:

- DICOM Items:
- DICOM Post-Op MR ENTIRE Post-Op Series must be submitted along with the RT data
- DICOM CT Data Set
- DICOM Dose – Initial
- DICOM Dose – Boost
- DICOM Dose – Composite

- DICOM RT Plan – Initial
- DICOM RT Plan – Boost

5.2.13 Radiation Therapy Adverse Events

Acute

Expected acute radiation-induced toxicities include hair loss, fatigue, and erythema or soreness of the scalp. Potential acute toxicities include nausea and vomiting as well as temporary aggravation of brain tumor symptoms such as headaches, seizures, and weakness. Reactions in the ear canals and on the ear should be observed and treated symptomatically; these reactions could result in short-term hearing impairment. Dry mouth or altered taste have been occasionally reported.

Early Delayed

Possible early delayed radiation effects include lethargy and transient worsening of existing neurological deficits occurring 1 – 3 months after radiotherapy treatment.

Late Delayed

Possible late delayed effects of radiotherapy include radiation necrosis, endocrine dysfunction, and radiation-induced neoplasms. In addition, neurocognitive deficits, which could lead to mental slowing and behavioral change, are possible. Permanent hearing impairment and visual damage are rare. Cataracts can be encountered.

5.3 Temozolomide (TMZ)

Because TMZ as prescribed in this study is considered the standard-of-care (SOC) treatment for this indication, commercial sources will be used for TMZ drug supply, unless otherwise mandated by the country. AbbVie may provide or reimburse for TMZ to participating sites as required based upon availability or local regulations.

5.3.1 TMZ Administration

5.3.1.1 Chemoradiation

TMZ will be administered continuously from Day 1 of radiotherapy to the last day of radiation at a daily oral dose of 75 mg/m^2 (for a maximum of 49 days). The timing of each daily dose will be at the discretion of the Investigator.

The dose will be determined using actual body surface area (BSA) as calculated in square meters at the beginning of the concomitant treatment. The BSA will be calculated from the height

obtained at the screening visit and the weight obtained at the visit immediately before the first day of treatment. The dose of TMZ does not have to be adjusted unless there has been at least a 10% change in body weight; recalculation of dose for < 10% weight changes is allowed at the discretion of the Investigator. Recalculations for subsequent changes in height are permissible but not required. The dose will also not be capped for those that are overweight. The daily dose will be rounded to the nearest 5 mg. The exact dose administered should be recorded in the eCRF. Each daily dose should be given with the least number of capsules.

Subjects should be instructed to swallow the capsules whole, in rapid succession, without chewing them. If vomiting occurs during the course of treatment, no re-dosing of the subject is allowed before the next scheduled dose. The capsules should be taken on an empty stomach, therefore a minimum of 2 hours after eating and with no food consumption for at least 1 hour after TMZ administration.

Antiemetic prophylaxis is usually not required for the continuous daily dosing schedule (during radiation). However, prophylaxis with a 5-hydroxytryptamine3 (5-HT3) antagonist is recommended prior to administration of the first few TMZ doses and should be administered orally 30 to 60 minutes before TMZ treatment. Most subjects report optimal nausea control with the use of a 5-HT3 antagonist. Routine use of antiemetics is recommended during the adjuvant phase of treatment.

IV temozolomide (as per local institutional standard) may be used instead of oral TMZ if there is a change in the subject's social situation (e.g., move to a nursing home or changes in drug reimbursement) after treatment TMZ initiation such that oral dosing of temozolomide is no longer possible.

5.3.1.2 Adjuvant Treatment

TMZ will be administered orally once per day for 5 consecutive days (Days 1 – 5) of a 28-day (+/– 3 day) cycle. The starting dose for the first cycle will be 150 mg/m^2/day, with a single dose escalation to 200 mg/m^2/day in subsequent cycles if no treatment-related adverse events > Grade 2 are noted. The timing of each daily dose will be at the discretion of the Investigator.

The start of the first cycle will be scheduled approximately 28 days after the last day of radiotherapy. The start of all subsequent cycles (Cycles 2 – 12) will be scheduled every 4 weeks (28 days ± 3 days) after the first daily dose of TMZ of the preceding cycle.

The dose will be determined using the BSA calculated at the beginning of each treatment cycle. The BSA will be calculated from the height obtained at the screening visit and from the weight

obtained at the visit immediately before each cycle. More frequent assessment and use of height and/or weight and calculation of BSA are permitted throughout the study. The dose of TMZ does not have to be adjusted unless there has been at least a 10% change in body weight; recalculation of dose for < 10% weight changes is allowed at the discretion of the Investigator. The dose will also not be capped for those that are overweight. The daily dose will be rounded to the nearest 5 mg (where dosage strengths are available to accommodate rounding to 5 mg). The exact dose administered should be recorded in the eCRF. Each daily dose should be given with the least number of capsules.

Prior to each treatment cycle with TMZ a complete blood count (CBC) will be obtained (within 72 hours prior to dosing). Subjects should be instructed to fast at least 2 hours before and 1 hour after TMZ administration. Water is allowed during the fast period. Subjects will be instructed to swallow the capsules whole, in rapid succession, without chewing them.

If vomiting occurs during the course of treatment, no re-dosing of the subject is allowed before the next scheduled dose.

Antiemetic prophylaxis with a 5-HT3 antagonist is strongly recommended and should be administered 30 to 60 minutes before TMZ administration (Section 5.8).

IV temozolomide (as per local institutional standard) may be used instead of oral TMZ if there is a change in the subject's social situation (e.g., move to a nursing home or changes in drug reimbursement) after treatment TMZ initiation such that oral dosing of temozolomide is no longer possible.

Subjects will be treated with post-radiation TMZ for 6 cycles unless there is evidence of tumor progression (RANO) or treatment-related toxicity (Section 8.3).

Subjects demonstrating continued benefit and no unacceptable toxicity from adjuvant TMZ may continue TMZ for an additional 6 cycles (12 cycles in total) at the discretion of the investigator if this is considered an acceptable standard of care per local regulations. TMZ treatment for more than 12 cycles will not be allowed.

5.3.2 Chemotherapy Review

Chemotherapy reviews will be ongoing and performed by the Neuro-Oncology/Medical Oncology study chair or his/her designee.

5.4 ABT-414 / Placebo Treatment

During the Chemoradiation Phase, subjects in Arm A will receive blinded ABT-414 at 2.0 mg/kg IV infusion over 30 – 40 minutes once every 2 weeks (Day 1 of Weeks 1, 3, and 5 of the 6-week regimen). Subjects in Arm B blinded placebo IV infusion over 30 – 40 minutes once every 2 weeks (Day 1 of Weeks 1, 3, and 5 of the 6-week regimen). The dosing interval must be at least 12 days after the previous dose of ABT-414/placebo, and the doses must be administered no later than the last day of radiation treatment.

During the Adjuvant Therapy Phase, subjects in Arm A will receive blinded ABT-414 at 1.25 mg/kg on Day 1 (± 2 days) and Day 15 (± 2 days) of each 28-day cycle as a 30 – 40 minute infusion, and subjects in Arm B will receive blinded placebo IV infusion on Day 1 and Day 15 of each 28-day cycle for 12 cycles. If, after completing 12 cycles of study drug, the subject is tolerating the drug and the Investigator believes the subject is continuing to benefit from ongoing study drug treatment, the Adjuvant Phase may be extended following consultation with the Neuro-Medical Oncology Chair or AbbVie Medical Monitor. ABT-414/placebo will continue according to the same dosing schedule at the discretion of the Investigator as long as disease progression has not been determined.

The mg/kg dose will be determined from the weight on Day 1 of the Chemoradiation Phase and need not change during the Chemoradiation Phase unless there is a weight change by more than 10% from Week 1 Day 1. Recalculation of dose for < 10% weight changes is allowed at the discretion of the Investigator. There will be no cap on the weight of the subject or on the number of milligrams administered for overweight subjects. More frequent assessment and use of height and/or weight and calculation of BSA are permitted throughout the study.

If TMZ treatment is discontinued due to intolerance during either the Chemoradiation Phase or Adjuvant Phase, subjects will continue receiving study drug (ABT-414 or placebo) infusions according to the same study schedule.

The ABT-414 (active and placebo) will be provided as a lyophilized powder in vials. Each 100 mg vial of ABT-414 and placebo will be reconstituted with 5.0 mL of sterile water for injection to provide a 20 mg/mL ABT-414 active or a placebo solution. Each 20 mg vial of ABT-414 and placebo will be reconstituted with 1.0 mL of sterile water for injection to provide a 20 mg/mL ABT-414 active or a placebo solution. The ABT-414 is dosed as a fixed dose [or] based on body weight. The contents of two or more reconsitituted vials may be diluted to accomplish the desired dose. The total volume administered will be dependent upon the assigned dose for that dosing period and/or the tolerability of the ABT-414/placebo. The

ABT-414 and placebo solution(s) will be administered via intravenous (IV) infusion. Specific dose preparation and documentation details will be provided to the site pharmacy outside of this protocol.

Guidelines for ABT-414 dose preparation, volume, and rate of infusion will be supplied by AbbVie to study site staff, within the study manual.

The dosing schedule for the hepatic impairment sub-study can be found in Appendix IX.

5.5 Eye Drops for Prophylactic Treatment of ABT-414 Eye Toxicity

Eye drops are to be used regardless of any systemic (oral/IV) corticosteroids that the subject may be taking concurrently.

All subjects will receive prophylactic eye drops with each dose of ABT-414/placebo for 7 consecutive days, starting from 2 days prior to infusion and continuing until 4 days after infusion. The eye drop formulations recommended for the study, ranked by steroid potency from Level 1 (non-steroid artificial tears) to Level 4 (high-potency steroid where available), and dosing schedule for each are listed in Table 7. Alternatives may be discussed with the sponsor in cases where the recommended formulation(s) for one or more levels are not available locally. All subjects will begin on a Level 3 (moderate-potency) steroid at the initiation of the Chemoradiation Phase. Subjects will be monitored with regular ophthalmologic examinations (with additional symptom-driven examinations as needed) using the ABT-414-TOE (Section 4.2). The potency of the eye drop formulation given with subsequent ABT-414/placebo doses will be adjusted upward or downward, as needed, based on corneal findings from the ABT-414-TOE, as shown by the decision algorithm in Table 8. To minimize unnecessary risks associated with prolonged administration of ocular steroids (including potential for infection, glaucoma, and cataracts), the algorithm requires a step-down in the level of eye drop potency for subjects with Grade 1 or no eye toxicity who have no evidence of corneal microcysts on ophthalmic examination. The rationale for this approach is described in further detail in Section 5.12.4.

Though not well understood, ocular steroids may slow down the turn-over of transient amplifying cells in the eye and thereby protect them from damage caused by the MMAF toxin portion of ABT-414 that targets cells in rapid division. Although early use has shown that steroid eye drops may reduce the severity of symptoms related to microcyst formation, they generally do not prevent them completely. Because steroid eye drops are used to protect transient amplifying cells during exposure to MMAF, the best time to administer them is around

the time of infusion when the levels of MMAF are at their peak. Prolonged use of steroid eye drops outside of the time when there is MMAF exposure is not recommended, as they may cause other side effects and prevent the healing process.

Table 7: Eye Drop Recommended Dosing Regimen

All subjects will start on Level 3 eye drop regimen. The choice of specific prophylactic eye drop formulation is at the Investigators discretion.

LEVEL	PRIMARY CHOICE	ALTERNATIVE CHOICES	DOSE SCHEDULE
Level 1	**Artificial Tears** (non-steroid)	Dexpanthenol Visine Thera Tears Refresh Systane	1 – 2 drops (gtts) in each eye (OU) TID for 7 days, starting 48 hours before each infusion
Level 2	**0.12% prednisolone acetate suspension**	0.1% fluorometholone 1% rimexolone suspension 0.25% desonide solution Medrysone 0.2% Ioteprednol Hydrocortisone sodium phosphate	1 – 2 drops (gtts) in each eye (OU) TID** for 7 days, starting 48 hours before each infusion
Level 3 (Initial Strategy^)	**1% prednisolone acetate suspension***	0.1% dexamethasone phosphate solution 0.5% Ioteprednol etabonate Dexamethasone sodium phosphate Betamethasone	1 – 2 drops (gtts) in each eye (OU) TID** for 7 days, starting 48 hours before each infusion
Level 4	**0.05% difluprednate emulsion** (if locally available)		1 – 2 drops (gtts) in each eye (OU) TID** for 7 days, starting 48 hours before each infusion

* 1% prednisolone is the preferred steroid for Level 3. TID = three times daily.

** Dosing more frequently than TID is allowed at investigator discretion.

^ Level 3 is the starting level for all subjects.

Table 8: Decision Algorithm for Adjusting Prophylactic Eye Drop Levels

Microcysts/Edema Scale	Description of Lesions	Suggestions
0	None	**Decrease to Level 2 if no findings at 2 consecutive exams (Required).** **Decrease to Level 1 if findings of steroid-related side effects are observed (Required).**
+0.5 (trace)	Trace, localized epithelial haze	• May continue at current level or adjust level or frequency of prophylactic drops as per Investigator discretion • Fully utilize supportive care measures*
+1 (mild)	Dull glass appearance that may include fine individual microcystic changes	
+2 (moderate)	Dull glass appearance of epithelium with large number of vacuoles with or without stromal edema	
+3 (severe)	Epithelial Bullae and/or whorl keratopathy, localized or diffuse, with or without stromal striae	
Superficial Punctate Keratopathy Scale	Description of Lesions	Suggestions
0	None	**Decrease to Level 2 if no findings at 2 consecutive exams (Required).** **Decrease to Level 1 if findings of steroid-related side effects are observed (Required).**
+0.5	1 – 5 puncta	• May continue at current level or adjust level or frequency of prophylactic drops as per Investigator discretion • Fully utilize supportive care measures*
+1 (mild)	6 – 20 puncta	
+2 (moderate)	> 20 puncta, but countable	
+3 (severe)	Too many puncta to count	

* Supportive care measures (e.g., lubricating eye drops, ointments, therapeutic bandage contact lens, antibiotic drops, punctal plugs etc.) play a major role in maximizing tolerability.

5.6 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the treatment plan overview, Section 5.1, or until one of the following criteria applies:

- Subject experiences disease progression (except as noted below)
- Subject experiences intercurrent illness that prevents further administration of treatment
- Subject experiences excessive toxicity precluding further therapy with either ABT-414 or TMZ, according to the Investigator
- Subject decides to withdraw consent for participation in the study

- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the Investigator
- Subject become pregnant while on study

Subjects unable to continue either TMZ or ABT-414/placebo due to excessive drug-specific toxicity will be allowed to continue therapy with the other, tolerated therapy components until one of the other criteria above is met.

Subjects discontinuing therapy in the absence of progression should not receive any other cancer treatment before their disease progresses, unless this is clearly not in the interest of the subject.

ABT-414 treatment may be continued at the investigator's discretion if for any reason there is uncertainty about whether true disease progression has occurred. As anecdotal cases of drug-related pseudoprogression have been reported, which were associated with both initial clinical and radiological deterioration and appeared to have a different temporal course and characteristics to traditional radiotherapy-related pseudoprogression, investigators may consider biopsy prior to study drug discontinuation. If, after treatment discontinuation, there is additional clinical information leading the investigator to conclude that the reason for discontinuation is no longer valid, the subject may resume study treatment as long as no other chemotherapy, radiotherapy, immunotherapy, NovoTTF, or other treatment with antineoplastic intent has been received, with the exception of surgical intervention that yields histology not demonstrative of tumor progression.

After progression, the treatment will be left to the discretion of the Investigator. Any anti-cancer therapy other than the study drug will not be considered as part of the protocol treatment. However, treatments will be recorded.

The protocol or any portion of the protocol may also be discontinued or placed on hold by AbbVie due to unacceptable toxicity events, inadequate drug supply, or other reasons after the study sites have been notified in writing.

If subject withdraws consent, the type of withdrawal should be specifically indicated (further treatment with TMZ, ABT-414/placebo, any follow up for progression, or any follow-up of toxicity, or any follow up for survival). In any case, data collected until the date of withdrawal will remain available for study analysis.

5.7 Integral Assay/Biomarker

***EGFR* Amplification Testing**

Subjects must consent to provide tumor tissue, a portion of which will be used to assess *EGFR* amplification status, *MGMT* promoter methylation, and *EGFRvIII*. Only subjects with tumors that demonstrated *EGFR* gene amplification by centralized testing using the study designated *EGFR* FISH assay as well as sufficient tissue for *MGMT* testing will be eligible for enrollment. Tissue should be prepared and shipped to central lab as described in the study specific laboratory manual. Sites will be provided with *EGFR* amplification results.

***EGFRvIII* Mutation Testing**

Subjects tumors will be assessed for *EGFRvIII* mutation status by centralized testing using a designated RT-PCR assay. *EGFRvIII* testing will be performed at the same time as *EGFR* amplification testing to reduce delay and will be used to determine stratification for subject randomization. Tissue should be prepared and shipped to central lab as described in the study specific laboratory manual. Study sites will be provided with *EGFRvIII* results.

***MGMT* Testing**

Subjects tumors will be assessed for *MGMT* methylation status by centralized testing using a PCR assay. *MGMT* methylation status will be assessed in parallel with *EGFR* amplification testing to reduce delay and will be used to determine stratification for subject randomization. Tissue should be prepared and shipped to central lab as described in the study specific laboratory manual. Study sites will be provided with *MGMT* results.

If the subject has a previously available valid result from an approved vendor such as LabCorp, Laboratory Corporation of America, or Covance which use the same central assay (or in limited cases local *MGMT* testing performed for clinical or research purposes if, upon review of the local *MGMT* testing methodology, approval is granted by RTOG or AbbVie), then those *MGMT* results will be accepted for eligibility and stratification in this study. If the *MGMT* results tested as part of this study (central results) are or become available prior to randomization, then the central results will be used for stratification UNLESS the central results obtained are "insufficient tissue," indeterminate, or invalid, in which case the valid result from the approved non-central *MGMT* assay will be used for stratification.

Other

Remaining tissue, serum, plasma and whole blood will be retained to conduct exploratory research to investigate biomarkers where allowed by local regulations. If local regulations do not allow for tissue shipment or storage, the tissue will be returned or destroyed immediately after eligibility testing. Types of biomarkers analyzed may include (but are not limited to): nucleic acids, proteins, transcriptome profile, or metabolites. Evaluation may include biomarkers related to pathway(s) targeted by drug, those believed to be related to the disease or to drug response. The samples may be analyzed as part of a multi-study assessment of factors involved in the response to therapy or the disease state. The information learned from these collected samples may be used to investigate factors influencing response to treatment, scientific questions related to cancer, and/or in the development of new therapies and diagnostic tests. The results of exploratory biomarker testing may not be included with the study summary.

AbbVie (or people or companies working with AbbVie) will store and analyze the samples in a secure space with adequate measures to protect confidentiality. The samples will be retained for analysis while research on ABT-414, or drugs of this class, or GBM (or related oncology diseases), continues up to, but no longer than, 20 years from the end of the study, or per local requirements.

Pharmacogenetic Testing

DNA samples may be sequenced and data analyzed for genetic factors contributing to the disease or to the subject's response to ABT-414, or other study treatment in terms of pharmacokinetics, efficacy, tolerability, and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, genes believed to be related to the disease or to drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to ABT-414, drugs of this class, or the disease state. The samples may also be used for the development of diagnostic tests related to ABT-414, drugs of this class, or the disease state. The results of pharmacogenetic analyses may not be reported with the study summary.

5.7.1 Availability of Results

Sites will be provided with *EGFR* amplification, *EGFRvIII*, and *MGMT* results, but not other pharmacodynamics, pharmacogenetic, or exploratory results.

5.8 General Concomitant Medication and Supportive Care Guidelines

Any medication or vaccine (including over-the-counter, prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment, receives during the study, and continuing for 49 days following the last dose of study drug must be recorded in source documents and electronic case report forms (eCRFs). The reason for use, date(s) of administration (e.g., start, ongoing, and end date), dosage information, including dose and frequency must be entered into the database.

Non-pharmacologic supportive care measures for ocular toxicities (e.g., use of bandage contact lenses, punctal plugs, sunglasses, etc.) that the subject is receiving at the time of enrollment, receives during the study, and continuing for 49 days following the last dose of study drug must be recorded in source documents and electronic case report forms (eCRFs), including the reason for use and date(s) of administration (e.g., start, ongoing, and end date), must be entered into the database.

Both corticosteroid therapy and continuous TMZ therapy induce lymphocytopenia. Subjects receiving either of these drugs or both concomitantly are at an increased risk for opportunistic infections. Therefore, a prophylaxis against Pneumocystis (*jirovecii*) pneumonia (PCP) for all subjects receiving TMZ during radiation therapy such as trimethoprim-sulfamethoxazole (Bactrim forte®, Bactrim DS®), monthly pentamidine inhalations, dapsone, or as required by local regulation guidelines for TMZ administration. Prophylaxis during adjuvant TMZ is at the discretion of the Investigator per the local prescribing information for TMZ.

Best supportive care and treatment should be given as appropriate to each subject (antibiotics, transfusions, oxygen therapy, nutritional support, palliative treatment for pain or cough, etc.).

5.8.1 Permitted Supportive/Ancillary Care and Concomitant Medications

Antiemetic prophylaxis with a 5-HT3 antagonist is strongly recommended and should be administered 30 to 60 minutes before TMZ administration for at least the first few doses during the Chemoradiation Phase and all doses of the Adjuvant Phase.

All supportive therapy for optimal medical care will be given during the study period at the discretion of the treating Investigator. The locally approved product label, institutional guidelines, local practice, or applicable Summary of Product Characteristics (SmPC) should be referenced for any concomitant therapy guidelines.

5.8.2 Prohibited Therapies

- Growth factors and transfusions are permissible for routine supportive care in treatment of patients with chemotherapy per local prescribing regulations and Investigator discretion. However, they are not permitted to induce elevations in neutrophil, hemoglobin, hematocrit or platelet count for the purposes of: (1) protocol eligibility; or (2) administration of TMZ on the scheduled dosing interval without delay when a delay would otherwise be required by cytopenias; (3) allowing treatment with TMZ at a higher dose; or (4) avoiding interruption of the treatment during concomitant radiotherapy that would otherwise be required for cytopenias.
- Dacarbazine hypersensitivity is a contraindication for TMZ administration. No other investigational anti-neoplastic drugs will be allowed during the study. Subjects who come off study after progression of disease may be allowed to use other investigational drugs. Every effort should be made to document the use of post-progression therapies.
- Use of other types of surgery, chemotherapy, immunotherapy or biologic therapy during study treatment (prior to disease progression) as an anticancer therapy is prohibited. Any medication or vaccine (including over-the-counter, prescription medicines, vitamins and/or herbal supplements) used for antineoplastic intent is prohibited. Further, additional stereotactic boost radiotherapy during study treatment (prior to disease progression) is not allowed. If any of these treatments are required, the subject will not receive further therapy with TMZ and ABT-414 or placebo according to this protocol; however, the subject will continue to be followed for disease progression and survival information. All therapy after study treatment discontinuation is at the Investigator's discretion, but should be recorded in the eCRF.

