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Protocol for Study M16-534

Glioblastoma: Management of Depatuxizumab Mafodotin (ABT-414) Ocular Side Effects

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FULL TITLE: Phase 3b Study for Management of Ocular Side Effects in Subjects with EGFR-Amplified Glioblastoma Receiving Depatuxizumab Mafodotin (ABT-414)

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1 SYNOPSIS

Title: Phase 3b Study for Management of Ocular Side Effects in Subjects with EGFR-Amplified Glioblastoma Receiving Depatuxizumab Mafodotin (ABT-414)	
Background and Rationale:	Depatuxizumab mafodotin is being investigated in late phase clinical trials of patients with glioblastoma (GBM) that demonstrate epidermal growth factor receptor (EGFR) amplification. The dose-limiting toxicities (DLTs) observed after depatuxizumab mafodotin exposure have been limited to ocular side effects (OSEs). The optimization of prophylactic eye treatment and/or symptom-driven intervention would potentially decrease the severity of OSEs, reduce depatuxizumab mafodotin dose interruptions and discontinuations, and allow subjects with EGFR-amplified GBM to achieve the overall desired treatment dose prescribed for depatuxizumab mafodotin.
Objective(s) and Endpoint(s):	This exploratory study is designed to evaluate several depatuxizumab mafodotin-related OSE management strategies that may improve upon the standard steroid prophylactic treatments currently utilized in the depatuxizumab mafodotin program. Three different prophylactic treatment regimens (standard steroids [SS], standard steroids with vasoconstrictors and cold compress [SS/VC], and enhanced steroids with vasoconstrictors and cold compress [ES/VC]) will be used for various depatuxizumab mafodotin-related OSE in subjects receiving depatuxizumab mafodotin for the treatment of epidermal growth factor receptor (EGFR)-amplified GBM. The primary objective of this study is to evaluate the effect of several prophylactic strategies on the proportion of subjects requiring a change in OSE management due to inadequate control of OSEs. The primary endpoint is defined as percentage of subjects with either a ≥ 3-line decline from baseline (≥ +0.3 on LogMAR scale) in visual acuity (with baseline correction) or ≥ Grade 3 OSE severity on the Corneal Epithelial Adverse Event (CEAE) scale, either of which will indicate inadequate control of OSEs requiring a change in OSE management strategy. Secondary objectives include assessment of the effects of intervention with bandage contact lenses (BCL) on visual acuity and OSE symptom severity for subjects who meet protocol-defined criteria, defined above, for intervention due to inadequate control of OSEs. Secondary endpoints include assessment of the change from baseline in visual acuity, OSE symptom severity, time to BCL intervention, percentage of subjects with depatuxizumab mafodotin dose interruption/dose reduction, time to depatuxizumab mafodotin dose interruption/dose reduction, time to re-initiation of depatuxizumab mafodotin treatment after drug interruption, time to OSE symptom resolution after drug discontinuation.
Investigator(s):	Multicenter, multi-national
Study Site(s):	Approximately 30

Study Population and Number of Subjects to be Enrolled:	Subjects with newly diagnosed GBM. All subjects must be EGFR amplified. Approximately 90 subjects
Investigational Plan:	This is a Phase 3b open-label, randomized study. Subjects will be randomized 1:1:1 to one of the 3 prophylactic treatment arms, in patients with newly diagnosed GBM.
Key Eligibility Criteria:	The eligibility criteria for this study are consistent with previous depatuxizumab mafodotin clinical studies where eye toxicities are the most common treatment-related adverse events observed, and these toxicities define the DLT for depatuxizumab mafodotin. Subjects have histologically confirmed newly diagnosed grade IV glioblastoma or gliosarcoma, supratentorial in location, with EGFR amplification.
Study Drug and Duration of Treatment:	Subjects will receive depatuxizumab mafodotin 2.0 mg/kg during the chemoradiation phase (consisting of radiation and temozolomide [RT/TMZ]) and depatuxizumab