5.8.3 Unblinding Procedure

AbbVie, the RTOG, the investigator, the study site personnel and subject will remain blinded to each subject's treatment with ABT-414 or placebo throughout the course of the study, except in two situations:

- rare cases where the sponsor has determined that unblinding is necessary for subject safety, or
- after unequivocal disease progression has been documented, where knowledge of the study drug treatment assignment is necessary to determine the subject's eligibility for a subsequent clinical trial or is necessary, in the judgment of the investigator, for appropriate management of the subject.

The IRT will provide access to blinded subject therapy information for an individual subject in the case of a medical emergency or if necessary, after confirmed disease progression, to determine eligibility for a subsequent clinical trial or to appropriately manage the subject. In the event the investigator believes that knowledge of study treatment is required, every effort must be made to contact the Neuro-Medical Oncology Chair or the AbbVie Medical Monitor (or qualified designee) listed at the top of the study protocol prior to contacting the IRT for unblinding (as long as subject safety is not compromised). In the case of unblinding for reasons other than safety (e.g., to determine eligibility for another clinical trial), eCRFs confirming the date and criteria for establishing disease progression must be completed prior to performing unblinding. The date and reason that the blind was broken must be conveyed to AbbVie and recorded on the appropriate eCRF. In the event the AbbVie Clinical Project Team should break the blind, the reason will be documented in a note to study file and on the appropriate eCRF.

5.9 Method of Assigning Subjects to Treatment Groups

At the Screening Visit, all subjects will be assigned a unique subject number through the use of IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number, assigned at the Screening Visit, throughout the study. For enrollment of eligible subjects into the study, the study site will utilize the IRT system in order to receive unique study drug kit numbers and a unique randomization number. Subjects will be randomized to either Arm A or Arm B in a 1:1 ratio. The randomization will be stratified, as described in Section 3.1. The randomization number will be used only by AbbVie for loading the treatment assignments into the database. The study drug kit numbers and randomization numbers will be assigned according to schedules computer-generated before the start of the study by the AbbVie Statistics Department. Upon receipt of study drug, the study site will acknowledge receipt in the IRT system.

5.10 Treatment Compliance

The Investigator or his/her designated and qualified representatives will administer study drug only to subjects enrolled in the study in accordance with this Protocol M13-813. The study drug must not be used for reasons other than that described in the protocol. Subjects will be supervised at the time of study drug administration.

5.11 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact at the appropriate temperature and in the correct amounts. This will be documented by signing and dating the Proof of Receipt or similar document or via direct recording in the IRT. An accurate (running) inventory of study drug will be kept by the site, and will include the lot number, Proof of Receipt number(s), kit numbers, the number of vials dispensed, subject initials, initials of person who administered the drug and the date study drug was administered for each subject. An overall accountability of the study drug will be performed and verified by AbbVie monitor throughout the study and at the study site closeout visit.

After verification of drug accountability, used vials must be destroyed at the site according to local regulations governing hazardous waste. Disposal of used study supplies must be documented in IRT. All study drug must be inventoried, accounted for, and returned to AbbVie or destroyed per instructions from AbbVie and according to local regulations. A copy of the Return Shipment Form, in accordance with instructions provided by the AbbVie monitor, will also be included in the shipment.

Labels must remain attached to the containers. If pre-arranged between AbbVie and the site, destruction of the study drug may be performed at the site.

5.12 Discussion and Justification of Study Design

5.12.1 Discussion of Study Design and Choice of Control Groups

The background treatment regimen for the current study—6 weeks of concomitant radiation and TMZ treatment, followed by 6 cycles of adjuvant TMZ therapy (dosed on Days 1 – 5 of each 28-day cycle) is currently an established standard-of-care treatment for newly diagnosed GBM.[25] Consistent with other recent or ongoing trials of experimental therapies (bevacizumab, Opdivo, and NovoTTF) in this indication, ABT-414 will be prescribed as add-on treatment to the RT/TMZ standard of care. The study will be placebo-controlled and double-blind, which is the gold standard for assessing efficacy. The original design was a seamless Phase 2b/3 that allowed early termination of the study and reduced unnecessary subject exposures to an ineffective treatment if the Phase 2b results demonstrated futility. However, rapid acceleration in the enrollment rate of INTELLANCE-1 suggested that the Phase 3 portion of the study would likely be finished enrolling before results of the planned PFS-based futility analysis would be available. In addition, recent information gathered from the INTELLANCE-2 trial, suggesting an OS benefit of the ABT-414/TMZ combination in recurrent GBM and a safety profile consistent with

previous Phase 1 results, provide increased confidence that the addition of ABT-414 to standard frontline therapy would demonstrate a statistically significant and clinically relevant benefit for OS, as well as an acceptable safety profile, in newly diagnosed subjects in the INTELLANCE-1 study. For these reasons, the study design has been modified to eliminate the PFS-based Phase 2b interim futility analysis and to complete the study as a Phase 3 study based on the gold standard efficacy endpoint of OS.

5.12.2 Appropriateness of Measurements

OS, the primary efficacy endpoint for the study, is widely accepted as the most clinically relevant endpoint for oncology trials. PFS is a clinically relevant endpoint but does not always correlate with OS. PFS will be studied as a secondary endpoint. Standard pharmacokinetic, statistical, clinical and laboratory procedures will be utilized in this study.

5.12.3 Suitability of Subject Population

The study population is restricted to subjects with newly diagnosed GBM whose tumors exhibit *EGFR* amplification (including that subset of the population with *EGFRvIII* mutation). Selective efficacy for the *EGFR*-amplified population is consistent with the understood mechanism of ABT-414, as the antibody selectively targets *EGFR*-amplified tumors, and is strongly supported by clinical data from the ongoing Phase 1 Study M12-356. As of April 2015, there have been 6 subjects with confirmed objective responses to ABT-414, all of whom have tested positive for *EGFR* amplification. There have been no subjects who have tested negative for *EGFR* amplification with a confirmed objective response.

5.12.4 Selection of Doses in the Study

Radiotherapy and TMZ Treatment

Radiation and drug doses for the background treatment in this study, consisting of 6 weeks of concomitant radiotherapy (~60 Gy over 30 fractions) and TMZ (at 75 mg/m^2 daily), followed by 6 cycles of adjuvant TMZ (at 150 – 200 mg/m^2 for 5 days of each 28-day cycle) is the established standard of care for treatment of newly diagnosed GBM.[25] TMZ will be prescribed as per local guidelines.

ABT-414 Dose Selection

For the Chemoradiation Phase, the recommended ABT-414 dose of 2.0 mg/kg infused once every 2 weeks was selected based on results from Arm A of Study M12-356, in which all subjects received ABT-414 combined with concomitant radiation and TMZ treatment. During

dose escalation at this level, no Grade 3 or higher toxicities were observed. Higher doses were associated with at least 1 dose-limiting toxicity event and were not well tolerated. Compared to dosing with TMZ alone, ABT-414 appears to be better tolerated when given with concomitant RT and TMZ.

For the Adjuvant Phase, the recommended ABT-414 dose of 1.25 mg/kg infused once every 2 weeks was selected based on results from Arm B of Study M12-356, in which all subjects received ABT-414 along with maintenance TMZ. During dose escalation at this level (and with steroid prophylaxis) during maintenance TMZ cycles, 2/10 subjects had ocular DLTs, but only 1 was attributable to ABT-414. Since the 1.25 mg/kg dose was chosen for an expanded safety cohort added to that study, this dose level has been generally well tolerated, only approximately 20% of subjects developing ocular adverse events (Grade 3 or greater) requiring a dose reduction.

As previously mentioned, the ocular manifestations of microcystic keratopathy to date have been reversible after withholding ABT-414, usually after 4 to 6 weeks. Subjects who restart ABT-414 at lower doses (~1.0 mg/kg) have less severe toxicities and can generally tolerate further therapy.

Prophylactic Eye Drop Dosing Strategy

The strategy for dosing prophylactic eye drops to manage the eye toxicity associated with ABT-414 in this study, which starts all subjects (including those assigned to placebo instead of ABT-414) on moderate potency ocular steroid drops, was designed to help preserve the study blind needed to conduct a successful controlled study while minimizing the risk associated with prolonged use of ocular steroids. Placebo subjects unblinded to their treatment assignment in this study population are expected to have unacceptably high dropout rates, leading to systematic bias and increased risk of a failed study due to a loss of statistical power. A recent trial evaluating the efficacy of rindopepimut (ACT III trial) in the same newly diagnosed GBM population and a similar treatment paradigm—with rindopepimut added to standard-of-care therapy with RT/TMZ—was originally designed as an open-label study with a standard-of-care treatment arm as a control group. However, due to high attrition rates for the subjects assigned to the standard-of-care treatment arm, the study had to be redesigned as a single-arm trial without a control group.[26]

During Phase 1 studies, use of prophylactic steroid eye drops (for 7 days of each 14-day dosing interval) was deemed necessary for all subjects taking ABT-414 in order to minimize the severity of ocular adverse events related to microcystic keratopathy, the adverse effect characteristic of ABT-414. To avoid systematic unblinding in this study, placebo subjects must receive eye drops

matching those given to subjects receiving ABT-414. Using blinded placebo eye drops in this study was considered but found to be infeasible due to differences in the packaging and visual appearance of the eye drops themselves between the ocular steroid suspensions/solutions to be used for prophylaxis and available saline or lubricant formulations. Therefore, all subjects in this study will receive moderate potency steroid eye drops (e.g., prednisolone acetate 1% suspension) with the first two doses of ABT-414/placebo. Targeted ophthalmologic examinations, to assess and grade any objective findings characteristic of ABT-414-mediated corneal toxicity, will be performed regularly, starting no later than after the first two infusions ABT-414/placebo, and the steroid potency of the eye drops for subsequent doses will be adjusted based on these objective findings. Subjects who have no evidence of microcystic keratopathy on ophthalmic examination are required to step down to a Level 2, low-potency steroid safer for long-term use, or in certain cases, to a Level 1 non-steroid solution.

Because the appearance of microcystic keratopathy seen with ABT-414 is a relatively unique and specific finding unlikely to occur spontaneously or with other drugs used for GBM, it is highly unlikely that a placebo-assigned subject would continue on a moderate-potency steroid for a prolonged period.

In addition to the step-down in steroid potency required for subjects without objective findings of microcystic keratopathy, risks related to prolonged steroid use are further reduced by a) the fact that subjects are off steroid drops for 7 days of each 14-day dosing interval, and b) the requirement for scheduled ophthalmologic examinations (including assessments for steroid-related effects such as increased intraocular pressure/glaucoma or cataract formation) at least every 4 weeks during the Chemoradiation Phase and first 2 cycles of the Adjuvant Phase, followed by every 8 weeks thereafter, or more frequently if indicated by eye symptoms. Based on this dosing schedule and frequent safety monitoring for potential steroid-related effects, long-term term use of Level 2 (low-potency steroid) eye drops constitutes a minimal safety risk to subjects. Maintaining subjects on low potency steroid eye drops is expected to improve study retention, because receiving active eye drops will support the subjects' belief that they may have been assigned to ABT-414. (While not recommended, subjects who have no evidence of microcystic keratopathy may be required, on an individual site-level basis, to step down to a Level 1, non-steroid eye drop if that site's IRB/EC or regulatory authority has determined that long-term use of ocular steroids at any potency is unacceptable in such subjects.)

6.0 REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

6.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study treatment at any time. In addition, the Investigator may discontinue a subject from the study at any time if the Investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol.

Subjects who withdraw consent to continue study therapy will be encouraged to continue participation with other study procedures and assessment unless unwilling to do so. Clinical assessment needed for the 49-Day safety assessment after ABT-414 discontinuation and to determine the occurrence and timing of disease progression (for PFS) and/or death (for OS) should be prioritized. Subject may withdraw from the treatment without withdrawing consent for follow up of PFS, OS or drug toxicities.

A subject will be withdrawn from the study treatment if any of the following occur:

1) The subject or subject's legally acceptable representative withdraws consent.
   - In the event a subject withdraws from the study, stored biomarker samples will be retained unless the subject also withdraws consent for use of unused stored biomarker samples. If the subject changes his/her consent, and the samples have already been tested, those results will still remain part of the overall research data.

     If a subject withdraws consent or discontinues from the main study, their optional sub-study samples will continue to be stored and analyzed until sub-study consent is withdrawn as well.
   - Unless the withdrawal of consent specifically withdraws consent from follow up of OS, subjects will continue to be followed for OS, and OS will be recorded. The opt out of OS follow-up must be clearly documented. Of note, OS may still be obtainable from a query of publically available information unless prohibited by local regulations.
2) The subject experiences radiographic disease progression per RANO (Appendix I). Progression is defined by any of the following:
   - at least 25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids;
   - a significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events;
   - the appearance of any new lesions;
   - clear progression of nonmeasurable lesions;

- definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose;
- Failure to return for evaluation as a result of death or deteriorating condition.

The phenomenon of pseudoprogression should be considered when determining if there is disease progression, particularly during the first 3 months after radiotherapy. Pseudoprogression refers to the occurrence of "early delayed radiation reactions" that occur usually within the first 3 months post radiation treatment. These transient adverse signs and symptoms may spontaneously improve without therapy or with supportive care such as corticosteroids. Thus, care should be taken in making the diagnosis of tumor progression or recurrence (Appendix I).

Clinical Progression and Other Factors

Note that increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Subjects with stable imaging studies, whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor, do not qualify for stable disease or progression. Subjects should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first time point at which corticosteroid increase was necessary.

The definition of clinical deterioration is left to the discretion of the Investigator, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose.

Subjects with nonmeasurable enhancing disease whose lesions have significantly increased in size and become measurable (minimal bidirectional diameter of at least 10 mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0-mm skip) will also be considered to have experienced progression. The transition from a nonmeasurable lesion to a measurable lesion resulting in progression can theoretically occur with relatively small increases in tumor size (e.g., a 9 × 9 mm lesion [nonmeasurable] increasing to a 10 × 11 mm lesion [measurable]). Ideally, the change should be significant (at least 5 mm increase in maximal diameter or at least 25% increase in sum of the products of perpendicular diameters of enhancing lesions).

In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression. If there is uncertainty regarding whether there is progression, the subject may continue on treatment and remain under close observation (e.g., evaluated at 4-week intervals). If subsequent evaluations suggest that the subject is in fact experiencing progression, then the date of progression should be the time point at which the issue was first raised.

Note: During the first 12 weeks after completing chemoradiation: progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (e.g., solid tumor areas [i.e., more than 70% tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy. In addition, subjects who remain clinically stable and/or are suspected to have pseudoprogression based on metabolic or vascular imaging should continue with their current therapy (Appendix I).

3) The subject experiences unacceptable toxicity with ABT-414 in combination with TMZ.
4) The subject requires a dose modification for ABT-414 below 0.5 mg/kg.
5) The subject requires other anti-cancer treatment, such as surgery or alternate anti-cancer agents, during the study period.
6) The subject experiences a ≥ Grade 3 allergic reaction.
7) Significant noncompliance with the protocol that could impact subject safety or data integrity.
8) The Investigator believes it is in the best interest of the subject.
9) The subject has a positive pregnancy test result.

If, after treatment discontinuation, there is additional clinical information leading the Investigator to conclude that the reason for discontinuation is no longer valid, the subject may resume study treatment as long as no other chemotherapy, radiotherapy, immunotherapy, NovoTTF, or other treatment with antineoplastic intent has been received, with the exception of surgical intervention that yields histology not demonstrative of tumor progression.

6.1.1 Discontinuation of Temozolomide

Subjects should discontinue TMZ if any of the criteria for discontinuation, as described in the guidelines provided in local approved regulatory prescribing information are met.

6.1.2 Discontinuation of ABT-414 or Placebo

Study drug (ABT-414/placebo) will be continued as discussed above in Section 5.4 unless toxicities prohibit further use. Severe allergic reactions (Grade 3 or Grade 4) require the immediate interruption of ABT-414/placebo and discontinuation from the study.

6.1.3 Discontinuation of Radiation

Subjects should discontinue radiation if any of the criteria for discontinuation, as described in the institutional guidelines or local approved regulatory prescribing information are met.

6.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

If the study is prematurely discontinued to due safety or futility reasons, study drug will no longer be provided once the entire study is discontinued. When possible, AbbVie and the Investigator will develop a plan to provide ABT-414/placebo as required by local regulations.

7.0 ADVERSE EVENTS

7.1 Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product after it is released for distribution. The investigational product in this trial contains biologic compound(s).

7.2 Medical Complaints

The Investigator will monitor each subject for clinical and laboratory evidence of adverse events (AE) on a routine basis throughout the study. The Investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the Investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

Adverse event reporting is required for all protocol treatment modalities: ABT-414/placebo, TMZ, and radiation therapy.

The NCI CTCAE v.4 will be used for adverse event reporting/grading of event severity.

All ophthalmology exam reports will be reviewed by the Investigator (or medically qualified delegate). With the exception of the corneal findings described below, decisions on *which* findings from ophthalmologic examinations, if any, will be reported as adverse events, as well as the *grading* of any such events, will be made according to the Investigator's judgment. These events will be graded according to NCI CTCAE v.4[27] criteria, and *not* according to the grading system used for the ophthalmology examinations.

To ensure consistent reporting of the corneal findings characteristic of ABT-414 that are not well described by the MedDRA preferred terms or CTCAE grading, any abnormal finding on either the "Microcysts/Edema" or "Superficial Punctate Keratopathy" field of

the ABT-414-TOE must be recorded as an adverse event of "microcystic keratopathy" with severity grading as shown in Table 5 (see Section 4.2 for additional details).

7.2.1 Definitions

7.2.1.1 Adverse Event

An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria (regarding toxicity management, (Section 8)) or if the Investigator considers them to be adverse events. When Grade 3 or higher elevations in glucose, cholesterol or triglycerides is reported under non-fasting conditions, the Investigator may choose not to report the abnormality as an adverse event until it has been confirmed by repeated testing under fasting conditions. Repeat testing for such confirmation may be done at the next scheduled laboratory visit or earlier. An elective surgery/procedure scheduled to occur during the study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

7.2.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the Investigator being made aware of the serious adverse event:

Death of Subject An event that results in the death of a subject.

Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility, hospitalization for respite care, or hospitalization due solely to progression of the underlying cancer. This does not include hospitalization for elective or diagnostic procedures.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

7.2.1.3 Adverse Events Expected Due to Study Related Endpoints

7.2.1.3.1 Deaths

For this study, mortality is an efficacy endpoint. Deaths that occur during the protocol specified adverse event reporting period (Section 7.3) that are more likely related to disease progression will therefore be an expected adverse event and will not be subject to expedited reporting.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

7.2.1.3.2 Expected Adverse Events Due to Glioblastoma

Adverse Events that may be expected due to the subject's underlying glioblastoma or its standard therapy include headache, seizure, neutropenia and progression of underlying GBM, and progression of GBM leading to death, etc. These events are considered expected AEs for this study regardless of ABT-414 treatment. As such, individual subject cases of these events, when considered serious, will not be reported in expedited fashion as individual cases, but will be evaluated during aggregate reviews by the IDMC. Appendix III includes a complete list of the adverse events that will be considered as expected for reporting purposes, based on events commonly related to underlying glioblastoma or complications from glioblastoma standard therapy.

7.3 Adverse Event Severity

The Investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.0)[27]

For adverse events not captured by the Common Terminology Criteria, the following should be used:

Grade 1	The adverse event is transient and easily tolerated by the subject (mild).
Grade 2	The adverse event causes the subject discomfort and interrupts the subject's usual activities (moderate).
Grade 3	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating (severe).
Grade 4	Life threatening; urgent intervention.
Grade 5	The adverse event resulted in death of the subject (severe).

Relationship to Protocol Treatment

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of protocol treatment, with separate assessments for each component of therapy (ABT-414/placebo, TMZ and radiation therapy):

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship.

Reasonable possibility is defined such that the specific treatment (ABT-414/placebo, TMZ, or radiation therapy) is more likely to be the cause of the event than any other reason, whereas no reasonable possibility is defined as the Other cause of the event is more likely. For causality assessments, events assessed as having a reasonable possibility of being related to protocol treatment will be considered "associated." Events assessed as having no reasonable possibility of being related to protocol treatment will be considered "not associated." In addition, when the Investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an Investigator's opinion of no reasonable possibility of being related to protocol treatment is given, an Other cause of event must be provided by the Investigator for the serious adverse event.

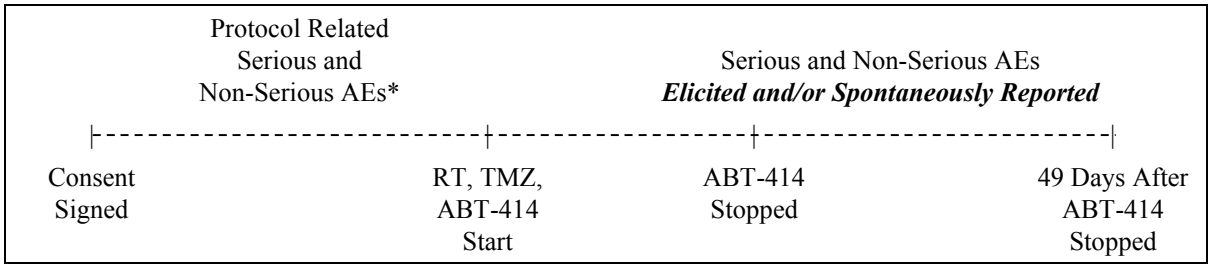
7.4 Adverse Event Collection Period

All protocol related serious adverse events and non-serious adverse events must be reported as follows:

- From time the study-specific informed consent is signed, but prior to the initial administration of component therapy, will only be collected if they are considered by the Investigator to be causally related to the study-required procedures.
- From first day of component therapy administration until 49 days after last administered dose of ABT-414.

Adverse event information will be collected as shown in Figure 1.

Figure 1. Adverse Event Collection



* Only if considered by the Investigator to be causally related to study required procedures.

7.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with protocol treatment or not, the Investigator will notify AbbVie Clinical Pharmacovigilance within 24 of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the EDC or EDC is not operable should complete the SAE Non-CRF paper forms and be faxed to AbbVie Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

Email to	[redacted]
FAX to:	

For serious adverse event concerns, contact the AbbVie Oncology Safety Team at:

Oncology Safety Management
AbbVie
1 North Waukegan Road
[redacted]
North Chicago, IL 60064

Contact Information:
Safety Line:
Email:
Fax:
[redacted]

For any subject safety concerns, please contact the RTOG physician listed below:

[redacted]

For questions that need to be addressed by the study sponsor, please contact the AbbVie physician below:

Primary Clinical Monitor:
[redacted]
AbbVie

Telephone Contact Information:
Mobile:
Email:
[redacted]

Primary Medical Monitor:
[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Telephone Contact Information:
Office:
Mobile:
Fax:
Email:
[redacted]

In emergency situations involving study subjects when the primary Medical Monitor is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup Medical Monitor MD.

Phone: [redacted]

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the European Union (EU) countries will be the most current version of the Investigator's Brochure for ABT-414 or Summary of Product Characteristics for TMZ.

Serious adverse events which are considered expected due to the underlying disease of GBM[28] as described in Appendix III would not be expedited as individual safety case reports to regulatory authorities.

7.6 Pregnancy

In the event of a positive pregnancy test, subjects must immediately discontinue protocol therapy and must be discontinued from the study. The Investigator must report the positive pregnancy test to the appropriate contact listed in protocol Section 7.4 within 1 working day of the site becoming aware of the pregnancy.

All subjects should be informed that contraceptive measures should be taken throughout the study and for 6 months after discontinuing study drug. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. The Investigator must follow the pregnancy to completion and provide an update to AbbVie after delivery.

Male subjects should be informed that contraceptive measures should be taken by their female partners. If the subject's partner should become pregnant during the study, this should also be reported and data may be collected. In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

Pregnancy in a study subject is not considered an adverse event. The medical outcome for either mother or infant, meeting any serious criteria including elective or spontaneous abortion, is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

8.0 TOXICITY MANAGEMENT AND DOSE MODIFICATIONS

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the Investigator. The table of clinical toxicity grades modified from the NCI CTCAE Version 4.0 (available on the CTEP home page http://ctep.cancer.gov) is to be used in the grading of adverse events and laboratory abnormalities that are reported as adverse events, each of which will be followed to satisfactory clinical resolution.

A drug-related toxicity is an adverse event or laboratory value outside of the reference range that is judged by the Investigator or AbbVie as having a reasonable possibility of being related to protocol treatment. A toxicity is deemed "clinically significant" on the basis of the Investigator's medical judgment.

Dose reductions or delays should be made for the likely causative agent. If one of the agents should be stopped for any reason other than disease progression, the subject can continue on the other single agent alone at the same dose and schedule.

8.1 ABT-414/Placebo Toxicity Management

Subjects will be closely monitored for treatment-related adverse events, especially allergic reactions, during all infusions. For the initial ABT-414/placebo infusion, pre infusion vital signs will be taken and direct observation is required for the first 15 minutes of the infusion. Also for the initial ABT-414/placebo infusion, subjects must remain at the site for monitoring for 60 minutes post infusion. For subsequent infusions, post-infusion monitoring is not required; however, pre-infusion vital signs should still be taken. Longer observation periods and more frequent vital sign checks may be required in subjects who experience infusion reactions.

Institutional standards should be used to treat all allergic reactions.

Based upon results from the first clinical and preclinical safety pharmacology evaluation of ABT-414, experience with other inhibitors of *EGFR*, and experience with MMAF ADCs, potential toxicities may include fatigue, vomiting, thrombocytopenia, allergic reactions, rash, eye complaints, and liver function test abnormalities.

8.1.1 Dose Modifications for ABT-414/Placebo

For all observed toxicities, subjects should be assessed for inter-current illness or other causes and treated as appropriate.

Starting doses and suggested dose level reductions are shown in Table 9, and subsequent subsections discuss when dose reductions should be considered or are required. More aggressive dose reductions are always allowed if the Investigator believes that it is in the best interest of the subject.

With the exception of ophthalmologic toxicities as described in Section 8.1.2 and hepatic laboratory abnormalities as described in Section 8.1.6, all dose reductions are permanent unless a toxicity initially attributed as potentially related to ABT-414/placebo is later re-attributed as not potentially related and discussed with the Neuro-Medical Oncology study chair, AbbVie Medical Monitor or their designee.

Table 9. ABT-414/Placebo Dose Modification Table during Chemoradiation and Adjuvant Phase

	Dose	
Dose Level	**Chemoradiation Phase**	**Adjuvant Phase**
Starting Dose	2.0 mg/kg	1.25 mg/kg*
1st Reduction	1.5 mg/kg	1.0 mg/kg
2nd Reduction	1.0 mg/kg	0.75 mg/kg
3rd Reduction	-	0.5 mg/kg
	-	Discontinue

* If CTCAE Grade 3 eye toxicity is observed during the Chemoradiation Phase, then 1.0 mg/kg is recommended, but not required, as the starting dose for the Adjuvant Phase.

8.1.2 Ophthalmologic Toxicities

Microcystic keratopathy is a very common adverse effect of ABT-414, occurring in over 50% of subjects. Key elements in the overall management of microcystic keratopathy include subject education, use of prophylactic eye drops to reduce severity, supportive care measures, and careful ophthalmological monitoring to identify microcystic changes or steroid-related adverse effects and guide supportive treatment.

8.1.2.1 Ophthalmologic Monitoring and Prophylactic Eye Drop Use

As described in Section 4.2, subjects will receive ophthalmological examinations at regular intervals throughout the study, and additional examinations may be done as needed. The ABT-414-TOE examinations are intended to systematically identify and grade objective findings of ABT-414-related eye toxicity and to assess for adverse effects potentially related to ocular steroid use.

Administration of prophylactic eye drops for 7 days is required with each administration of ABT-414/placebo, from 2 days prior until 4 days after drug infusion. A description of the steroid-potency levels and dosing schedule for each, as well as considerations for adjusting prophylactic eye drop levels or frequency based on ophthalmologic findings, is described in Section 5.5.

Prophylactic and symptomatic use of cold compresses over the eyes and ophthalmologic vasoconstrictors around the time of ABT-414 infusions is allowed, as it may reduce drug uptake in the cornea.

8.1.2.2 Treatment of Ophthalmologic Toxicity Once Symptoms Occur

Supportive care measures (e.g., lubricating eye drops, therapeutic bandage contact lenses, punctal plugs, antibiotic drops, etc.) play a pivotal role in ABT-414 treatment, as they can provide considerable relief for symptoms of ABT-414-related eye toxicity, including photophobia, blurry vision and eye discomfort. Therefore, supportive care measures should be used early and extensively to minimize the need for ABT-414 dose interruptions and dose reductions.

Once corneal microcysts have formed, there are no known therapies that can remove them from the cornea. Thus, only therapies that can control symptoms and promote healing are indicated. Use of steroid eye drops outside the prescribed prophylactic period is allowed but may not be the best strategy, as it may inhibit the healing process. Supportive care measures should be actively considered and fully utilized when symptoms of ABT-414-related eye toxicity occur, as they are the most effective way to manage eye symptoms and maximize ABT-414 dosing.

Use of supportive care measures should be individually tailored for each subject based on frequent monitoring by an ophthalmologist to inform the best treatment for the subject. The choice and timing of supportive care measures is not restricted by the study protocol, and all choices are at the discretion of the study investigator in consultation with the ophthalmologist as needed. Supportive measures can be used throughout the treatment cycle, including days on which prophylactic eye drops are used, and they may be initiated prior to the onset of symptoms at the discretion of the investigator.

Lubricating eye drops may be used liberally throughout treatment and are commonly prescribed prior to onset of eye symptoms.

Feedback from ophthalmologists with experience managing ABT-414 ocular toxicity suggest that use of therapeutic bandage contact lenses can have a major impact on improving eye

symptoms, including photophobia, blurred vision and various forms of eye discomfort, and thus minimize the need for ABT-414 dose interruptions and dose reductions. Therefore, use of therapeutic bandage contact lenses should be strongly considered whenever toxicity suggesting the need for ABT-414 dose modification is present, and they may also be used for lower grade symptoms.

8.1.2.3 Discussions with Subjects

It is important that subjects understand this toxicity and the importance of following the recommendations for the prophylactic eye drops and supportive care measures, as well as the rapid reporting of their symptoms. It is also important to let them know that at this time, in all of the subjects, symptoms have improved over time and there is no evidence to suggest that there is any permanent damage done to the cornea. It does take some time, however, for symptoms to resolve and thus an immediate reversal of symptoms should not be promised. At least 3 – 4 weeks must take place for the regeneration of the cornea; this is an approximate timeline for when symptoms should improve and corneal healing should take place. Tumor responses to ABT-414 have been sustained in subjects who require treatment holds for 4 or more weeks.

8.1.2.4 ABT-414 Dose Adjustment for Ophthalmologic Toxicity

Guidelines for ABT-414/placebo dose modifications for ophthalmologic toxicities considered by the investigator to be related to ABT-414 are shown in Table 10. Decisions on dose adjustments will be based on CTCAE grades assigned by the Investigator (not on the ABT-414-TOE grades). Re-treatment at a lower dose of ABT-414 has generally resulted in less severe toxicities. However, it is important to fully utilize supportive measures as needed in order to minimize the need for dose interruptions and dose reductions.

If, after a dose reduction for ocular symptoms, changes in supportive care interventions lead to significant improvement in ocular symptoms for subsequent ABT-414/placebo doses, the ABT-414/placebo dose may be re-escalated to the previous higher dose at the discretion of the investigator after discussion with the Neuro-Medical Oncology study chair or his/her designee.

Table 10. Guidelines for ABT-414/Placebo Dose Interruption and Re-Initiation During Chemoradiation and Adjuvant Phase for Ophthalmologic Toxicities

Ocular Adverse Event CTCAE Grade^	ABT-414 / Placebo Dosing Modifications	
	Dose Interruption*	**Dose Reduction***
1 – Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated^	• Not indicated	• Not indicated
2 – Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL^	• Not indicated, but allowed at investigator's discretion • Investigator should fully utilize supportive care measures** as needed to manage ocular findings	• Not indicated, but allowed at investigator's discretion • Investigator should fully utilize supportive care measures** as needed to manage ocular findings
3 – Decline in vision (worse than 20/40 but better than 20/200); limiting self-care ADL^	• Recommended but not required; at investigator's discretion to interrupt study drug until AE resolves to at least Grade 2 • Investigator should fully utilize supportive care measures** as needed to manage ocular findings	• Recommended but not required; at investigator's discretion unless otherwise noted • Investigator should fully utilize supportive care measures** as needed to manage ocular findings
4 – Perforation or blindness (20/200 or worse) in the affected eye^	• Interrupt study drug until AE resolves to at least Grade 2 (required) • Investigator should fully utilize supportive care measures** as needed to manage ocular findings	• **Required** if Grade 4 toxicity present despite full utilization of supportive care measures**

^ Grading criteria shown are for the term "microcystic keratopathy." For other ocular adverse events considered by the investigator to be related to ABT-414, use the applicable CTCAE grading criteria for that term.

* If use of supportive measures reduces severity of eye toxicity, the lower CTCAE grade severity (the grade in the presence of ongoing supportive measures) may be used to guide potential dose modifications.

** Supportive care measures include but are not limited to lubricant drops, bandage contact lens, antibiotic drops, ointments, punctal plugs and sunglasses.

8.1.3 Severe Allergic Reactions (Grade 3 or Grade 4)

These require the immediate interruption of ABT-414/placebo treatment and discontinuation from the study. Appropriate medical therapy including epinephrine, systemic corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.

8.1.4 Moderate Allergic Reactions (Grade 1 or Grade 2)

These will also require the immediate interruption of ABT-414/placebo infusion. Once symptoms have resolved, retreatment is allowed with an infusion over 60 to 70 minutes. All subsequent infusions will also be administered over 60 to 70 minutes.

8.1.5 Dermatologic Toxicities

Subjects developing dermatologic toxicities while receiving ABT-414/placebo should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. In subjects with mild and moderate (Grade 1 or Grade 2) skin toxicity, treatment should continue without dose delay or modification. Treatment with topical and/or oral antibiotics should be considered.

If a subject experiences severe (Grade 3 or Grade 4) acneiform rash, ABT-414/placebo treatment adjustments should be made based on a discussion between the Investigator, the RTOG Neuro-Medical Oncology Study Chair and AbbVie Medical Monitor.

Subjects who experience a grade 3 or higher dermatological toxicity will be treated as following: The subject will require a dose interruption and ABT-414/placebo may be reintroduced at a reduced dose (per the guidance previously stated above) if the toxicity returns to ≤ grade 1 within 4 weeks.

8.1.6 Hepatic Laboratory Abnormalities (ABT-414/Placebo)

Guidelines for ABT-414/placebo dose modifications related to hepatic laboratory abnormalities are presented in Table 11.

Table 11. ABT-414/Placebo Dose Modification Guidelines for Hepatic Laboratory Abnormalities

Hepatic Laboratory Abnormality	ABT-414/Placebo
ALT or AST > 5 × ULN* but ≤ 20 × ULN (and TBL ≤ 2 × ULN)	• **Hold drug regardless of assessed relationship to drug.** See Section 8.4 for guidelines on repeat testing (ALT, AST, ALP, TBL) and evaluation. • **Dosing may not be resumed until ALT and AST have recovered to ≤ 5 × ULN*** • Dosing may be resumed at the **same dose** if ALT or AST was elevated >5 × ULN* for less than 2 weeks. Additionally, dosing may be resumed at the same dose if another likely cause has been identified. • Dosing must be resumed at a reduced dose (see Table 9)** if ALT or AST was elevated > 5 × ULN* for more than 2 weeks and no other likely cause has been identified. • Following dose reduction, if ALT and AST remain ≤ 5 × ULN* after 2 doses at the reduced dose level, then **re-escalation** to the previous dose is allowed at the investigator's discretion. • If a subsequent dose reduction is required due to hepatic laboratory abnormalities, then re-escalation is not allowed.
ALT or AST > 20 × ULN or ALT or AST > 3 × ULN and TBL > 2 × ULN	**Hold drug regardless of assessed relationship to drug.** See Section 8.4 for guidelines on repeat testing (ALT, AST, ALP, TBL) and evaluation. If another clear cause has been identified, drug may be resumed when ALT and AST ≤ 5 × ULN and TBL ≤ 2 × ULN In general, if no other cause has been identified, drug should be permanently discontinued, and rechallenge not attempted. Rechallenge can be considered after consultation with the sponsor if **all** of the following are met: • the subject has shown important benefit from the drug and other options are not available, • ALT and AST have recovered to ≤ 5 × ULN and TBL has recovered to ≤ 2 × ULN, • the subject has been informed of the potential risk and has consented to the rechallenge, • close follow-up of the subject is feasible.

ALP = alkaline phosphatase, ALT = alanine transferase, AST = aspartate transferase, TBL = total bilirubin

* If elevated at baseline, either 5 × the baseline value or 8 × ULN, whichever is lower.

** Unless the next planned dose is already a lower dose per the protocol (i.e., start of the adjuvant phase).

8.1.7 Other Toxicities

For all other toxicities considered by the investigator to be potentially related to ABT-414/placebo, the general guidelines to be used for dose interruptions and/or dose reductions are shown in Table 12.

Table 12. General Guidelines for ABT-414/Placebo Dose Interruptions and Re-Initiation During Chemoradiation and Adjuvant Phase (Except Ophthalmologic, Allergic, Dermatologic Toxicities and Hepatic Laboratory Abnormalities)

CTCAE Grade	ABT-414	
	Dose Interruption	**Dose Reduction**
Grade 1	Not indicated	Not indicated
Grade 2	Not indicated	Not indicated, but at investigator's discretion
Grade 3	Interrupt study drug until AE resolves to at least Grade 1 (or baseline if higher than Grade 1)	Recommended but not required; at investigator's discretion
Grade 4	Interrupt study drug until AE resolves to at least Grade 1 (or baseline if higher than Grade 1)	Required

8.2 Ocular Steroid Toxicity Management

Adverse effects related to ocular steroid use should be managed as clinically indicated in consultation with the ophthalmologist. The decision whether to continue prophylactic eye drops at the same steroid potency level should weigh both the potential benefits and risks of continuing treatment. As described in Section 5.5, prophylactic eye drops must be reduced to Level 1 (non-steroid drops) if there is evidence of ocular steroid-related toxicity in the complete absence of any corneal epithelial abnormalities on the ABT-414-TOE.

8.3 Temozolomide Toxicity Management

TMZ should be administered per the local prescribing regulations. If local prescribing information and the instructions in Section 8.3.1 or Section 8.3.2 conflict, then either local prescribing information or protocol language can be used at the discretion of the investigator.

See Section 8.4 for guidelines on repeat testing and evaluation of hepatic laboratory abnormalities regardless of the assessed relationship to study treatments.

8.3.1 Temozolomide During Concomitant Radiation Therapy

Prophylaxis against Pneumocystis *jirovecii* pneumonia (PCP) should be per local regulation guidelines for all subjects receiving concomitant TMZ and radiotherapy.

No TMZ dose reduction will be made, but delay or discontinuation of TMZ administration will be decided weekly according to hematologic and non-hematologic adverse events (AEs), as specified below.

If the administration of TMZ has to be interrupted, the radiotherapy will proceed normally. Missed doses of TMZ will not be made up at the end of radiotherapy. The total number of days and total dose of TMZ will be recorded on the eCRFs.

If one or more of the following are observed:

- ANC ≥ 0.5 and $< 1.5 \times 10^9$/L
- Platelet count ≥ 10 and $< 100 \times 10^9$/L
- Grade 2 non-hematologic AE considered possibly related to TMZ (except alopecia, nausea and vomiting while on maximal antiemetic therapy, and fatigue)

then treatment with concomitant TMZ will be withheld until all of the following conditions are met:

- ANC $\geq 1.5 \times 10^9$/L
- Platelet count $\geq 100 \times 10^9$/L
- Grade ≤ 1 non-hematologic AE (except alopecia, nausea and vomiting, and fatigue)

In case of hematologic AE as defined above, a complete blood count (CBC) should be performed at least twice weekly. In case of non-hematologic AE, the subject should be assessed at least weekly with relevant laboratory test(s). As soon as all of the above conditions are met, the administration of TMZ will resume at the same dose as used initially.

If one or more of the following are observed:

- ANC $< 0.5 \times 10^9$/L (Grade 4)
- Platelet count $< 10 \times 10^9$/L (Grade 4)
- Grade 3 or 4 non-hematologic AE considered possibly related to TMZ (except alopecia, nausea and vomiting unless the subject has failed maximal antiemetic therapy, and fatigue)

then treatment with concomitant TMZ should be stopped.

If the duration of radiotherapy exceeds 7 weeks, then concomitant treatment with TMZ should be stopped after 49 days of TMZ treatment.

Summary of Temozolomide Delay or Discontinuation During Concomitant Radiation Therapy

AE	Value	Action
ANC	≥ 0.5 and $< 1.5 \times 10^9$/L	**Delay** temozolomide until: ---ANC $\geq 1.5 \times 10^9$/L ---Platelet $\geq 100 \times 10^9$/L ---Non-hem AE $\leq$ Grade 1
Platelet count	≥ 10 and $< 100 \times 10^9$/L	
Non-hematologic (except alopecia, nausea/vomiting unless on maximal antiemetic therapy)	NA	
ANC	$< 0.5 \times 10^9$/L	**Stop** concomitant temozolomide
Platelet count	$< 10 \times 10^9$/L	
Non-hematologic (except alopecia, nausea/vomiting)	NA	

8.3.1.1 Concomitant Temozolomide, if Radiotherapy Is Interrupted

If radiotherapy has to be temporarily or permanently interrupted for technical or medical reasons unrelated to the TMZ administration, then treatment with daily TMZ should continue.

8.3.2 Post-Radiation (Adjuvant) Temozolomide

Continued dosing administration is based on adverse events (AEs) during the prior treatment cycle. If multiple AEs are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single AE.

Dose Level	Temozolomide Dose, mg/m^2/day	Remarks
–1	100	Reduction if prior AE
0	150	Starting dose cycle 1 (adjuvant)
+1	200	Escalated dose at cycle 2, for cycles 2 – 12 in absence of AE

Delay

On Day 1 of each cycle (within the prior 72 hours), ANC $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L and all treatment-related grade 3 or 4 non-hematologic AEs (except alopecia, nausea, and vomiting) must have resolved (to grade ≤ 1).

If AEs persist, treatment should be delayed by 2 weeks for up to 4 consecutive weeks, so that the TMZ dosing can coincide with the administration of the ABT-414 or placebo. If, after 4 weeks of delay, all AEs have still not resolved, then any further adjuvant treatment with TMZ should be stopped. When possible, TMZ treatment when resumed should start on either Day 1 or Day 15 of a cycle so that it may coincide with ABT-414/placebo treatment.

Dose Escalation

If, during the first cycle, all non-hematologic AEs observed were grade ≤ 2 (except alopecia, nausea and vomiting) and with platelets ≥ 100×10^9/L and ANC ≥ 1.5×10^9/L, then the TMZ dose should be escalated to dose level 1 and this dose should be used as the starting dose for subsequent cycles. If treatment after cycle 1 has to be delayed because of ongoing non-hematologic AEs of grade ≥ 2, then no escalation is possible. If the dose was not escalated at cycle 2, then the dose should not be escalated in further cycles (Cycles 3 – 6).

Dose Reductions

If any non-hematologic AE observed was grade > 2 (except alopecia, nausea and vomiting) and/or if platelets < 50×10^9/L and/or ANC < 1×10^9/L, then the dose should be reduced by one dose level. For subjects who would require dose reductions to a dose level < 100 mg/m^2/day, TMZ will be stopped. Also, if any of the same non-hematologic grade 3 AE recurs (except alopecia, nausea and vomiting) after reduction for that AE, then TMZ will be stopped.

If any treatment-related non-hematologic AE observed was grade 4 (except alopecia, nausea and vomiting) then adjuvant TMZ treatment should be stopped.

Subsequent cycles (Cycles 3 – 12): Any dose reductions of TMZ will be determined according to (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the nadir (lowest/worst) ANC and platelet counts observed. No dose escalation should be attempted. The same dose reductions as for the second cycle should be applied.

Important: If the dose was reduced or delayed for adverse events, there will be no dose escalation.

The reason(s) for dose reduction and/or delay must be documented in the eCRF.

Summary of Dose Modification or Discontinuation During Post-Radiation Temozolomide

Worst Non-Hematologic AE (Except Alopecia, Nausea and Vomiting) During the Previous Cycles	
Grade	**Dose Modification**
0 – 2	No dose modifications for non-hematologic AEs. Dose escalations (only for cycle 2) or reductions based on ANC and platelet counts are applicable.
3	Reduce by one dose level (except alopecia, nausea and vomiting). Dose modifications (escalations or reductions) based on ANC and platelet counts are not applicable. No further escalation is possible. If the same non-hematologic grade 3 AE recurs (except alopecia, nausea and vomiting) after reduction for that AE, then stop temozolomide.
4	Stop temozolomide (except for alopecia, nausea and vomiting). Dose modifications (escalations or reductions) based on ANC and platelet counts are not applicable.

Nadir Values

ANC	**Action**
$\geq 1.5 \times 10^9$/L	Escalation to DL 1 (cycle 2 only)
≥ 1 & $< 1.5 \times 10^9$/L	Dose unchanged
$< 1 \times 10^9$/L	Reduce by 1 dose level
Platelets	
$\geq 100 \times 10^9$/L	Escalation to DL 1 (cycle 2 only)
$50 – 99 \times 10^9$/L	Dose unchanged
$< 50 \times 10^9$/L	Reduce by 1 dose level

Note: A complete blood count must be performed on Day 22 (+/– 3 days) of each adjuvant treatment cycle.

Hematologic AE on Day 1 of Each Cycle (Within 72 Hours Before)

AE	Delay
ANC $< 1.5 \times 10^9$/L and/or Platelet count $< 100 \times 10^9$/L	Delay up to 4 weeks until all resolved. If unresolved after 4 weeks then stop temozolomide. If resolved, dose delay/reductions based on non-hematologic AEs are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

Non-Hematological AE (Except for Alopecia, Nausea and Vomiting) on Day 1 of Each Cycle (Within 72 Hours Before)

Grade	Delay
2 – 3	Delay up to 4 weeks until all resolved (to grade ≤ 1). If unresolved after 4 weeks, then stop temozolomide. If resolved, dose delay/reductions based on ANC and platelets are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

8.4 Hepatic Laboratory Abnormalities

This section provides information on safety monitoring, evaluation of potential causes, and appropriate documentation for subjects with hepatic laboratory abnormalities suggesting potential drug-induced liver injury (DILI). It was adapted with modifications from the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf) in consultation with a hepatologist with expertise in DILI.

Information derived from the scientific literature and public databases on liver injury attributable to prescription and nonprescription medications, herbals and dietary supplements can be found at the LiverTox database (https://livertox.nlm.nih.gov).

If a subject develops one of the following laboratory abnormalities, hepatic laboratory abnormalities should be confirmed by repeat testing, and the subject should be monitored and evaluated as described in this section, **regardless of the assessed relationship to the study treatments:**

- ALT or AST > 3 × ULN **and** TBL > 2 × ULN, or
- ALT or AST > 5 × ULN (or > 5 × the baseline value if elevated) or > 8 × ULN, whichever is lower

Confirmation of Liver Test Abnormalities

For subjects meeting either of the criteria above, confirmation of hepatic laboratory abnormalities should be done as follows:

- **Repeat testing of all four of the usual measures (ALT, AST, alkaline phosphatase, and TBL) should be performed within 3 days of the initial abnormality** to confirm the abnormalities and to determine if they are increasing or decreasing.
    - Serum transaminases may rise and fall quite rapidly, and waiting a week or two before obtaining confirmation of elevations may lead to a false conclusion that the initially observed abnormality was spurious.
    - The need for prompt repeat testing is especially great if AST or ALT is > 3 × ULN **and** TBL > 2 × ULN.
    - If the subject is unable to return to the trial site promptly, the subject should be retested locally, with results and normal laboratory ranges recorded in the CRFs.

- **Inquire about concurrent new or escalating symptoms** (e.g., right upper quadrant pain or tenderness, fever, rash). Although non-specific in the setting of GBM treatment, fatigue nausea, and vomiting should also be assessed as clinical symptoms potentially associated with liver injury.

It is appropriate to initiate *close observation* (described below) to determine whether the abnormalities are improving or worsening and to consider whether the subject meets criteria for stopping study drug if symptoms suggestive of liver injury persist or if repeat testing shows:

- ALT or AST > 5 × ULN (or > 5 × baseline if elevated or > 8 × ULN, whichever is lower) or
- ALT/AST > 3 × ULN **and** total bilirubin > 2 × ULN.

Close Observation

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible DILI (as described above), and not to wait until the next scheduled visit or monitoring interval. The primary goal of close observation is to determine as quickly as possible whether observed abnormal findings are transient and will resolve spontaneously or will progress to marked serum aminotransferase elevation or evidence of *functional* impairment, as indicated by rising bilirubin or INR, which represent substantial liver injury.

Close observation includes:

- **Repeating liver enzyme and serum bilirubin tests two or three times weekly. If total bilirubin is elevated, obtain direct bilirubin.** Frequency of retesting can decrease to once a week or less if abnormalities stabilize or drug has been discontinued and the subject is asymptomatic.
- **Obtaining additional tests, as appropriate, to evaluate liver function, (e.g., international normalized ratio [INR]); diagnostic measures (e.g., ultrasound of the liver), serum ammonia, etc.**
- Obtaining a more detailed history of symptoms and prior or concurrent diseases. Update the appropriate eCRFs (if applicable).
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets. Update the appropriate eCRFs (if applicable).
- Ruling out other immediately apparent possible causes of aminotransferase (ALT or AST) elevation and hyperbilirubinemia, as described below.

- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

Relevant supplemental information must be collected and entered in the appropriate eCRF(s),

Evaluating Data for Alternative Causes

An important purpose of close observation is to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, such as one of the following common causes:

- **Acute viral hepatitis.** The usual onset of hepatocellular DILI is indistinguishable from acute viral hepatitis A or B. Hepatitis C is much less often acute in its onset and tends to be insidious, but it sometimes can resemble acute DILI. The presence of acute viral hepatitis A, B, and C should be evaluated by serological markers. Viral hepatitis D (requires concomitant hepatitis B infection) and E are relatively rare in the United States. Hepatitis E is more common in developing countries, including Southeast Asia, and should be considered in recent travelers to those countries and in patients in trials conducted in those countries. Also rare are hepatocellular liver injuries caused by Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, and parvovirus, although these infections are seen more typically in immuno-suppressed individuals. Adolescent and young adult patients with possible DILI should be tested for Epstein-Barr virus. Hepatitis is common among transplant patients with cytomegalovirus disease.
- **Alcoholic and autoimmune hepatitis.** Acute alcoholic hepatitis usually is recurrent, with a history of binging exposure to alcohol preceding episodes, and it has some characteristic features, such as associated fever, leukocytosis, right upper quadrant pain and tenderness, hepatomegaly, and AST > ALT, that may help distinguish it from other causes of liver injury. Other features of the physical examination may include the presence of stigmata of cirrhosis, such as spider nevi, palmar erythema, estrogenic changes in males, and Dupuytren's contractures. Alcoholic and autoimmune hepatitis should be assessed by history, physical examination, and laboratory testing, including serologic testing (e.g., antinuclear or other antibodies).
- **Hepatobiliary disorders.** Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if alkaline phosphatase is increased. Malignant interruption of the biliary tract also should be considered.
- **NASH.** NASH may be seen in obese, hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels, and hepatic and

sometimes splenic enlargement. It is sometimes associated with cirrhosis and portal hypertension.

- **Cardiovascular causes.** Cardiovascular disease, especially right heart failure and hypotension or any cause of impaired oxygenation of the liver, may cause acute centrilobular hypoxic cell necrosis (ischemic hepatitis) with rapid and sometimes spectacular increases of serum transaminases (e.g., ALT or AST > 10,000 U/L). Cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure, should be assessed by physical examination and history.
- **Concomitant treatments.** It is critical to discover concomitant treatments, including exposure to nonprescription and dietary supplement products that might be responsible for injury. The possible exposure to potentially toxic herbal or dietary supplement mixtures (sometimes of unknown composition), nonprescription medications such as acetaminophen, or to occupational chemical agents may not be volunteered unless subjects are specifically questioned.

Follow-Up to Resolution

All subjects showing hepatic laboratory abnormalities suggestive of possible DILI should be followed until satisfactory resolution of the laboratory abnormalities). DILI may develop or progress even after the causative drug has been stopped. Local lab results should be recorded on appropriate eCRFs.

Dose Modifications for Study Drugs

See the dose modification guidelines for each respective drug.

9.0 DRUG INFORMATION

9.1 TMZ

Study sites must refer to the TMZ package insert for detailed pharmacologic and safety information.

See Section 5.3 for TMZ administration instructions. Refer to the current package insert/SmPC provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.1.1 TMZ Supply

TMZ is commercially available.

9.2 ABT-414

9.2.1 Identification of Investigational Product(s)

Information about ABT-414 formulations to be used in this study is presented in Table 13.

Table 13. Identification of Investigational Product(s)

Study Drug	Formulation	Dosage Form	Strength (mg)	Manufacturer
ABT-414	Sucrose, histidine, polysorbate 80	Sterile lyophilisate in a vial (to be reconstituted and further diluted for IV infusion)	100 mg 20 mg	AbbVie
Placebo for ABT-414	Sucrose, histidine, polysorbate 80	Sterile lyophilisate in a vial (to be reconstituted and further diluted for IV infusion)	100 mg 20 mg	AbbVie

9.2.2 Packaging and Labeling of Blinded ABT-414/Placebo

Vials containing ABT-414 lyophilized powder or placebo will be packaged in cartons in a blinded fashion. Vials containing ABT-414 lyophilized powder designated for the hepatic impairment sub-study will be packaged in cartons in an open-labeled fashion. Each vial and carton will be labeled per country requirements.

9.2.3 Storage and Disposition of ABT-414/Placebo

The ABT-414 and placebo lyophilisate for injection must be stored refrigerated at 2°C to 8°C/36°F to 46°F, protected from light, and must not be frozen.

The reconstituted ABT-414 or Placebo should be refrigerated at 2°C to 8°C/36°F to 46°F, for no more than 20 hours. After storage at 2°C to 8°C/36°F to 46°F, the solution can be allowed to come to room temperature and be administered within 4 hours. From start to reconstitution until the infusion is completed, a total of 24 hours should not be exceeded. If maintained at room temperature, the solution should be used within 4 hours.

Storage temperature logs will be maintained to document proper storage conditions. The refrigerator temperature must be recorded on a daily basis on the temperature logs to record proper function. Temperature excursions must be reported to AbbVie immediately.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to AbbVie.

9.2.4 Preparation/Reconstitution of Dosage Form

ABT-414/placebo Study Medication Preparation Guidelines will be provided as a separate document outside of this protocol.

9.2.5 Product Complaint

9.2.5.1 Definition

A Product Complaint is any Complaint related to the biologic or drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

9.2.5.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the Investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

10.0 PATHOLOGY/BIOSPECIMENS

Tumor tissue for *EGFR* assessment should be prepared and sent to central lab as described in the study specific laboratory manual and outlined in Section 4.2.

11.0 DATA AND RECORDS

11.1 Source Documents

Source documents are defined as original documents, data and records. These may include hospital records, clinical and office charts, laboratory data/information, subject diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Source document data may be transcribed onto electronic case report forms (eCRFs) as required. Data collected during this study must be recorded on the appropriate source document.

For all adverse events, the onset date and event description will be captured in source documents. Other adverse event data points required for eCRF completion can be entered directly in the eCRF and may serve as the source document and should be printed, signed and dated by the Investigator.

The Investigator/institution will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

11.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system with the exception of the ePRO information which will be integrated into the eCRFs electronically. All data entered into the eCRF will be supported by source documentation.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the

corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from Investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

12.0 QUALITY ASSURANCE REVIEWS FOR DRUG AND RADIATION THERAPY

Drug and radiation therapy reviews will be performed by the Neuro-Medical Oncology and Radiation Therapy study chairs or their designees. The goal of these reviews is to evaluate protocol treatment compliance within each of these areas. These reviews will be ongoing and are contingent on timely submission of treatment data.

13.0 PROTOCOL DEVIATION

Intentional/prospective deviations from the protocol are not allowed under any circumstances (unless intended to eliminate an apparent immediate hazard to subjects), should not be sought, and will not be approved. This includes deviations from eligibility, as well as abbreviated or lengthened radiotherapy courses (such as hypofractionated schedules in subjects aged at least 70). The principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol violation occurs (or is identified) after a subject has been enrolled, the local principal Investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable and per local policies), and the following AbbVie Clinical Monitor(s):

Primary Contact: [redacted]

[redacted]
Oncology
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Telephone Contact Information:
Office:
Cell:

Fax:
Email:

[redacted]

Alternate Contacts: [redacted]

[redacted]
Oncology
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Office:
Cell:

Fax:
Email:

[redacted]

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design

This is a Phase 3 study. The primary objective of the study is to assess whether ABT-414 in combination with concomitant TMZ/RT followed by combination of ABT-414 with adjuvant TMZ improves ***overall survival*** (OS) compared to concomitant TMZ/RT + adjuvant TMZ in subjects with EGFR-amplified GBM. A total of 640 evaluable subjects will be randomized.

14.2 Statistical Methods

This is a comparative randomized, placebo controlled, double-blinded Phase 3 trial. All efficacy analyses will be performed in the Full Analysis Set (defined below). OS (primary efficacy endpoint for the overall study) and PFS (secondary efficacy endpoint) will be compared between treatment Arms A and B using stratified log-rank test statistics or a weighted version of this test (to be pre-specified in the Statistical Analysis Plan document (the SAP)), adjusting for the study stratification factors. PFS is defined as time from randomization to progression of disease (per RANO criteria) or death, whichever occurs first.

Randomization and Stratification

MGMT methylation status and RPA (referenced in Appendix VI) are demonstrated to be prognostic of survival for newly diagnosed GBM subjects. For this study, subjects will be stratified by *MGMT* methylation status (methylated versus unmethylated), RPA class (III versus IV versus V), region of the world (US/Canada versus other) and *EGFRvIII* mutation status (mutated versus other), where *EGFRvIII* other is defined as wild type, indeterminate due to test failure, invalid, or insufficient tissue. *EGFRvIII* is a stratification factor because it is potentially prognostic and because it is related to the mechanism of action of ABT-414 which binds to both activated wild type *EGFR* and *EGFRvIII*. After stratification, subjects will be randomized to either Arm A or Arm B in a 1:1 ratio.

Analysis Sets

The following analysis sets will used for analysis of safety and primary and secondary efficacy endpoints of the study:

- Full Analysis Set (FAS) will comprise all randomized subjects regardless of whether they received study treatment. Subjects will be classified according to the treatment they were assigned at the time of randomization. The FAS will be the primary analysis set for the analysis of efficacy endpoints.

- Safety Analysis Set (SAS) will comprise all randomized subjects who receive at least one dose of study treatment (either RT, TMZ or ABT-414). Subjects will be classified according to treatment received. Thus a subject randomized to Arm A who receives RT+TMZ but does not receive ABT-414 will be considered in the control group (Arm B) for safety analysis.
- Per-protocol Set (PPS) will comprise all randomized subjects excluding those with major deviation from study inclusion and exclusion criteria, compliance with procedures. Subjects will be classified according to treatment assigned. The PPS will be used for supportive analysis of efficacy endpoints.

14.3 Primary Endpoints Study Design

14.3.1 Primary Endpoint

The primary endpoint for this study is OS, defined as time from randomization to death from any cause. For subjects who are not reported to have died at the time of an analysis, OS will be right-censored at the last date the subject is documented to be alive.

14.3.2 How Primary Endpoint Will Be Analyzed

Efficacy analysis for the overall study will be performed in the FAS which includes all randomized subjects regardless of whether or not they received study treatment. The PPS will be used for supportive analysis of efficacy endpoints. The primary endpoint for the overall study is overall survival (OS). To meet the primary objective, OS will be compared between treatment Arms A and B for the FAS and PPS using stratified log-rank test statistics or a weighted version of the test, adjusting for the study stratification factors and additional independent prognostic factors as deemed appropriate, to be specified in the SAP. If a weighted version is considered to be more appropriate in view of potentially delayed treatment effect, it will be pre-specified in the SAP prior to conducting any unblinded analysis of study data. The hazard-ratio of OS for ABT-414 Arm A compared to placebo Arm B will be estimated by fitting Cox-proportional hazards regression models adjusting for the main-effects of the stratification factors and additional independent prognostic factors as deemed appropriate, to be specified in the SAP.

Type I Error Control

To maintain overall type I error control for the overall study, each secondary endpoint will be tested in the order listed if the primary endpoint (OS) and all preceding secondary endpoints show statistically significant results at the one-sided 0.025 level of significance.

The O'Brien-Fleming method will be implemented to protect the one-sided type I error of 0.025. Specifically, a nominal alpha level of 0.00965 will be used for the interim efficacy analysis for OS. For the final analysis, the primary efficacy endpoint will be tested at the one-sided nominal alpha level of 0.0221 after adjusting for the interim looks at efficacy data.

14.3.3 Sample Size and Power Calculations

The sample sizes are calculated based on the approach of doing the primary endpoint analyses (OS) using the FAS.

A total of 640 evaluable subjects are expected to be randomized. With 441 deaths, there will be approximately 85% power to detect a 25% reduction in the hazard of death (HR = 0.75) using a log-rank test at a one-sided 2.5% level of significance. Median OS of 16 months is expected in the control arm.

14.4 Study Monitoring of Primary Objectives

Interim Reporting for the DMC

The Independent Data Monitoring Committee (IDMC), as coordinated by RTOG Foundation, will review the study at least twice a year with respect to subject accrual, pretreatment characteristics of accrued subjects, the frequency and severity of toxicities and morbidity. The IDMC is also available to review the study on an "as needed" basis.

Safety

AbbVie will assess adverse events, laboratory data and vital signs throughout the study. Analyses of adverse events will include only "treatment-emergent" events, i.e., those that start or worsen on or after the day of the first dose of study drug. Adverse event severity and laboratory evaluation changes will be assessed by utilizing National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Adverse events will be summarized by preferred terms within a System and Organ Class according to the most current Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters. Shifts in laboratory values from baseline NCI CTCAE grades to maximum and final post-baseline grades will be assessed.

Interim Superiority and Futility Analysis of Efficacy Data

An interim superiority and futility analysis of efficacy data will be performed when 75% (332) of the 441 required maximum number of deaths are observed. The analysis will be performed using the Full Analysis Set, with all randomized cases being included in the treatment arm to which they were randomized regardless of what treatment the subjects actually received. The primary endpoint of OS will be compared between treatment Arms A and B using stratified log-rank test statistics (or, a weighted version, as pre-specified in the SAP) adjusting for the study stratification factors and additional independent prognostic factors as deemed appropriate, to be specified in the SAP. The hazard-ratio of OS for ABT-414 Arm A compared to placebo Arm B will be estimated by fitting Cox-proportional hazards regression models adjusting for the main-effects of the stratification factors and additional independent prognostic factors as deemed appropriate, to be specified in the SAP. Adjustment of the level of significance (alpha) for multiple testing will be made using the O'Brien-Fleming group sequential spending function for early rejection of the null hypothesis to declare superiority. Superiority will therefore be assessed at a one-sided significance level of 0.00965, which is corresponding to a Z-score superiority boundary at –2.34. The trial may also be stopped for futility following this interim analysis if the estimated Cox hazard ratio of ABT-414 Arm A to placebo Arm B at interim analysis exceeds 0.9.

The unblinded interim results will first be reviewed by the IDMC, and the trial will be considered for early stopping if the IDMC makes such a recommendation after consideration of the OS results and all supportive evidence including all secondary endpoints and safety. For the final analysis, the primary efficacy endpoint will be tested at the one-sided nominal alpha level of 0.0221 after adjusting for the interim looks at efficacy data. Details for the interim efficacy analysis will be provided in the IDMC charter.

14.5 Accrual/Study Duration Considerations

Subjects will be accrued for a total of 640 evaluable subjects randomized in the study. Once the target accrual is met, subjects will then be followed for another 18 months following randomization of the last subject to observe 441 deaths overall for comparison of OS. The total study duration and accrual duration is thus projected to be 48 months and 29 months, respectively.

14.6 Secondary or Exploratory Endpoints (Including Correlative Science Aims)

14.6.1 Secondary Hypotheses and Endpoints

The secondary efficacy endpoints include PFS, OS for the MGMT unmethylated and methylated subgroups , time to deterioration in symptom severity score (MDASI-BT), time to deterioration in symptom interference score (MDASI-BT), time to deterioration in verbal memory (HVLT-R) total recall score, OS for the *EGFRvIII* mutated tumor subgroup, and PFS for the *EGFRvIII* mutated tumor subgroup.

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Each secondary endpoint will be tested in the order listed only after the superiority of treatment Arm A with respect to the primary efficacy endpoint (OS) is established. . To protect overall Type I error across primary and all the secondary endpoints, "overall hierarchical" testing strategy[34] will be used for testing the primary and secondary endpoints. Unless otherwise specified, the secondary time-to-event type efficacy endpoints (OS, PFS and time to deterioration) will be compared between treatment Arms A and B using stratified log-rank test statistics or a weighted version of this test (to be pre-specified in the Statistical Analysis Plan document), adjusting for the study stratification factors and additional independent prognostic factors as deemed appropriate, to be specified in the SAP. The hazard ratio for ABT-414 Arm A compared to placebo Arm B will be estimated by fitting Cox proportional hazards regression models adjusting for the main-effects of the stratification factors and additional independent prognostic factors as deemed appropriate, to be specified in the SAP.

Progression Free Survival (PFS)

PFS is defined as time from randomization to progression of disease (per RANO criteria) or death, whichever occurs first. For subjects who are not documented to have experienced a PFS event at the time of an analysis, PFS will be right-censored on the date of their last adequate radiographic assessment of disease. PFS will be analyzed in similar way to OS. That is, PFS will be compared between treatment Arms A and B for the FAS using stratified log-rank test statistics or a weighted version of this test (to be pre-specified in the Statistical Analysis Plan document, adjusting for the study stratification factors and additional independent prognostic factors as deemed appropriate, to be specified in the SAP. The hazard-ratio of PFS for ABT-414 Arm A compared to placebo Arm B will be estimated by fitting Cox-proportional hazards regression models adjusting for the main-effects of the stratification factors and additional independent prognostic factors as deemed appropriate, to be specified in the SAP.

A sensitivity analysis will be conducted to evaluate the robustness of the results, as exploratory and supportive of the primary PFS analysis. Accounting for subjects who died or progressed after more than one (> 1) missed visit, the following sensitivity analysis will be performed: Considering the date of the earliest missed radiological assessment following the last adequate radiological assessment prior to a subject's progression or death, as a date of progression.

No imputation will be used for subjects with no more than one missed visit in the sensitivity analysis. Details for the sensitivity analysis will be provided in the SAP.

Overall Survival for the MGMT Methylated, MGMT Unmethylated and EGFRvIII-Mutated Tumor Subgroups

OS analysis will be performed in the subgroup of patients with MGMT methylated MGMT unmethylated and EGFRvIII-mutation. The same methodology as for the primary OS analysis in the FAS will be applied.

Progression Free Survival for the EGFRvIII-Mutated Tumor Subgroup

PFS analysis will be performed in the subgroup of patients with EGFRvIII-mutation. The same methodology as for the PFS analysis in the FAS will be applied.

Time to Deterioration in Verbal Memory (HVLT-R)

In the Phase 3 part of the study, time to deterioration in verbal memory, based on the HVLT-R Total Recall, will be analyzed as a separate secondary endpoint. Other individual components and outcome from HVLT-R and FAS verbal fluency will be analyzed on an exploratory basis.

The HVLT-R Total Recall score will be computed by summing the total number of words recalled across 3 trials. Standardized scores (mean = 0, SD = 1) for each test are calculated using published normative data from a healthy population. At each assessment, change in the HVLT-R total recall score relative to baseline will be calculated and verbal memory performance will be categorized as declined or not using the reliable change index (RCI) criterion based on the raw scores.

The deterioration is defined as satisfying the deterioration criteria without further improvement within 8 weeks or occurrence of death. TTD endpoints will be derived as follows:

TTD = Date of first occurrence of first deterioration event or censoring – date of randomization + 1.

Time to deterioration in verbal memory will be assessed using the standard log-rank test. The hazard-ratio for ABT-414 Arm A compared to placebo Arm B will be estimated by fitting the Cox PH models with stratification factors included as the covariates.

Time to Deterioration in Symptom Severity and Symptom Interference (MDASI-BT)

In the Phase 3 part of the study, the symptom severity and the symptom interference scores of the MDASI-BT will be used as the outcome of interest for this analysis. Data will be scored according to the MDASI user manual. A change of ≥ 1 point on a 10-point scale at follow-up assessment with respect to baseline will be considered as clinically relevant. The scores for symptom severity and symptom interference are calculated by averaging the scores of the symptom severity- and symptom interference-related questions, respectively. Changes in symptom severity score and symptom interference score at each time point will be classified into 3 categories: improved (≤ -1), stable (> -1 and < 1), and deteriorated (≥ 1).

Time to deterioration in overall symptom burden and interference will be analyzed using the similar approach for time to deterioration in neurocognitive failure.

14.7 Exploratory Hypothesis and Endpoints

- OS at 1 year
- OS at 2 years
- PFS at 1 year
- PFS at 2 years
- OS for non-*EGFRvIII* subjects (comparison between arms)
- PFS for non-*EGFRvIII* subjects (comparison between arms)
- PFS for the MGMT unmethylated and methylated sub-groups
- OS and PFS for Total *EGFR* expressions levels
- To compare change from baseline in neurocognitive functioning (HVLT-R and COWA-FAS)
- To evaluate changes from baseline in HRQoL based on the EORTC QLQ-C30/BN20
- To evaluate changes from baseline in performance status based on KPS scores
- To compare median time that KPS score was maintained at 70 or higher
- Change from baseline in Vision item on the MDASI-BT and EORTC BN20
- *EGFR* amplification and *EGFRvIII* prognostic value
- Changes in *EGFR* molecular profile during therapy among subjects who undergo additional surgery as part of routine care
- Change from baseline in symptom severity factor groupings (MDASI-BT neurologic,

cognitive, treatment and symptom interference (activity-related, mood-related))

- Pharmacokinetics of ABT-414, total ABT-806, and unconjugated cys-mcMMAF
- To evaluate changes from baseline in average daily corticosteroid dosing during post-treatment period.

OS and PFS at 1 year and 2 years will be summarized and reported by treatment arm.

For the endpoint on the OS and PFS comparison for non-*EGFRvIII EGFR* amplified subjects, the treatment group differences will be evaluated using the similar methodology as for analyses in the FAS. Analysis details will be provided in the Statistical Analysis Plan.

Scoring for the EORTC QLQ-C30, QLQ-BN20, MDASI-BT will be based on their corresponding user manuals.[31-33] Summary statistics of the EORTC QLQ-C30, QLQ-BN20, MDASI-BT, HVLT-R, COWA-FAS, and KPS including their changes from baseline will be calculated at each assessment time point for both study arms. Analysis details will be provided in the Statistical Analysis Plan.

Pharmacokinetic:

Peak and trough concentrations (maximum observed plasma concentration [C_{max}] and C_{trough}) of ABT-414 and total ABT-806 antibody will be summarized from the observed concentration data. Population pharmacokinetic parameters of ABT-414, total ABT-806 and cys-mcMMAF such as clearance and volume of distribution will be estimated using a nonlinear mixed effect modeling analysis.

15.0 ETHICS

15.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The Investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports or any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

15.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) GCP guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical Investigator are specified in Appendix V.

15.3 Subject Information and Consent

Prior to the initiation of any screening or study-specific procedures, the Investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Subjects who provide optional samples for analysis will also sign an informed consent regarding the collection of these samples (i.e., pharmacogenetic [PG] blood sample and tissue samples). Each informed consent will be reviewed, signed and dated by the subject, the person who administered the informed consent, and any other signatories according

to local requirements. A copy of each informed consent will be given to the subject and each original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Post-treatment tissue collection and analysis will only be performed if the subject has voluntarily signed and dated a separate post-treatment tissue informed consent (or indicated consent within the main study informed consent form), approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The post-treatment tissue informed consent must be signed before the tissue collection and analysis is performed. If a subject does not consent to the post-treatment tissue collection and analysis, it will not impact the subject's participation in the study.

A sample for pharmacogenetic analysis will only be collected if the subject has voluntarily signed and dated a separate pharmacogenetic informed consent (or indicated consent within the main study informed consent form), approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The pharmacogenetic informed consent must be signed before the pharmacogenetic testing is performed. If the subject does not consent to the pharmacogenetic testing, it will not impact the subject's participation in the study.

In the event a subject withdraws from the study stored biomarker samples will also be destroyed upon request (samples will not be stored for more than 20 years from the time the Clinical Study Report is completed). In the event that destruction is not possible, they will no longer be linked to the subject. If the subject changes his/her consent, and the samples have already been tested, those results will still remain part of the overall research data.

16.0 DATA QUALITY ASSURANCE

Prior to enrolling any subject in the study, an initiation meeting will be held with AbbVie personnel, the Investigator(s), and the study coordinators/project manager(s). This meeting will include a detailed discussion and review of the protocol and essential documents, performance of study procedures, case report form completion and specimen collection methods.

The AbbVie monitor will monitor the study site throughout the study. Source document review will be made against entries on the case report forms and a quality assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations. In addition, after the case report forms are retrieved, a review of the data will be conducted by a physician or representative at AbbVie.

All data hand entered in the database will be verified at AbbVie. Any discrepancies will be reviewed against the hard-copy case report form and corrected on-line. After completion of the entry process, computer logic and manual checks will be created to identify such items as inconsistent study dates. Any necessary corrections will be made to the database via the appropriate change form/electronic CRF.

Routine hematology, serum chemistry and serology, and urinalysis tests will be conducted using a certified clinical laboratory. Laboratory reference ranges will be obtained prior to the initiation of the study. A review of all laboratory results will be conducted by the AbbVie monitor, the Investigator and other appropriate personnel from AbbVie.

17.0 USE OF INFORMATION

All information concerning ABT-414 and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of ABT-414. This information may be disclosed as deemed necessary by AbbVie to other clinical Investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study, including each subject's name, subject number, address, phone number and emergency contact information. This list will be maintained at the study site with other study records under adequate security and restricted access, and will not be retrieved by AbbVie.

Any pharmacogenetic and exploratory biomarker research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or subject management. Hence, neither the Investigator, the subject, nor the subject's physician (if different from the Investigator) will be informed of individual subject results should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate pharmacogenetic and exploratory biomarker information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic and exploratory biomarker information will be published or presented only in a way that does not identify any individual subject.

18.0 COMPLETION OF STUDY

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator and AbbVie. The Investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The Investigator must retain any records related to the study according to local requirements. If the Investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory coordinating Investigator from the Investigators who participate in each multi-center study. Selection criteria for this signatory Investigator will be based on level of participation, and significant knowledge of the clinical research, investigational drug, and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

The end of study is defined as the date of the last subject's last visit.

19.0 INVESTIGATOR'S AGREEMENT

1. I have received and reviewed the Investigator's Brochure for ABT-414.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Randomized, Placebo Controlled Phase 3 Study of ABT-414 with Concurrent Chemoradiation and Adjuvant Temozolomide in Subjects with Newly Diagnosed Glioblastoma (GBM) with Epidermal Growth Factor Receptor (*EGFR*) Amplification (Intellance1)

Protocol Date: 26 May 2019

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

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APPENDIX I SUMMARY OF RANO RESPONSE CRITERIA

Tumor assessments will be assessed using the RANO criteria as outlined below according to Wen, et al, "Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group."

Table 1. Criteria for Determining First Progression Depending on Time from Initial Chemoradiotherapy

First Progression	Definition
Progressive disease < 12 weeks after completion of chemoradiotherapy	Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (e.g., solid tumor areas [i.e., > 70% tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy.
Progressive disease ≥ 12 weeks after chemoradiotherapy completion	1. New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids. 2. Increase by ≥ 25% in the sum of the products of perpendicular diameters between the first post-radiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids. 3. Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence. 4. For patients receiving anti-angiogenic therapy, significant increase in T2/FLAIR non-enhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not be a result of comorbid events (e.g., effects of radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).

FLAIR = fluid-attenuated inversion recovery

Pseudoprogression and Radiation Effects

The proposed new response criteria suggest that within the first 12 weeks of completion of radiotherapy, when pseudoprogression is most prevalent, progression can only be determined if the majority of the new enhancement is outside of the radiation field (for example, beyond the high-dose region or 80% isodose line) or if there is pathologic confirmation of progressive disease. It is recognized that the proposed histologic criteria have important limitations, but they

provide guidance on the type of findings that are suggestive of progressive disease. For patients in whom pseudoprogression cannot be differentiated from true tumor progression, enrollment onto trials for recurrent gliomas should not be permitted. Patients who remain clinically stable and/or are suspected to have pseudoprogression based on metabolic or vascular imaging should continue with their current therapy.

Enhancement as a Result of Surgery and Other Therapies

Increased enhancement often develops in the wall of the surgical cavity 48 to 72 hours after surgery. To avoid interpretation of post-operative changes as residual enhancing disease, a baseline MRI scan should ideally be obtained within 24 to 48 hours after surgery and no later than 72 hours after surgery. The inclusion of diffusion weighted imaging in the immediate post-operative MRI scan can be helpful in determining whether new enhancement developing in the subsequent weeks or months is caused by sequelae of ischemia or by tumor recurrence. In addition, a transient increase in enhancement that can be difficult to distinguish from recurrent disease can also occur after locally administered therapies. These include chemotherapy wafers, immunotoxins delivered by convection enhanced delivery, regionally administered gene and viral therapies, immunotherapies, and focal irradiation with brachytherapy and stereotactic radiosurgery. Imaging modalities such as perfusion imaging, magnetic resonance spectroscopy, and positron emission tomography scans may sometimes be helpful in differentiating treatment effects from recurrent tumor. However, no imaging modality currently has sufficient specificity to conclusively differentiate recurrent tumor from treatment effects, and surgical sampling may occasionally be needed to obtain a definitive diagnosis.

Definition of Clinical Deterioration

The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the Eastern Cooperative Oncology Group and WHO performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration.

For those subjects who have measurable disease post resection, RANO criteria for assessment of CR, PR, SD and PD can be applied. See the below tables for the definitions to be used.

Definition of Radiographic Response

Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smallest tumor measurement at either pretreatment baseline should be used for determination of progression. The criteria for radiographic changes after therapy are listed in Table 1. In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patient closely, for example at 4-week intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan at which this issue was first raised. The determination of radiographic response after treatment with agents that affect vascular permeability is particularly difficult. In these patients, consideration should be given to performing a second scan at 4 weeks to confirm the presence of response or stable disease. All measurable and nonmeasurable lesions should be assessed using the same techniques as at baseline. Ideally, patients should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

Patients with nonmeasurable enhancing disease whose lesions have significantly increased in size and become measurable (minimal bidirectional diameter of ≥ 10 mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0 mm skip) will also be considered to have experienced progression. The transition from a nonmeasurable lesion to a measurable lesion resulting in progression can theoretically occur with relatively small increases in tumor size (e.g., a 9 × 9 mm lesion [nonmeasurable] increasing to a 10 × 11 mm lesion [measurable]). Ideally, the change should be significant (> 5 mm increase in maximal diameter or ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions). In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression. If there is uncertainty regarding whether there is progression, the patient may continue on treatment and remain under close observation (e.g., evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is in fact experiencing progression, then the date of progression should be the time point at which this issue was first raised.

Table 2. Summary of the Proposed RANO Response Criteria

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA**
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

RANO = Response Assessment in Neuro-Oncology; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; FLAIR = fluid-attenuated inversion recovery; NA = not applicable

* Progression occurs when this criterion is present.

** Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

APPENDIX II RTOG 3508/ABBVIE STUDY M13-813 PROTOCOL SYNOPSIS

AbbVie Inc.	**Protocol Number:** M13-813
Name of Study Drug: ABT-414	**Phase of Development:** 3
Name of Active Ingredient: ABT-414	**Date of Protocol Synopsis:** 26 May 2019
Protocol Title: A Randomized, Placebo Controlled Phase 3 Study of ABT-414 with Concurrent Chemoradiation and Adjuvant Temozolomide in Subjects with Newly Diagnosed Glioblastoma (GBM) with Epidermal Growth Factor Receptor (*EGFR*) Amplification (Intellance1)	
Primary Objective: To determine whether the addition of ABT-414 to concomitant radiotherapy and TMZ plus adjuvant TMZ prolongs Overall Survival (OS) among subjects with newly diagnosed GBM harboring *EGFR* amplification. **Secondary Objectives:** To determine whether the addition of ABT-414 to concomitant radiotherapy and TMZ plus adjuvant TMZ improves outcomes among subjects with newly diagnosed GBM harboring *EGFR* amplification for the following endpoints: • PFS • OS for the MGMT unmethylated tumor subgroup • OS for the MGMT methylated tumor subgroup • Time to deterioration in symptom severity score (MDASI-BT) • Time to deterioration in symptom interference score (MDASI-BT) • Time to deterioration in neurocognitive functioning on the Hopkins Verbal Learning Test Revised (HVLT-R) total recall score • OS for the EGFRvIII-mutated tumor subgroup • PFS for EGFRvIII-mutated tumor subgroup Safety: • Assessment of comparative safety **Tools:** Symptom Inventory: MD Anderson Symptom Index for Brain Tumors (MDASI-BT). Neurocognitive Functioning: The Hopkins Verbal Learning Test-Revised (HVLT-R) for memory; and COWA-FAS verbal fluency test for executive function. Quality of Life: (Exploratory Objective) European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 with EORTC-QLQ-BN20 (brain tumor module) and EQ-5D-5L	
Investigators: Multicenter, multi-national	
Study Sites: Approximately 200	
Study Population: Newly diagnosed GBM subjects with *EGFR* amplification.	
Number of Subjects to be Enrolled: Approximately 640	

Mechanism of Action:

ABT-414 is a newer generation ADC consisting of: (1) a veneered "humanized" recombinant IgG1κ antibody that has binding properties specific to a unique epitope of human *EGFR* with (2) non-cleavable maleimido-caproyl linkers each attached to (3) a potent antimicrotubule agent, monomethylauristatin F (MMAF). The antibody binds to the activated *EGFR* epitope (even in the absence of the *EGFRvIII* mutation), is internalized, and then intracellular enzymes release the toxin leading to inhibition of microtubule function, the disruption of critical cellular processes, and cell death. Importantly, ABT-414 binds to an epitope that is available predominantly on tumor cells with either the *EGFR*de2-7 (*EGFRvII*) deletion mutant or on tumor cells with activated wild-type *EGFR* (i.e., with *EGFR* amplification). The epitope is largely inaccessible when *EGFR* is expressed at normal physiological levels; thus, ABT-414 has limited binding to non-activated, wild-type *EGFR* expressed on normal tissues. These properties, therefore, favor limited effects of the toxin on normal tissues while maintaining a high degree of activity on *EGFR*-amplified tumor cells.

Methodology:

This is a Phase 3 randomized double-blind, placebo-controlled trial comparing the efficacy and safety of ABT-414 versus placebo, each as concurrent treatment with standard-of-care therapy of radiation/TMZ plus adjuvant TMZ and followed by ABT-414/placebo monotherapy, in subjects with newly diagnosed GBM.

The study comprises a Screening Period of up to 7 weeks from surgery; a 6-week concomitant Chemoradiation Phase; an Adjuvant Phase beginning approximately 4 weeks after completion of chemoradiation, and a Follow-Up Phase. The Adjuvant Phase is comprised of 28-day cycles, with subjects receiving concomitant TMZ and study drug (ABT-414/placebo) for the first 6 cycles, and study drug (ABT-414/placebo) monotherapy for the following 6 cycles. Subsequent cycles will start approximately 28 days from the start of the previous cycle, and the cycle schedule will not be affected by delays or interruptions in TMZ or ABT-414/placebo dosing. Adjuvant treatment will be discontinued once disease progression has been determined. A Final Study Drug Visit will be performed upon discontinuation of study drug (ABT-414/placebo) for any reasons, followed by a 35-Day and 49-Day Follow-up Visits (± 3 days). Subjects who are unable to attend the 49 Day Follow-up will be phoned to obtain adverse event and concomitant medication information. In the Follow-Up Phase, subjects who complete adjuvant treatment or discontinue study drug prior to disease progression will continue to undergo MR imaging and assessment of neurocognitive functioning and patient reported outcomes (PRO) approximates every 8 weeks up to and including at the time of disease progression, starting 8 weeks after the last scheduled PRO assessments in the Adjuvant Phase. After disease progression, overall survival will continue to be assessed quarterly.

A sample of pre-treatment tumor tissues will be collected and sent to central laboratories to confirm diagnosis of GBM (required to enroll in the trial) and test for *EGFR* amplification (required to enroll in the trial), *MGMT* promoter methylation (a stratification factor), *EGFRvIII* mutation (a stratification factor) and other biomarkers prior to starting chemoradiation. If a subject has a repeat surgery before initiating treatment, then the tissue from either biopsy/resection may be used for histologic and EGFR amplification, *EGFRvIII* mutation and *MGMT* promoter methylation testing. If molecular results are discordant between multiple specimens from the same patient, then the results that permit eligibility will be used. Remaining sample tissue will be retained for other exploratory molecular analysis where allowed by local regulations. If local regulations do not allow tissue shipment or storage, the tissue will be immediately returned or destroyed after eligibility testing.

Screening procedures must be completed prior to Day 1 of the Chemoradiation Phase. Screening procedures will include signing of a study consent form, medical history, Karnofsky Performance Scale (KPS) assessment and recursive partitioning analysis (RPA) classification, baseline ECG, physical, ophthalmologic and neurological examinations, Patient Reported Outcomes (PRO) and neurocognitive assessments, laboratory tests (≤ 21 days from treatment start), and pregnancy test (≤ 7 days from treatment start) if applicable. If a subject starts chemoradiation more than 28 days after surgery, the subjects will have a brain MRI 21 (but preferably fewer) days prior to Day 1 Week 1 of the Chemoradiation Phase to be used as the baseline for efficacy analyses; the timing of the MRI should allow sufficient time to revise the radiation therapy plan if needed due to a significant change in tumor since surgery. Safety-related evaluations will be conducted within 14 or fewer days prior to Day 1 of the Chemoradiation Phase. Subjects who screen positive for *EGFR* amplification in the tumor tissue may enter the study if all inclusion/exclusion criteria are met.

Methodology (Continued):

Upon study entry, subjects will be stratified according to the following 4 factors: region of the world (US/Canada or other), RPA classes (III, IV or V), *MGMT* methylation (methylated or unmethylated), and *EGFRvIII* status (mutated or other). Subjects will be randomized within each stratum on a 1:1 ratio to receive either ABT-414 Arm A or Placebo Arm B during the Chemoradiation and Adjuvant therapy phases.

During the Chemoradiation Phase, all subjects will undergo focal RT, with one treatment of approximately 2 gray (Gy) given daily 5 days per week for a total of approximately 60 Gy over approximately 6 weeks (and no more than 7 weeks). TMZ will be administered continuously from Day 1 of radiotherapy to the last day of radiation (including weekends and holidays) at a daily oral dose of 75 mg/m^2 for a maximum of 49 days. Subjects in Arm A will receive blinded ABT-414 at 2.0 mg/kg IV infusion over 30 – 40 minutes once every 2 weeks (Day 1 of Weeks 1, 3, and 5 of the 6-week regimen). Subjects in Arm B will receive blinded placebo IV infusion over 30 – 40 minutes once every 2 weeks (Day 1 of Weeks 1, 3, and 5 of the 6-week regimen). Treatment in the Chemoradiation Phase must begin ≤ 7 weeks after biopsy/surgery.

The start of the first cycle during the Adjuvant Therapy Phase will be scheduled approximately 28 days after the last day of radiotherapy. During the Adjuvant Therapy Phase, all subjects will receive oral TMZ 150 – 200 mg/m^2 once daily on Days 1 – 5 of each 28-day cycle for 6 cycles unless there is disease progression, unacceptable toxicity, or other reasons to discontinue. Subjects in Arm A will receive blinded ABT-414 at 1.25 mg/kg by intravenous infusion on Day 1 and Day 15 of each 28-day cycle for 12 cycles. Subjects in Arm B will receive blinded placebo IV infusion on Day 1 and Day 15 of each 28-day cycle for 12 cycles.

If, after completing 12 cycles of adjuvant treatment, the subject is tolerating study drug (ABT-414 or placebo) and the Investigator believes the subject is continuing to benefit from ongoing study drug treatment, the Investigator may extend the Adjuvant Phase after consultation with the Neuro-Medical Oncology Chair or AbbVie Medical Monitor, as long as disease progression has not been determined.

Occurrence of disease progression to calculate PFS will be determined by the Investigator, based on local evaluation of images and other clinical information using the Response Assessment in Neuro oncology (RANO) criteria. Post-baseline scans will be obtained ≤ 14 days before Day 1 of each odd-numbered cycle (Cycles 1, 3, 5, etc.) of the Adjuvant Phase and ≤ 14 days before each visit (approximately every 8 weeks) of the Follow-Up Phase. MR images will also be reviewed centrally by an independent blinded reviewer for radiographic evidence of disease progression. When study drug is discontinued for any reason, a Final Study Drug Visit will be conducted. All subjects will have a 35-Day and 49-Day Follow-Up Visits (± 3 days) after the last dose of ABT-414/placebo. Overall survival will be assessed quarterly after study discontinuation.

All subjects will receive prophylactic eye drops with each dose of ABT-414/placebo for 7 consecutive days, starting from 2 days prior to infusion and continuing until 4 days after infusion. The eye drop formulations recommended for the study are ranked by steroid potency from Level 1 (non-steroid artificial tears) to Level 4 (high-potency steroid where available. Subjects will be monitored with regular ophthalmologic examinations (with additional symptom-driven examinations as needed). The potency of the eye drop formulation given with subsequent ABT-414/placebo doses will be adjusted upward or downward based on corneal findings. To minimize unnecessary risks associated with prolonged administration of ocular steroids there is a step-down in the level of eye drop potency for subjects who have received at least 2 doses of ABT-414/Placebo and with Grade 1 or no eye toxicity who have no evidence of corneal microcysts on 2 consecutive ophthalmic examinations.

Methodology (Continued):

During chemoradiation, subjects should receive antiemetic prophylaxis and antibiotics should be per local regulation guidelines to prevent Pneumocystis (*jirovecii*) pneumonia (PCP) while receiving TMZ. Supportive care including systemic corticosteroid use is allowed. Anti-cancer agents, other investigational anti-neoplastic drugs and some uses of growth factors are prohibited during the study. Any other type of chemotherapy, immunotherapy, biologic therapy, medication (including over the counter) or vaccine used for antineoplastic intent are also prohibited.

An open-label, single-group sub-study of ABT-414 use in newly diagnosed GBM subjects with mild to moderate hepatic impairment is included in Appendix IX.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Histologically confirmed de novo Grade IV glioma (GBM, gliosarcoma or other subvariants) confirmed by central pathology tissue screening.
2. *EGFR* amplification in tumor tissue confirmed by central assessment.
3. *Inclusion Criteria removed in Amendment 5.*
4. The subject must have recovered from the effects of surgery, post-operative infection, and other complications before enrollment including suture/staple removal from brain surgery and sufficient wound healing before randomization.
5. ≥ 18 years of age.
6. Karnofsky performance status ≥ 70 at assessment ≤ 14 days prior to randomization.
7. Results for required stratification factors (*EGFRvIII* status, *MGMT* methylation status, Recursive Partitioning Analysis (RPA) class, and region of world) available prior to randomization.
8. Subject has adequate bone marrow, renal, and hepatic function ≤ 21 days prior to randomization as follows:
   - Absolute neutrophil count (ANC) ≥ 1,500/mm3.
   - Platelets ≥ 100,000/mm3.
   - Hemoglobin (Hgb) ≥ 9.0 g/dL (Note: The use of transfusion or other intervention to achieve Hgb ≥ 9.0 g/dL is acceptable.).
   - Renal function: calculated creatinine clearance ≥ 30 mL/min by the Cockcroft-Gault formula.
   - Hepatic function: Total bilirubin ≤ 1.5 times upper limit of normal (ULN), Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT) ≤ 3 times upper limit of normal (ULN). Subjects with Gilbert's syndrome documented in medical history may be enrolled if total bilirubin is < 3 times ULN.
9. Electrocardiogram (ECG) without evidence of acute cardiac ischemia ≤ 21 days prior to randomization.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

10. Female subjects of childbearing potential (i.e., those who are not postmenopausal for at least 1 year or surgically sterile by bilateral salpingectomy, bilateral oophorectomy or hysterectomy) should practice at least one accepted method of birth control listed below during study entry, for the entire duration of the study and for at least 6 months after treatment with ABT-414 and TMZ treatment has ended. Male subjects should practice at least one of the accepted methods of birth control during study and for at least 6 months after ABT-414 and TMZ. If using a condom, practice at least one other methods of birth control listed below during the study and for at least 6 months after ABT-414 and TMZ:
    - Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1;
    - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1;
    - Bilateral tubal occlusion/ligation;
    - True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable];
    - A vasectomized male subject or a vasectomized partner of a female subject;
    - Intrauterine device, IUD (females);
    - Intrauterine hormone-releasing system, IUS (females);
    - Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or cream) unless not deemed acceptable as highly effective contraception by local regulations.
11. Women of child-bearing potential must have a negative pregnancy test (urine or serum) within 7 days prior to randomization.
12. Must voluntarily sign and date informed consent form, for tumor tissue biomarker testing and for study participation, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Main Exclusion:

1. Subject has multifocal GBM, defined as discrete sites of disease without contiguous T2/FLAIR abnormality that require distinct radiotherapy ports.
    - Note that satellite lesions that are associated with a contiguous area of T2/FLAIR abnormality as the main lesion(s) and that are encompassed within the same radiotherapy port as the main lesion(s) are permitted. For any questions, please contact the Sponsor.
2. *Exclusion criteria removed in Amendment 5.*
3. Subject has recurrent GBM.
4. *Exclusion criteria removed in Amendment 5.*
5. Subject has metastatic GBM.
6. Prior chemotherapy or radiosensitizers for cancers of the head and neck region; note that prior chemotherapy for a different cancer is allowable, except prior TMZ.
7. Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation fields.
8. Any prior therapy for glioblastoma except surgery (intra-operative techniques to guide resection are allowed as are experimental imaging techniques).
9. Prior invasive malignancy (except for non-melanomatous skin cancer; carcinoma in situ of the breast, oral cavity, or cervix) unless disease free for $\geq$ 2 years.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

10. Prior, concomitant, or planned concomitant treatment with anti-neoplastic intent including but not limited to Novo Tumor Treatment Fields (Novo TTF, *EGFR*-targeted therapy (including *EGFRvIII*-directed therapy), bevacizumab, Gliadel wafers or other intratumoral or intracavitary anti-neoplastic therapy, or other experimental therapeutics intended to treat the tumor. Diagnostic or imaging studies, quality of life, biomarker or epidemiological studies; surgery and operative guides to improve extent of resection are allowed.
11. Subject has had major immunologic reaction to an IgG-containing agent.
12. Subject has had LASIK (laser-assisted in situ keratomileusis) procedure within the last 1 year or cataract surgery within the last 3 months.
13. Subject has a history of hypersensitivity to TMZ or excipients, ABT-414 components or excipients, and dacarbazine (contraindication for TMZ).
14. Subject is unsuitable for receiving ocular steroids:
    - Subject has any active viral disease of the cornea or conjunctiva, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella; mycobacterial infection of the eye; fungal diseases of ocular structures; or any other contraindication for ocular steroid use.
    - Subject has a known or suspected hypersensitivity to any ocular steroid.
    - Subject has primary open angle glaucoma or a history of steroid-induced intraocular pressure elevation.
15. Subject is a lactating or pregnant female.
16. Severe, active co-morbidity, defined as follows:
    - Severe hepatic impairment (Child-Pugh category C or higher [score of 10 or higher (Appendix VII)]): Subjects with mild or moderate hepatic impairment (Child-Pugh score of 5 – 9) may be eligible for treatment, as described in Appendix IX.
    - Unstable angina and/or congestive heart failure within the last 6 months.
    - Transmural myocardial infarction within the last 6 months.
    - Evidence of recent myocardial infarction or ischemia by the findings of S-T elevations of $\geq$ 2 mm using the analysis of an EKG performed within 21 days prior to enrollment.
    - New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 12 months prior to enrollment (Appendix IV).
    - History of stroke, cerebral vascular accident (CVA) or transient ischemic attack within 6 months.
    - Serious and inadequately controlled cardiac arrhythmia.
    - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of enrollment.
    - Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of enrollment.
    - Subjects with clinically defined Acquired Immune-Deficiency Syndrome (AIDS)-defining illness. This is necessary to ensure subjects are likely to be able to receive the full TMZ regimen.
    - Active connective tissue disorders, such as lupus or scleroderma that in the opinion of the Investigator may put the subject at high risk for radiation toxicity.
    - Any other major medical illnesses or psychiatric impairments that in the Investigator's opinion will prevent administration or completion of protocol therapy.
17. Subjects treated on any other therapeutic clinical protocols within 30 days prior to study entry or during participation in the study except intra-operative therapy to guide resection or experimental imaging without therapeutic intent.
18. Inability to undergo contrast-enhanced MRI scans.

Background Therapy:

All subjects will receive standard-of-care treatment for newly diagnosed glioblastoma, per local prescribing information and local institutional guidelines, as background therapy.

Chemoradiation Phase: All subjects will undergo focal radiotherapy, 60 Gy in 30 fractions (or 59.4 Gy in 33 fractions) over approximately 6 weeks (and no more than 7 weeks). TMZ will be administered continuously from Day 1 of radiotherapy to the last day of radiation (including weekends and holidays) at a daily oral dose of 75 mg/m^2 for a maximum of 49 days.

Adjuvant Phase: During the Adjuvant Therapy Phase, all subjects will receive oral TMZ 150 – 200 mg/m^2 once daily on Days 1 – 5 of each 28-day cycle for 6 cycles unless there is disease progression, unacceptable toxicity, or other reasons to discontinue. The start of the first cycle during the Adjuvant Therapy Phase will be scheduled approximately 28 days after the last day of radiotherapy.

Investigational Product:	ABT-414
Doses:	20 mg and 100 mg vials sterile lyophilisate to be reconstituted and further diluted for IV infusion
Mode of Administration:	Intravenous (IV) infusion administered over 30 to 40 minutes.
Reference Therapy:	Placebo solution
Doses:	To match 20 mg and 100 mg vials sterile lyophilisate to be reconstituted and further diluted for IV infusion
Mode of Administration:	Intravenous (IV) infusion administered over 30 to 40 minutes
Reference Therapy:	Temozolomide (TMZ)
Doses:	Daily Day 1 to maximum 49 days in chemoradiation phase Daily Days 1 – 5 every 28 days in adjuvant phase
Mode of Administration:	Oral

Duration of Treatment:

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the Treatment Plan Overview, Section 5.1, or until one of the following criteria applies:

- The subject experiences disease progression
- The subject experiences intercurrent illness that prevents further administration of treatment
- The subject experiences excessive toxicity precluding further therapy with either ABT-414 or TMZ, according to the Investigator
- Subject decides to withdraw consent for participation in the study
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the Investigator
- Subject becomes pregnant while on study

Subjects unable to continue either TMZ or ABT-414/placebo due to excessive drug-specific toxicity will be allowed to continue therapy with the other, tolerated therapy components until one of the other criteria above is met.

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint will be OS.

Secondary endpoints are as follows:

- PFS
- OS for the *MGMT unmethylated* tumor subgroup
- OS for the *MGMT methylated* tumor subgroup
- Time to deterioration in symptom severity score (MDASI-BT)
- Time to deterioration in symptom interference score (MDASI-BT)
- Time to deterioration neurocognitive functioning on the Hopkins Verbal Learning Test-Revised (HVLT-R) total recall score
- OS for *EGFRvIII*-mutated tumor subgroup
- PFS for *EGFRvIII*-mutated tumor subgroup

Safety:

- Assessment of comparative safety

Tools:

Symptom Inventory: MD Anderson Symptom Index for Brain Tumors (MDASI-BT).

Neurocognitive Functioning: HVLT-R for verbal memory, and COWA-FAS for executive function.

Quality of Life: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) with the EORTC-QLQ-BN20 (brain tumor) module, EQ-5D-5L and EQ-5D-VAS for health status; National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) for visual function and impact on daily activities.

Pharmacokinetic:

Blood samples for assay of ABT-414, total ABT-806, anti-drug antibodies (ADA), neutralizing anti-drug antibodies (nADA) and unconjugated cys-mcMMAF will be collected at designated time points throughout the study.

Pharmacodynamic:

Plasma and serum will be collected at designated time points throughout the study. Tumor tissues obtained during biopsy or surgery will also be used for pharmacodynamic studies.

Safety:

Adverse events, laboratory profiles, physical exams, ECGs, and vital signs will be assessed throughout the study. Eye examinations will be assessed at baseline and throughout the study.

Statistical Methods

Analysis Sets:

The following analysis sets will used for analysis of safety and primary and secondary efficacy endpoints of the study:

- Full Analysis Set will comprise all randomized subjects regardless of whether they received study treatment. Subjects will be classified according to the treatment they were assigned at the time of randomization. The Full Analysis Set will be the primary analysis set for the analysis of efficacy endpoints.
- Safety Analysis Set (SAS) will comprise all randomized subjects who receive at least 1 dose of study treatment (either RT, TMZ, or ABT-414). Subjects will be classified according to treatment received. Thus, a subject randomized to Arm A who receives RT + TMZ but does not receive ABT-414 will be considered in the control group (Arm B) for safety analysis.
- Per-protocol Set (PPS) will comprise all randomized subjects excluding those with major deviation from study inclusion and exclusion criteria and compliance with procedures. Subjects will be classified according to treatment assigned. The PPS will be used for supportive analysis of efficacy endpoints.

Statistical Methods (Continued):

Efficacy Analysis:

Analysis of OS and PFS:

The primary efficacy endpoint for the study is OS and PFS is considered as one of the secondary efficacy endpoints. Overall survival is defined as time from randomization to death. For subjects who are not reported to have died at the time of an analysis, OS will be right-censored at the last date the subject is documented to be alive. PFS is defined as time from randomization to progression of disease (per RANO criteria) or death, whichever occurs first. For subjects who are not documented to have experienced a PFS event at the time of an analysis, PFS will be right-censored on the date of their last adequate radiographic assessment of disease. To meet the primary and secondary objectives, OS and PFS will be compared between treatment arms A and B using stratified log-rank test statistics or a weighted version of this test (to be pre-specified in the Statistical Analysis Plan document (the SAP), adjusting for the study stratification factors and additional independent prognostic factors as deemed appropriate, to be specified in the SAP. The hazard-ratio of OS and PFS for ABT-414 Arm A compared to placebo Arm B will be estimated by fitting Cox-proportional hazards regression models adjusting for the main-effects of the stratification factors and additional independent prognostic factors as deemed appropriate, to be specified in the SAP.

Interim Analysis

An interim superiority and futility analysis of efficacy data will be performed when 75% (332) of the 441 required maximum number of deaths are observed. The analysis will be performed using the Full Analysis Set, with all randomized cases being included in the treatment arm to which they were randomized regardless of what treatment the subjects actually received. The primary endpoint of OS will be compared between treatment Arms A and B using stratified log-rank test statistics or a weighted version, as pre-specified in the SAP, adjusting for the study stratification factors and additional independent prognostic factors as deemed appropriate, to be specified in the SAP. The hazard-ratio of OS for ABT-414 Arm A compared to placebo Arm B will be estimated by fitting Cox-proportional hazards regression models adjusting for the main-effects of the stratification factors and additional independent prognostic factors as deemed appropriate, to be specified in the SAP. Adjustment of the level of significance (alpha) for multiple testing will be made using the O'Brien-Fleming group sequential spending function for early rejection of the null hypothesis to declare superiority. In addition, futility analysis will be carried at same time. If the estimated Cox HR exceeds 0.90 then trial may be stopped for futility.

The unblinded interim results will first be reviewed by the IDMC, and the trial will be considered for early stopping if the IDMC makes such a recommendation after consideration of the OS results and all supportive evidence including all secondary endpoints and safety.

Statistical Methods (Continued):

Sample-Size Justification:

The sample sizes are calculated based on the approach of doing the primary endpoint analyses (OS) using the FAS.

A total of 640 evaluable subjects are expected to be randomized. With 441 deaths there will be 85% power to detect a 25% reduction in the hazard of death (HR = 0.75) using a log rank test at a one-sided 2.5% level of significance. Median OS of 16 months is expected in the placebo arm.

Type I Error Control:

To maintain overall type I error control for the overall study, each secondary endpoint will be tested in the order listed if the primary endpoint (OS) and all preceding secondary endpoints show statistically significant results at the 1-sided 0.025 level of significance. The O'Brien-Fleming method will be implemented to protect the one-sided type I error of 0.025. A nominal alpha level of 0.00969 will be used for the interim efficacy analysis for OS. For the final analysis, the primary efficacy endpoint will be tested at the one-sided nominal alpha level of 0.0221 after adjusting for the interim look at efficacy data.

Pharmacokinetic:

Peak and trough concentrations (C_{max} and C_{trough}) of ABT-414 and total ABT-806 antibody will be summarized from the observed concentration data. Population pharmacokinetic parameters of ABT-414, total ABT-806 and cys-mcMMAF such as clearance and volume of distribution will be estimated using a nonlinear mixed effect modeling analysis.

Safety Analysis:

AbbVie will assess adverse events, laboratory data, and vital signs throughout the study. Analyses of adverse events will include only "treatment-emergent" events, i.e., those that start or worsen on or after the day of the first dose of study drug. Adverse events severity and laboratory evaluation changes will be assessed by utilizing National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Adverse events will be summarized by preferred terms within a System and Organ Class according to the most current Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters. Shifts in laboratory values from baseline NCI CTCAE grades to maximum and final post-baseline grades will be assessed.

APPENDIX III ADVERSE EVENTS EXPECTED DUE TO GBM OR PROGRESSION OF GBM

Tinnitus
Diplopia
Dysphagia
Hypoaesthesia oral
Paraesthesia oral
Facial pain
Disease progression
Pyrexia
Subdural haematoma
Subdural haemorrhage
Abnormal loss of weight
Decreased appetite
Dehydration
Anaplastic astrocytoma
Glioblastoma
Glioblastoma multiforme
Malignant glioma
Malignant neoplasm progression
Neoplasm progression
VIIth nerve paralysis
Oculofacial paralysis
Facial nerve disorder
Facial paresis
Facial neuralgia
Hypoaesthesia
Burning sensation
Paralysis
Dementia
Dysarthria
Agnosia
Prosopagnosia
Apraxia
Hemiapraxia
Gait apraxia
Dyspraxia
Agraphia
Alexia
Cerebral haemorrhage
Cerebral haematoma
Hyperaesthesia
Ataxia
Cerebellar ataxia
Cerebral ataxia
Myoclonus
Post-anoxic myoclonus
Amnesia

Ataxia	
Atonic seizures	
Balance disorder	
Brain compression	
Brain oedema	
Cerebrospinal fluid retention	
Cerebrospinal thrombotic tamponade	
Cervicogenic headache	
Clonic convulsion	
Clumsiness	
Cluster headache	
Convulsion	
Convulsions local	
Coordination abnormal	
Cranial nerve disorder	
Cranial nerve palsies multiple	
Cranial nerve paralysis	
Epilepsy	
Epileptic aura	
Exertional headache	
Fumbling	
Headache	
Hemianopia	
Hemiparesis	
Hemiplegia	
IIIrd nerve paralysis	
IIIrd nerve paresis	
Incoherent	
Intracranial pressure increased	
IVth nerve paresis	
Language disorder	
Lethargy	
Loss of consciousness	
Memory impairment	
Movement disorder	
Myoclonic epilepsy	
Paraesthesia	
Paresis cranial nerve	
Partial seizures	
Partial seizures with secondary generalisation	
Postictal headache	
Postictal state	
Preictal state	
Quadranopia	
Sedation	
Seizure like phenomena	
Slow speech	
Somnolence	
Speech disorder	

Status epilepticus	
Stupor	
Tension headache	
Tonic clonic movements	
Tonic convulsion	
Tonic posturing	
Tunnel vision	
Typical aura without headache	
Vascular headache	
Vertigo CNS origin	
VIIIth nerve lesion	
Visual field defect	
Affect lability	
Agitation	
Anxiety	
Anxiety disorder	
Anxiety disorder due to a general medical condition	
Depressed mood	
Distractibility	
Elevated mood	
Executive dysfunction	
Hyposomnia	
Impaired reasoning	
Inappropriate affect	
Initial insomnia	
Insomnia	
Mood altered	
Mood swings	
Incontinence	
Urinary incontinence	
Intracerebral haematoma evacuation	
Subdural haematoma evacuation	
Drain of cerebral subdural space	
Deep vein thrombosis	
Thrombosis	

APPENDIX IV NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

The NYHA classifies heart failure into classes based on functional limitations and severity

Class	Patient Symptoms
Class I (Normal)	Few observable symptoms, no limitation in ordinary physical activity.
Class II (Mild)	Mild observable symptoms and slight limitation during ordinary activity. Comfortable at rest.
Class III (Moderate)	Marked limitation in physical activity due to symptoms even during less-than-ordinary activity. Comfortable only at rest.
Class IV (Severe)	End-stage heart failure. Severe limitations. Experience symptoms even while at rest.

APPENDIX V RESPONSIBILITIES OF THE CLINICAL INVESTIGATOR

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 19.0 of this protocol, the Investigator is agreeing to the following:

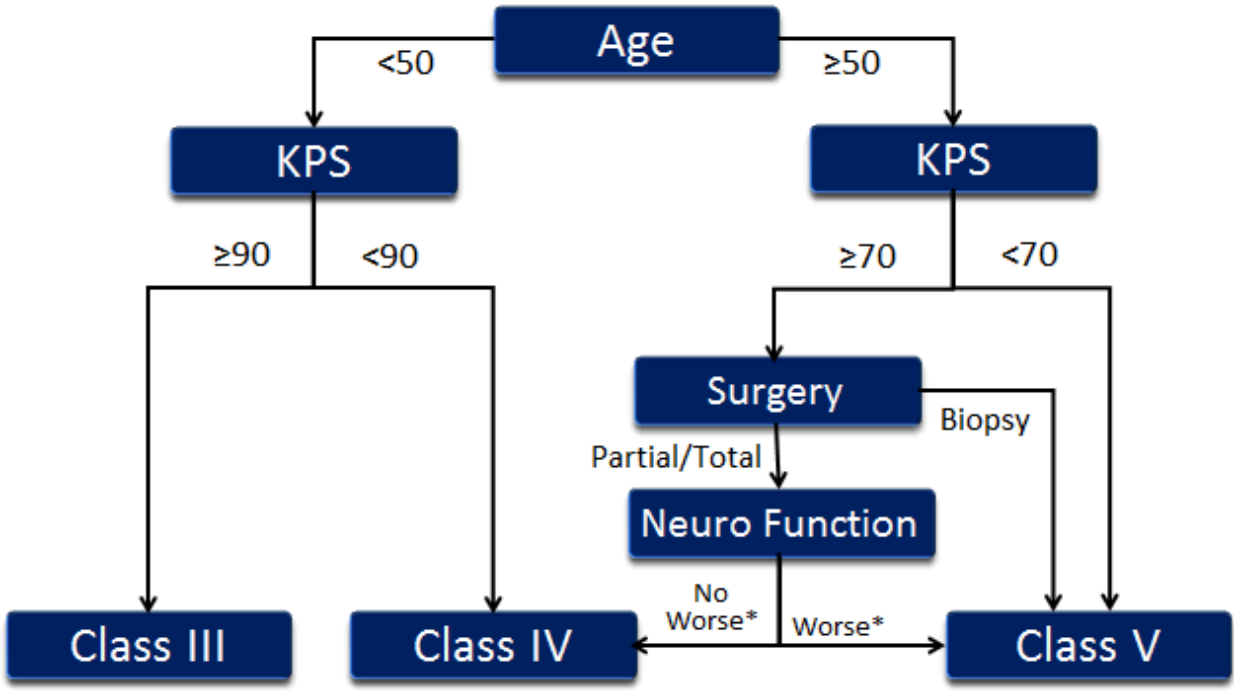
1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees [e.g., independent ethics committee (IEC) or institutional review board (IRB)] review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., Coordinating Investigator, Institution Director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

APPENDIX VI RPA CLASSIFICATION CRITERIA

RPA Class	Criteria
Class III	Age < 50 and KPS 90 – 100
Class IV	Age < 50 and KPS < 90: OR age ≥ 50 and KPS 70 – 100 and partially or total resected with no worse than minor neurofunction impairment
Class V	Age ≥ 50 and KPS 70 – 100 and underwent prior partial or total tumor resection with worse than minor neurofunction impairment: OR age ≥ 50 and KPS 70 – 100 and underwent prior tumor biopsy only

If a subject has a repeat surgery prior to randomization, the extent of surgical resection after the repeat surgery (biopsy-only vs. partial/total resection) will be used for determining RPA class.



APPENDIX VII CHILD-PUGH SCORE

	Points Assigned for Observed Findings		
Parameter	**1**	**2**	**3**
Total bilirubin, µmol/L (mg/dL)	< 34.2 (< 2)	34.2 – 51.3 (2 – 3)	> 51.3 (> 3)
Serum albumin, g/L (g/dL)	> 35 (> 3.5)	28 – 35 (2.8 – 3.5)	< 28 (< 2.8)
INR	< 1.7	1.7 – 2.3	> 2.3
Ascites	None	Slight	Moderate to severe
Hepatic encephalopathy*	None	Grade 1 or 2 (or suppressed with medication)	Grade 3 or 4 (or refractory)

* Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.

Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves.

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.

Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity.

The Child-Pugh classification is defined in terms of the sum of the scores for the five parameters, as shown in Appendix VII.

- A score of 5 or 6 indicates Child-Pugh Category A (mild hepatic impairment).
- A score of 7, 8, or 9 indicates Child-Pugh Category B (moderate hepatic impairment).

APPENDIX VIII LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

ADC	Antibody Drug Conjugate
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CTB	Clinical Trial Battery
CNS	Central Nervous System
COWA	Controlled Oral Word Association
CR	Complete Response
CT	Computerized tomography
CUSA	Cavetron Ultrasonic Aspirator
D	Day
Depatux-M	Depatuxizumab Mafodotin (ABT-414)
DICOM	Digital Imaging and Communications in Medicine
DLT	Dose Limiting Toxicities
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eCRFs	Electronic Case Report Forms
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	EuroQol 5 Dimensions
EQ-5D-VAS	EuroQol 5 Dimensions Value Sets
EU	European Union
FAS	Full Analysis Set
FFPE	Formalin-fixed Paraffin Embedded
FLAIR	Fluid Attenuated Inversion Recovery
GBM	Glioblastoma
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase

GTT	Eye drop(s)
Gy	Gray
Hgb	Hemoglobin
HRQoL	Health Related Quality of Life
HVLT-R	Hopkins Verbal Learning Test-Revised
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IGRT	Image-guided Radiation Therapy
IMRT	Intensity-modulated Radiation Therapy
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
K2EDTA	Potassium Edetic acid (ethylenediaminetetraacetic acid)
KPS	Karnofsky Performance Status
LDH	Lactate Dehydrogenase
mAbs	monoclonal antibodies
MCV	Mean Corpuscular Volume
MDASI-BT	M.D. Anderson Symptom Inventory Brain Tumor Module
MedDRA	Medical Dictionary for Regulatory Activities
MGMT	O6-methylguaninemethlytransferese
MMAF	monomethylauristatin F
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MV	Megavoltage
NCIC	National Cancer Institute of Canada
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire – 25
NOVOTTF	NovoTumor Treatment Fields
OU	Each Eye
OS	Overall Survival
PCP	Pneumocystis *jirovecii* pneumonia
PD	Progressive Disease
PE	Physical Exam
PFS	Progression-Free Survival
PG	Pharmacogenetic
PK	Pharmacokinetics
PPS	Per-protocol Set
PRO	Patient-Reported Outcomes

PR	Partial Response
PT	Prothrombin Time
RANO	Response Assessment in Neuro Oncology
RT	Radiation Therapy
RBC	Red Blood Cell Count
RPA	Recursive Partitioning Analysis
RTOG	Radiation Therapy Oncology Group
SAD	Source Axis Distance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Stable Disease
SGPT	Serum glutamic-pyruvic transaminase
SGOT	Serum glutamic-oxaloacetic transaminase
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reactions
SSD	Source Skin Distance
TOE	Targeted Ophthalmologic Examination
TPS	Treatment Planning System
TMZ	Temozolomide
TRIAD	Transmission of Imaging and Data
ULN	Upper Limits of Normal
VMAT	Volumetric Arc Therapy
WBC	White Blood Cell Count
5-HT3	5-hydroxytryptamine3

Pharmacokinetic and Statistical Abbreviations

C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration

APPENDIX IX. SUBJECTS WITH MILD TO MODERATE HEPATIC IMPAIRMENT

This appendix outlines the ABT-414 sub-study in subjects with hepatic impairment. The revised schedule of assessments for the hepatic impairment sub-study is provided in Table 3H below.

Sub-Study Objective

To assess the pharmacokinetics, safety and tolerability of ABT-414 in subjects with newly diagnosed *EGFR*-amplified GBM who have mild or moderate hepatic impairment.

Overview

This is a Phase 1, open-label, multicenter sub-study. Approximately 6 subjects with mild hepatic impairment and 6 subjects with moderate hepatic impairment will be enrolled if they meet all inclusion criteria and do not meet any of the exclusion criteria.

All subjects with hepatic impairment will be assigned to active treatment with ABT-414 during the Chemoradiation and Adjuvant Phases of treatment. Radiation therapy and TMZ therapy will be administered to hepatically impaired subjects the same way as those with normal hepatic function. The pharmacokinetics of TMZ in patients with mild-to-moderate hepatic impairment have been shown to be similar to those observed in normal hepatic function. Caution should only be exercised when TMZ is administered to patients with severe hepatic impairment. The visit schedule and study procedures will be the same as for other study subjects unless described otherwise in this appendix.

After meeting the selection criteria for subjects with hepatic impairment, as shown below, approximately 6 subjects will be assigned to each of the two cohorts according to their hepatic function as shown in Table 1H. Within each cohort, the first 3 subjects will be assigned to dose level 1. If the dose level 1 was tolerated, the subsequent subjects may be assigned to dose level 2.

Table 1H. Cohorts of Subjects with Hepatic Impairment and Treatment

Cohorts	Hepatic Function	Dose Level	Chemoradiation Phase	Adjuvant Phase (Cycles 1 – 2)	Maintenance Phase (Cycle 3 and After)
A	Child-Pugh A	1a	1.0 mg/kg	1.0 mg/kg	1.0 mg/kg
		2	2.0 mg/kg	1.25 mg/kg	1.25 mg/kg
B	Child-Pugh B	1b	1.0 mg/kg	0.5 mg/kg	1.0 mg/kg
		2	2.0 mg/kg	1.25 mg/kg	1.25 mg/kg

For subjects with hepatic impairment, pharmacokinetic assays will be performed as samples are received on an ongoing basis to inform dose selection for subsequent subjects throughout the study. Prior to proceeding with dose level 2 in each cohort, safety data and pharmacokinetic data for the subjects at dose level 1 within that cohort will be assessed by the sponsor and the Neuro-Medical Oncology Chair. The doses to be given for dose level 2 in each cohort may be reduced if indicated by safety and/or pharmacokinetic data from prior subjects.

Selection Criteria

Because reducing variability for efficacy evaluations is not necessary for the pharmacokinetic and safety objectives for these cohorts, eligibility criteria are only restricted to those ensuring the subject has *EGFR*-amplified GBM and those to ensure safety for subjects taking ABT-414 and ocular steroids.

Inclusion Criteria

A subject cannot be considered eligible for this study unless ALL of the following conditions are met.

Subjects may only be randomized if the additional criteria below are met:

1. Histologically confirmed de novo Grade IV glioma (GBM, gliosarcoma or other subvariants) confirmed by central pathology tissue screening.
2. *EGFR* amplification in tumor tissue confirmed by central assessment.
3. *Not applicable to this substudy.*
4. The subject must have recovered from the effects of surgery, post-operative infection, and other complications before enrollment including, suture/staple removal from brain surgery and sufficient wound healing before registration.
5. ≥ 18 years of age.
6. *Not applicable to this substudy.*
7. *Not applicable to this substudy.*
8. Subject has adequate bone marrow and renal function ≤ 21 days prior to randomization and has mild-to-moderate hepatic impairment as follows:
    a. Absolute neutrophil count (ANC) ≥ 1,500/mm^3;
    b. Platelets ≥ 100,000/mm^3;

c. Hemoglobin (Hgb) ≥ 9.0 g/dL (Note: The use of transfusion or other intervention to achieve Hgb ≥ 9.0 g/dL is acceptable.);

d. Renal function: calculated creatinine clearance ≥ 30 mL/min by the Cockcroft-Gault formula;

e. **Hepatic function (for subjects participating in the hepatic impairment sub-study only):** The subject has chronic liver disease and/or cirrhosis documented by the presence of at least 1 of the following:

- Liver biopsy with histologic findings consistent with cirrhosis
- Computerized tomographic or ultrasonographic evidence of liver disease
- Physical examination, clinical or laboratory evidence of chronic liver disease
- Colloid shift on a liver-spleen scan

And the subject has mild-to-moderate hepatic impairment, including Category A (score of 5 or 6) and Category B (score of 7, 8, or 9) impairment according to the Child-Pugh classification (see Table 2H for scoring), *with no clinical history of liver decompensation* based on clinical laboratory values and clinical findings assessed within 14 days prior to the start of Chemoradiation.

- Patients with biliary obstruction for which a shunt has been placed are eligible, provided the shunt has been in place for at least 10 days prior to the first dose of the study drug and the liver function has stabilized. Two measurements at least 2 days apart that put the patient in the same hepatic dysfunction stratum will be accepted as evidence of stable hepatic function. There should be no evidence of biliary sepsis. Electrocardiogram (ECG) without evidence of acute cardiac ischemia ≤ 21 days prior to randomization.

9. Female subjects of childbearing potential (i.e., those who are not postmenopausal for at least 1 year or surgically sterile by bilateral salpingectomy, bilateral oophorectomy or hysterectomy) and their male partners should practice at least one accepted method of birth control listed below during study entry, for the entire duration of the study and for at least 6 months after treatment with ABT-414 and TMZ treatment has ended. Male subjects and their female partners of childbearing potential should practice at least one of the accepted methods of birth control during study and for at least 6 months after ABT-414 and TMZ. In addition to the use of a condom, male subjects and their female partners of childbearing potential should practice at least one of the methods of birth control listed below during the study and for at least 6 months after ABT-414 and TMZ:

- Total abstinence from sexual intercourse beginning at least one complete menstrual cycle prior to study drug administration (of note: sexual abstinence as a method of

contraception should be limited to those cases where it is already established as the pre-existing lifestyle choice of the subject);

- A vasectomized male subject or a vasectomized partner of a female subject;
- Hormonal contraceptives (oral, parenteral or transdermal) for at least 3 months prior to study drug administration;
- Intrauterine device (females);
- Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or cream) unless not deemed acceptable as highly effective contraception by local regulations.

10. Women of child-bearing potential must have a negative pregnancy test (urine or serum) within 7 days prior to randomization.

11. Must voluntarily sign and date informed consent form, for tumor tissue biomarker testing and for study participation, approved by an Independent Ethics Committee (IEC)/ Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Exclusion Criteria

Subjects with one or more of the following conditions are NOT eligible for this study.

Randomization Criteria

1. *Not applicable to this substudy.*
2. *Not applicable to this substudy.*
3. Subject has recurrent GBM.
4. *Not applicable to this substudy.*
5. Subject has metastatic GBM.
6. Prior chemotherapy or radiosensitizers for cancers of the head and neck region; note that prior chemotherapy for a different cancer is allowable, except prior temozolomide.
7. Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation fields.
8. Any prior therapy for glioblastoma (intra-operative techniques to guide resection are allowed as are experimental imaging techniques).
9. Prior invasive malignancy (except for non-melanomatous skin cancer; carcinoma in situ of the breast, oral cavity, or cervix) unless disease free for ≥ 2 years.

10. Prior, concomitant, or planned concomitant treatment with NovoTumor Treatment Fields (Novo TTF), *EGFR*-targeted therapy (including *EGFRvIII*-directed therapy), bevacizumab, Gliadel wafers or other intratumoral or intracavitary anti-neoplastic therapy, or other experimental therapeutics intended to treat the tumor; the exceptions are diagnostic or imaging studies, quality of life, biomarker or epidemiological studies; and operative guides to improve extent of resection.

11. Subject has had major immunologic reaction to an IgG-containing agent.

12. Subject has had LASIK (laser-assisted in situ keratomileusis) procedure within the last 1 year or cataract surgery within the last 3 months.

13. Subject has a history of hypersensitivity to TMZ or excipients, ABT-414 components or excipients, and dacarbazine (contraindication for TMZ).

14. Subject is unsuitable for receiving ocular steroids:

    - Subject has any active viral disease of the cornea or conjunctiva, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella; mycobacterial infection of the eye; fungal diseases of ocular structures; or any other contraindication for ocular steroid use.
    - Subject has a known or suspected hypersensitivity to any ocular steroid.
    - Subject has primary open angle glaucoma or a history of steroid-induced intraocular pressure elevation.

15. Subject is a lactating or pregnant female.

16. Severe, active co-morbidity, defined as follows:

    - **Subject has *severe* hepatic impairment (Child-Pugh score of 10 or higher; see Table 2H)**
    - Unstable angina and/or congestive heart failure within the last 6 months;
    - Transmural myocardial infarction within the last 6 months;
    - Evidence of recent myocardial infarction or ischemia by the findings of S-T elevations of ≥ 2 mm using the analysis of an EKG performed within 14 days prior to enrollment;
    - New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 12 months prior to enrollment (Appendix IV);
    - History of stroke, cerebral vascular accident (CVA) or transient ischemic attack within 6 months;
    - Serious and inadequately controlled cardiac arrhythmia;

- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of enrollment;
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of enrollment;
- Subjects with clinically defined Acquired Immune-Deficiency Syndrome (AIDS)-defining illness. This is necessary to ensure subjects are likely to be able to receive the full TMZ regimen;
- Active connective tissue disorders, such as lupus or scleroderma, that in the opinion of the Investigator may put the subject at high risk for radiation toxicity;
- Any other major medical illnesses or psychiatric impairments that in the Investigator's opinion will prevent administration or completion of protocol therapy;

17. Subjects treated on any other therapeutic clinical protocols within 30 days prior to study entry or during participation in the study except intra-operative therapy to guide resection or experimental imaging without therapeutic intent.

18. Inability to undergo contrast-enhanced MRI scans.

Criteria for Cohort Assessment

The Child-Pugh classification presented in Table 2H will be used to categorize the degree of hepatic impairment for assignment into the mild and moderate hepatic impairment groups.

Table 2H. Child-Pugh Scale for the Assessment of Hepatic Impairment

	Points Assigned for Observed Findings		
Parameter	**1**	**2**	**3**
Total bilirubin, µmol/L (mg/dL)	< 34.2 (< 2)	34.2 – 51.3 (2 – 3)	> 51.3 (> 3)
Serum albumin, g/L (g/dL)	> 35 (> 3.5)	28 – 35 (2.8 – 3.5)	< 28 (< 2.8)
INR	< 1.7	1.7 – 2.3	> 2.3
Ascites	None	Slight	Moderate to severe
Hepatic encephalopathy*	None	Grade 1 or 2 (or suppressed with medication)	Grade 3 or 4 (or refractory)

* Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity

The Child-Pugh classification is defined in terms of the sum of the scores for the five parameters, as shown in Table 2H.

- A score of 5 or 6 indicates Child-Pugh Category A (mild hepatic impairment).
- A score of 7, 8, or 9 indicates Child-Pugh Category B (moderate hepatic impairment).

Table 3H. Tables of Activities for Hepatic Sub Study

Table 1. Study Activities – Chemoradiation Phase	**Screening[a]**		**Chemoradiation Phase[b]**						
Activity	**Screening 1**	**Screening 2**	**Day 1 Wk 1 (Fraction 1 of RT)**	**Day 1 of Wk 2**	**Day 1 of Wk 3**	**Day 1 of Wk 4**	**Day 1 of Wk 5**	**Day 1 of Wk 6**	**Day 1 of Wk 7**
Informed Consent	X								
Medical and Oncologic History		X							
Physical Exam (Including Weight and Karnofsky Performance Status)[c]		X	X		X		X		
Vital Signs		X	X		X		X		
Ophthalmology Exam		X				X[d]		X[d]	
ECG[e]		X							
Serum Pregnancy Test		X	X[f]						
Chemistry		X	X	X	X	X	X	X	X
Hematology		X	X	X	X	X	X	X	X
Urinalysis		X							
Coagulation		X							
MRI With and Without Contrast		X[k]							
Submit Tissue Sample for Confirmation of GBM, testing of *EGFR* amplification, *EGFRvIII* and *MGMT*	X								
Adverse Event Assessment/Concomitant Medications/Supportive Care			X		X		X		
Radiation Therapy[g]			X						
Temozolomide Administration			X[h]						
ABT-414 or Placebo Administration			X		X		X		
Prophylactic Eye Drop Administration			X[i]		X[i]		X[i]		
Enrollment			X						

Wk = Week; F/U = Follow-up; RT= Radiation Therapy; KPS = Karnofsky Performance Status

a. Screening procedures may be conducted before or after results of *EGFR* amplification are received.

b. Chemoradiation Phase will be approximately 6 weeks (up to 7 weeks) of treatment with RT, TMZ, and ABT-414.

c. Height will be assessed at Screening only. Weight will be collected at all visits. Complete physical examination will be performed at Screening only. Symptom directed physical examination will be performed at all other designated visits as clinically indicated.

d. Ophthalmology exams are to be performed 7 to 14 days after the 2^{nd} and 3^{rd} infusions of ABT-414/placebo and must be completed prior to the next infusion of ABT-414/placebo.

e. ECG will be performed at screening, final visit and when clinically indicated.

f. For female subjects of childbearing potential, a serum pregnancy test will be performed within 21 days before Day 1 of chemoradiation. A urine or serum pregnancy test will be done on Day 1 Week 1 if a serum pregnancy test was performed more than 7 days before Day 1.

g. During Chemoradiation Phase, radiation therapy will begin on Day 1, Week 1 (Fraction 1). 60 Gy will be administered in ~30 fractions over 6 weeks (up to 49 days) per the local prescribing information or local institutional guidelines.

h. During Chemoradiation Phase, temozolomide (75 mg/m^2) will be given once per day, continuously (including weekends), from Day 1, Week 1 until completion of radiotherapy (up to 49 days).

i. Prophylactic eye drops will be administered for 7 days, from 2 days before until 4 days after, each dose of study drug (ABT-414 or placebo), as described in Section 5.5.

j. Baseline measure can be done at any time during Screening, up to and including Day 1 of Chemoradiation Phase, but preferably after *EGFR* amplification has been confirmed. The assessments will be translated into the local languages.

k. A brain MRI scan with and without contrast, performed at any time after diagnostic biopsy/resection but prior to randomization, is required to serve as a baseline scan for RANO tumor response assessments. If a subject starts chemoradiation more than 28 days after surgery, the baseline MRI is to be performed no more than 21 (but preferably fewer) days prior to Day 1 Week 1 of Chemoradiation Phase and should allow sufficient time to revise the radiation therapy plan if needed due to a significant change in tumor since surgery.

Table 2. Study Activities – Adjuvant Phase	**Adjuvant Phase – 28-Day Cycles[a]**										
Activity	**Day 1 of Every Cycle (1, 2, 3 etc.)**	**Day 1 of Odd-Numbered Cycles (1, 3, 5, etc.)**	**Day 1 of Cycle 2**	**Day 15 of Every Cycle[b]**	**Day 22 of Every Cycle[c]**	**Final Study Drug Visit[d]**	**35 Day F/U[e]**	**49 Day F/U**	**Follow-Up Phase (Every 8 Weeks Until Disease Progression)[f]**	**At Progression**	**Survival**
Physical Exam (Including Weight and Karnofsky Performance Status)[g]	X			X		X[d]	X		X		
Vital Signs	X			X		X	X				
Ophthalmology Exam[h]		X	X				X[i]				
ECG						X					
Chemistry	X					X	X				
Hematology	X				X	X	X				
MRI and Clinical Disease Progression Assessment		X[j]				X[d,k]			X[j]		
Adverse Event Assessment/Concomitant Medications/Supportive Care	X			X		X	X	X[p]			
Temozolomide Administration	X[l]										
ABT-414 or Placebo Administration	X[m]			X[m]							
Prophylactic Eye Drop Administration	X[n]			X[n]							
Survival Assessment[o]											X

Wk = Week; F/U = Follow-up; RT = Radiation Therapy; KPS = Karnofsky Performance Status; EORTC-QLQ-C30/BN20 = EORTC Quality of Life Questionnaire, Cancer and Brain modules; MDASI-BT = MD Anderson Symptom Index for Brain Tumors; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire – 25;
HVLT-R = Hopkins Verbal Learning Test-Revised; COWA = Controlled Oral Word Association (FAS form); EQ-5D-5L = EuroQoL 5 Dimensions; VAS = Visual Analog Scale

a. Assessments in the Adjuvant Phase will be based on 28-day treatment cycles, with the first cycle starting approximately 4 weeks after completion of radiation therapy. Subjects will receive concomitant TMZ and study drug (placebo or ABT-414) for the first 6 cycles,and study drug monotherapy for an additional 6 cycles or until disease progression or study drug discontinuation. Subjects demonstrating continued benefit and no unacceptable toxicity from adjuvant TMZ can continue adjuvant TMZ to a maximum of 12 cycles at the discretion of the Investigator if this is considered an acceptable standard of care per local regulations. For subjects demonstrating continued benefit and no unacceptable toxicity with ABT-414/placebo after 12 cycles, the Adjuvant Phase may be extended at the discretion of the Investigator in discussion with the Neuro-Medical Oncology Chair or AbbVie Medical Monitor, with continued ABT-414/placebo treatment until disease progression is confirmed.

b. Day 15 visit will not be performed after discontinuation of study drug (ABT-414/placebo) treatment.

c. As per TMZ prescribing information, during the 28-day cycle of TMZ, a blood count for ANC and platelets should be performed 21 days (± 2 days) after the start of each TMZ cycle. If the ANC falls below 1,500/µL or if the platelet count falls below 100,000/mm^3, then blood counts should be performed weekly until recovery to these levels before TMZ dosing. A certified local lab may be used instead of central lab; if so, ANC and platelet results should be reported in the eCRF. Day 22 testing may be omitted for cycles in which TMZ is not administered or if local prescribing information allows for a different testing schedule for ANC and platelets.

d. Final Study Drug Visit to be performed approximately 14 days after last dose of ABT-414/placebo. The physical examination and MR imaging from the first visit of the Follow-Up Phase will be used for the Final Study Drug Visit if these visits coincide (e.g., if the subject completes 12 cycles of Adjuvant Phase).

e. To be performed 35 days (± 3 days) after the last dose of study drug (placebo or ABT-414). If the Final Study Drug Visit is more than 35/49 days after the last dose of study drug, then 35-day safety follow-up procedures will not be performed.

f. Visits in Follow-Up Phase to occur every 8 weeks, beginning 8 weeks after Day 1 of the last odd-numbered cycle in the Adjuvant Phase.

g. Height will be assessed at Screening only. Weight will be collected at all visits. Complete physical examination will be performed at Screening only. Symptom directed physical examination will be performed at all other designated visits as clinically indicated.

h. Ophthalmology exam to be performed prior to ABT-414/placebo dosing on Day 1 (or up to 7 days prior to Day 1) of Cycle 1, Cycle 2, and every odd-numbered cycle thereafter (Cycles 3, 5, 7, etc.). Ophthalmology exam for Cycle 1 Day 1 may be omitted if the subject had no corneal microcysts or ocular adverse events during or after the Chemoradiation Phase. Ophthalmology exams may be discontinued if the subject has been on Level 1 eye drops with no ocular toxicity for 2 consecutive eye exams.

i. Ophthalmology exam at Day 35 Follow-Up Visit to be done only if subject had corneal microcysts or other ocular findings related to ABT-414 or ocular steroids on previous exam and repeated at least every 8 weeks until satisfactory resolution of eye toxicities.

j. MRI to be performed ≤ 14 days before the start of each odd-numbered cycle or follow-up visit, starting at Cycle 1. If the subject discontinues study drug prior to disease progression, MRIs should continue to be obtained approximately every 8 weeks until disease progression is confirmed.

k. MRI to be performed, if not performed within last 3 weeks, if subject withdraws from study prior to disease progression.

l. TMZ will be administered once daily on Days 1 through 5 of each 28-day cycle for 6 cycles per the local prescribing information.

m. ABT-414 or placebo infusion will be administered on Day 1 and Day 15 of each 28-day cycle for 12 cycles. For subjects demonstrating continued benefit and no unacceptable toxicity with ABT-414/placebo after 12 cycles, the Adjuvant Phase may be extended at the discretion of the Investigator in discussion with the Neuro-Medical Oncology Chair or AbbVie Medical Monitor, with continued ABT-414/placebo treatment until disease progression is confirmed.

n. Prophylactic eye drops will be administered daily for 7 days with each dose of ABT-414/placebo, from 2 days before until 4 days after each dose of study drug (ABT-414 or placebo), as described in Section 5.5.

o. Survival will be assessed quarterly after treatment discontinuation until death.

p. If the subject is unable to return to the site for the Day 49 Follow-Up Visit, a phone call may be conducted to obtain AE and concomitant medication information.

Pharmacokinetic Evaluation

For all subjects in this sub-study, blood samples for PK and immunogenicity evaluation will be collected according to the schedule described in Table 4H. PK samples should be processed according to the guidelines in Section 4.2 and the laboratory manual.

Values for the pharmacokinetic parameters of ABT-414, Total ABT-806 and cys-mcMMAF, including the maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), the terminal phase elimination rate constant and the area under the plasma concentration time curve (AUC) from time 0 to the time of the last measurable concentration (AUC_t) and from time 0 to infinite time (AUC_∞), will be determined using noncompartmental methods. Confirmed positive ADA results will be reported in Titer units. Additional parameters may be calculated if useful in the interpretation of the data.

Plasma or serum concentrations and pharmacokinetic parameter values of each analyte will be tabulated for each subject and each dose level, and summary statistics will be computed for each sampling time and each parameter by hepatic impairment category.

An analysis of covariance (ANCOVA) will be performed for dose-normalized AUC_t and C_{max}. The factor of primary interest is hepatic function category. Body weight, sex, age and other variables will be considered as possible covariates. Covariates such as age, gender, and perhaps others that might explain some of the variability in the population will be included in the model initially. However, a covariate may be dropped from the model if the regression coefficient is not significant at level 0.10. The natural logarithmic transformation will be employed for AUC and C_{max} unless the data clearly indicate that other transformation or the untransformed variable provides more nearly symmetric probability distributions and/or more nearly homogenous variances across dose levels. Additional analyses will be performed if useful and appropriate.

Table 4H. Schedule of Pharmacokinetic Sampling for Subjects with Hepatic Impairment

Chemoradiation Phase							
Activity	**Day 1 Wk 1 (Fraction 1 of RT)**	**Day 2 of Wk 1**	**Day 3 of Wk 1**	**Day 5 of Wk 1**	**Day 1 of Wk 2**	**Day 1 of Wk 3**	**Day 1 of Wk 5**
PK – ABT-414 and Total ABT-806 Assays	0 hour (pre-dose), 0.5 hour (immediately after infusion), and 4 hour after start of infusion	Sample at 24-hour post-dose (within ± 4 hour)	Sample at 48-hour post-dose (within ± 4 hour)	Sample at 96-hour post-dose (within ± 4 hour)	Sample at 168-hour post-dose (within ± 4 hour)	0 hour (pre-dose) and within 30 min post-dose	0 hour (pre-dose) and within 30 min post-dose
PK – Cys-mcMMAF assay	0 hour (pre-dose), 0.5 hour (immediately after infusion), and 4 hour after start of infusion	Sample at 24-hour post-dose (within ± 4 hour)	Sample at 48-hour post-dose (within ± 4 hour)	Sample at 96-hour post-dose (within ± 4 hour)	Sample at 168-hour post-dose (within ± 4 hour)	0 hour (pre-dose) and within 30 min post-dose	0 hour (pre-dose) and within 30 min post-dose
PK – Antidrug Antibody	0 hour (pre-dose)					0 hour (pre-dose)	0 hour (pre-dose)

Adjuvant Phase – 28-day Cycles				
Activity	**Day 1 of Cycle 1**	**Day 1 of Cycles 2 – 12 (Every Cycle)**		
PK – ABT-414 and Total ABT-806 Assays	0 hour (pre-dose) and within 30 min post-dose on Day 1 of Cycle 1	0 hour (pre-dose)		
PK – Antidrug Antibody	0 hour (pre-dose)	0 hour (pre-dose)		

Radiation Therapy and Temozolomide Administration

Radiation therapy and temozolomide therapy will be administered as described in the main protocol.

ABT-414 Administration

At the Screening Visit, all subjects will be assigned a unique subject number that will indicate the subject is enrolling into the open label hepatic impairment sub-study. The subjects in this sub-study will be stratified by their Child-Pugh scores (mild or moderate impairment) as described in Table 2H.

Subjects will receive ABT-414 by IV infusion over 30 – 40 minutes once every 2 weeks during the Chemoradiation Phase (on Day 1 of Weeks 1, 3, and 5 of the 6-week regimen) and during the

Adjuvant Phase (on Day 1 and Day 15 of each 28-day cycle for 12 cycles). If, after completing 12 cycles of ABT-414 in the Adjuvant Phase, the subject is tolerating the drug and the Investigator believes the subject is continuing to benefit from ongoing ABT-414 treatment, the Adjuvant Phase may be extended following consultation with the Neuro-Medical Oncology Chair. ABT-414 will continue according to the same dosing schedule at the discretion of the Investigator as long as disease progression has not been determined.

The mg/kg dose for each dose will be as described in Table 1H. The mg/kg dose will be determined from the weight on Day 1 of the Chemoradiation Phase and need not change during subsequent treatment unless there is a weight change by more than 10% from baseline. Recalculation of dose for < 10% weight changes is allowed at the discretion of the Investigator. There will be no cap on the weight of the subject or on the number of milligrams administered for overweight subjects.

If TMZ treatment is discontinued due to intolerance during either the Chemoradiation Phase or Adjuvant Phase, subjects will continue receiving ABT-414 infusions according to the same study schedule.

ABT-414 Toxicity Management and Individual Subject Dose Modifications

Subjects will be closely monitored for treatment-related adverse events during all infusions. For the initial ABT-414 infusion, pre infusion vital signs should be taken and direct observation is required for the first 15 minutes of the infusion. Also for the initial ABT-414 infusion, subjects must remain at the site for monitoring for 60 minutes post-infusion. For subsequent infusions, post-infusion monitoring is not required; however, pre-infusion vital signs should still be taken. Longer observation periods and more frequent vital sign checks may be required in subjects who experience infusion reactions.

Recommendations for dose reductions (either as required by protocol or at the discretion of the investigator) are as follows: For a current dose of 1.5 – 2.0 mg/kg, it is recommended that the dose be reduced by 0.5 mg (or more, at the investigators discretion). For a current dose of 0.75 – 1.25 mg/kg, it is recommended that the dose be reduced by 0.25 mg (or more, at the investigators discretion).

APPENDIX X SUBJECTS CONTINUING PARTICIPATION AFTER MAIN STUDY

This appendix outlines the modifications to the study procedures and ABT-414 dosing in subjects who are currently receiving ABT-414 and who choose to continue ABT-414 treatment after the results from the pre-planned interim efficacy analysis. Subjects who received placebo will be discontinued from the study.

At the time of the interim efficacy analysis, there were approximately 48 subjects who remained on active ABT-414 treatment. The RTOG Steering Committee and AbbVie determined it was appropriate to allow subjects who are receiving ABT-414 to continue doing so based on investigator and subject decision.

Requirements for continuing treatment with ABT-414 after interim efficacy analysis

1. If the subject was receiving blinded treatment, they must be confirmed to be receiving ABT-414.
2. Must voluntarily sign and date the updated informed consent form, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

Study Activities

Only study activities necessary for study drug dosing, safety monitoring and adverse event reporting will be continued. The revised schedule of study assessments for these subjects is provided in Table 2b below.

Table 2b. Study Activities	28-Day Cycles[a]				Final Study Drug Visit[d]/At Progression	35-Day F/U[e]	49-Day F/U
Activity	Day 1 of Every Cycle (1, 2, 3 etc.)	Day 1 of Odd-Numbered Cycles (1, 3, 5, etc.)	Day 15 of Every Cycle[b]	Day 22 of Every Cycle[c]			
Symptom-directed Physical Exam	X[f]		X[f]				
Ophthalmology Exam		X[g]				X[g]	X[g]
Chemistry	X				X	X	
Hematology	X			X	X	X	
Adverse Event Assessment/Concomitant Medications	X		X		X	X	X[k]
Temozolomide Administration	X[h]						
ABT-414 Administration	X[i]		X[i]				
Prophylactic Eye Drop Administration	X[j]		X[j]				

F/U = Follow-up

a. Assessments will be based on 28-day treatment cycles, with the first cycle starting approximately 4 weeks after completion of radiation therapy. Subjects will receive concomitant TMZ and study drug (ABT-414) for the first 6 cycles, and study drug monotherapy for an additional 6 cycles or until disease progression or study drug discontinuation.

b. Day 15 visit will not be performed after discontinuation of study drug (ABT-414) treatment.

c. As per TMZ prescribing information, during the 28-day cycle of TMZ, a blood count for ANC and platelets should be performed 21 days (± 2 days) after the start of each TMZ cycle. If the ANC falls below 1,500/µL or if the platelet count falls below 100,000/mm^3, then blood counts should be performed weekly until recovery to these levels before TMZ dosing. A certified local lab may be used instead of central lab; if so, ANC and platelet results should be reported in the eCRF. Day 22 testing may be omitted for cycles in which TMZ is not administered or if local prescribing information allows for a different testing schedule for ANC and platelets.

d. Final Study Drug Visit to be performed approximately 14 days after last dose of ABT-414.

e. To be performed 35 days (± 3 days) after the last dose of study drug (ABT-414). If the Final Study Drug Visit is more than 35 days after the last dose of study drug, then 35-day safety follow-up procedures will not be performed.

f. Physical exams will be performed only as needed for safety management and adverse event reporting.

g. Ophthalmology exams will be performed only as needed for safety management and AE/SAE reporting. The last ophthalmology exam following discontinuation of ABT-414 may be done at the 35-Day F/U or 49-Day F/U Visit. Targeted ophthalmology exam data will not be collected by the Sponsor.

h. TMZ will be administered once daily on Days 1 through 5 of each 28-day cycle for 6 cycles per the local prescribing information.

i. ABT-414 infusion will be administered on Day 1 and Day 15 of each 28-day cycle for 12 cycles.

j. Prophylactic eye drops will be administered daily for 7 days with each dose of ABT-414, from 2 days before until 4 days after each dose of study drug (ABT-414), as described in Section 5.5 of the main study. Patients will receive management of ocular side effects as per investigator discretion. In this case, ABT-414 dose interruption and/or reduction may be used, and any available prophylactic or supportive care measures may be employed without restriction, at the discretion of the investigator.

k. If the subject is unable to return to the site for the Day 49 Follow Up Visit, a phone call may be conducted to obtain AE/SAE and concomitant medication information.

ABT-414 Administration and Individual Subject Discontinuation

ABT-414 will be administered as described in the main protocol.

Subjects may continue receiving ABT-414 while drug supply is available as long as disease progression has not been determined.

ABT-414 Toxicity Management and Individual Subject Dose Modifications

Section 8.0 of the main protocol provides guidance for toxicity management and dose modifications.

Adverse Events and Concomitant Medications

Adverse event and concomitant medication data will be collected to support regulatory safety reporting requirements.

APPENDIX XI PROTOCOL AMENDMENT: LIST OF CHANGES

Title Page
"Investigator:"
"Neurosurgery" previously read:

Has been changed to read:

Title Page
"Investigator:"
"Statistician" previously read:

Has been changed to read:

[redacted]

Section 1.0 INTRODUCTION AND BACKGROUND
Subsection Additional Safety Information
Delete: last paragraph

Taken together, the efficacy and safety data available to date demonstrate an acceptable benefit/risk profile of ABT-414 in patients with EGFR-amplified GBM (see Section 1.2) and support continued investigation of this investigational agent in the current trial.

Section 1.0 INTRODUCTION AND BACKGROUND
Subsection Summary of Results from Pre-planned Interim Efficacy Analysis
Add: new subsection title and text

Summary of Results from Pre-planned Interim Efficacy Analysis

An interim efficacy analysis based on a data cut of 30 April 2019 was performed by the RTOG Independent Data Monitoring Committee (IDMC), at which time 346 OS events had been observed out of 639 subjects included in the main part of the study. The primary analysis of OS based on the Intent-to-Treat (ITT) population showed no difference in OS between groups, with a median OS of 18.9 vs. 18.7 months for ABT-414 and placebo, respectively. The weighted (ρ = 0, γ = 0.2) stratified log-rank test p-value (1-sided) was 0.628, and the observed hazard ratio (HR) (95% CI) for OS was 1.01 (0.82, 1.25). The median PFS was 8.0 vs. 6.3 months for ABT-414 and placebo, respectively, with a stratified log-rank test p-value (1-sided) of 0.029. The observed hazard ratio (HR) (95% CI) for PFS was 0.84 (0.70, 1.02). Preliminary analysis of demographic and clinical characteristics did not reveal any factors predictive of OS benefit for the addition of ABT-414 to standard RT/TMZ therapy.

Overall, 99.4% and 97.8% of subjects experienced at least 1 adverse event, and 87.3% and 62.3% experienced a Grade 3 or higher AE in the ABT-414 and placebo arms, respectively. Overall, 94.7% and 36.1% of subjects experienced at least 1 ocular adverse event related to corneal epitheliopathy, 61.0% and 0.6% experienced a Grade 3 or higher AE related to corneal epitheliopathy, and 11.8% and 0% discontinued study drug (ABT-414 or placebo) in the ABT-414 and placebo arms due to corneal epitheliopathy, respectively. The most common (> 10%) events related to corneal epitheliopathy included keratopathy, vision blurred, photophobia, dry eye, eye pain, keratitis, and punctate keratitis. Excluding events related to corneal epitheliopathy, events for which the incidence in the ABT-414 group was ≥ 5% greater than in the placebo group included thrombocytopenia, gamma-glutamyltransferase increased, aspartate aminotransferase increased, alanine aminotransferase increased, constipation, blood alkaline

phosphatase increased, fatigue, and platelet count decreased. Excluding events related to corneal epitheliopathy, Grade 3 or higher events for which the incidence in the ABT-414 group was at least 5% and was ≥ 2% greater than in the placebo group included thrombocytopenia, gamma-glutamyltransferase increased, and alanine aminotransferase increased.

The interim efficacy analysis results overall indicate no survival benefit for adding ABT-414 to standard RT/TMZ therapy in newly diagnosed GBM patients. However, given that no new important safety risks were identified, the RTOG Steering Committee and AbbVie believe it is appropriate to allow subjects who are currently receiving ABT-414 to continue ABT-414 treatment if the investigator and subject believe it is in the subject's best interest. For those subjects who choose to continue ABT-414, study procedures have been modified as described in Appendix X. The appendix provides guidance for study drug administration and collection of safety data related to AEs and SAEs. No additional efficacy data will be collected.

APPENDIX X SUBJECTS CONTINUING PARTICIPATION AFTER MAIN STUDY
Add: new appendix title and text

APPENDIX X SUBJECTS CONTINUING PARTICIPATION AFTER MAIN STUDY

This appendix outlines the modifications to the study procedures and ABT-414 dosing in subjects who are currently receiving ABT-414 and who choose to continue ABT-414 treatment after the results from the pre-planned interim efficacy analysis. Subjects who received placebo will be discontinued from the study.

At the time of the interim efficacy analysis, there were approximately 48 subjects who remained on active ABT-414 treatment. The RTOG Steering Committee and AbbVie determined it was appropriate to allow subjects who are receiving ABT-414 to continue doing so based on investigator and subject decision.

Requirements for continuing treatment with ABT-414 after interim efficacy analysis

1. If the subject was receiving blinded treatment, they must be confirmed to be receiving ABT-414.
2. Must voluntarily sign and date the updated informed consent form, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

Study Activities

Only study activities necessary for study drug dosing, safety monitoring and adverse event reporting will be continued. The revised schedule of study assessments for these subjects is provided in Table 2b below.

Table 2b. Study Activities	28-Day Cycles[a]				Final Study Drug Visit[d]/At Progression	35-Day F/U[e]	49-Day F/U
Activity	Day 1 of Every Cycle (1, 2, 3 etc.)	Day 1 of Odd-Numbered Cycles (1, 3, 5, etc.)	Day 15 of Every Cycle[b]	Day 22 of Every Cycle[c]			
Symptom-directed Physical Exam	X[f]		X[f]				
Ophthalmology Exam		X[g]				X[g]	X[g]
Chemistry	X				X	X	
Hematology	X			X	X	X	
Adverse Event Assessment/Concomitant Medications	X		X		X	X	X[k]
Temozolomide Administration	X[h]						
ABT-414 Administration	X[i]		X[i]				
Prophylactic Eye Drop Administration	X[j]		X[j]				

F/U = Follow-up

a. Assessments will be based on 28-day treatment cycles, with the first cycle starting approximately 4 weeks after completion of radiation therapy. Subjects will receive concomitant TMZ and study drug (ABT-414) for the first 6 cycles, and study drug monotherapy for an additional 6 cycles or until disease progression or study drug discontinuation.

b. Day 15 visit will not be performed after discontinuation of study drug (ABT-414) treatment.

c. As per TMZ prescribing information, during the 28-day cycle of TMZ, a blood count for ANC and platelets should be performed 21 days (± 2 days) after the start of each TMZ cycle. If the ANC falls below 1,500/µL or if the platelet count falls below 100,000/mm^3, then blood counts should be performed weekly until recovery to these levels before TMZ dosing. A certified local lab may be used instead of central lab; if so, ANC and platelet results should be reported in the eCRF. Day 22 testing may be omitted for cycles in which TMZ is not administered or if local prescribing information allows for a different testing schedule for ANC and platelets.

d. Final Study Drug Visit to be performed approximately 14 days after last dose of ABT-414.

e. To be performed 35 days (± 3 days) after the last dose of study drug (ABT-414). If the Final Study Drug Visit is more than 35 days after the last dose of study drug, then 35-day safety follow-up procedures will not be performed.

f. Physical exams will be performed only as needed for safety management and adverse event reporting.

g. Ophthalmology exams will be performed only as needed for safety management and AE/SAE reporting. The last ophthalmology exam following discontinuation of ABT-414 may be done at the 35-Day F/U or 49-Day F/U Visit. Targeted ophthalmology exam data will not be collected by the Sponsor.

h. TMZ will be administered once daily on Days 1 through 5 of each 28-day cycle for 6 cycles per the local prescribing information.

i. ABT-414 infusion will be administered on Day 1 and Day 15 of each 28-day cycle for 12 cycles.

j. Prophylactic eye drops will be administered daily for 7 days with each dose of ABT-414, from 2 days before until 4 days after each dose of study drug (ABT-414), as described in Section 5.5 of the main study. Patients will receive management of ocular side effects as per investigator discretion. In this case, ABT-414 dose interruption and/or reduction many be used, and any available prophylactic or supportive care measures may be employed without restriction, at the discretion of the investigator.

k. If the subject is unable to return to the site for the Day 49 Follow Up Visit, a phone call may be conducted to obtain AE/SAE and concomitant medication information.

ABT-414 Administration and Individual Subject Discontinuation

ABT-414 will be administered as described in the main protocol.

Subjects may continue receiving ABT-414 while drug supply is available as long as disease progression has not been determined.

ABT-414 Toxicity Management and Individual Subject Dose Modifications

Section 8.0 of the main protocol provides guidance for toxicity management and dose modifications.

Adverse Events and Concomitant Medications

Adverse event and concomitant medication data will be collected to support regulatory safety reporting requirements.

Document Approval

Study M13813 - A Randomized, Placebo Controlled Phase 2b/3 Study of ABT-414 with Concurrent Chemoradiation and Adjuvant Temozolomide in Subjects with Newly Diagnosed GliobLastoma (GBM) with Epidermal Growth Factor Receptor (EGFR) Amplification (Intellance 1) - (RTOG 3508) - Amendment 9 - EudraCT 2015-001166-26 - 26May2019

Version: 1.0 **Date:** [redacted] 02:51:25 AM **Company ID:** 05282019-00F9F68422615E-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	[redacted]	Approver
		Approver
		Approver
		Approver
		Approver

RTOG FOUNDATION COLLABORATION WITH ABBVIE INC.

RTOG 3508/AbbVie M13-813
(EudraCT 2015-001166-26)

AMENDMENT 9
A Randomized, Placebo Controlled Phase 2b/3 Study of ABT-414 with Concurrent Chemoradiation and Adjuvant Temozolomide in Subjects with Newly Diagnosed Glioblastoma (GBM) with Epidermal Growth Factor Receptor (EGFR) Amplification (Intellance 1)

Sponsor: AbbVie Inc. (AbbVie)
AbbVie IND AbbVie Investigational Product: ABT-414
Date: 26May2019

Principal Investigator/Neuro-Medical Oncology [redacted]

Study Co-Chairs
Neuro-Medical Oncology:
Radiation Oncology:

Neurosurgery:
Neuropathology/Correlative Biology:

Ophthalmology:

Patient-Reported Outcomes Endpoints (Quality of Life):
Neurocognitive Function:

Statistician:

[redacted]

Protocol Acceptance

On behalf of RTOG Foundation, Inc.

[redacted]

[redacted]

Date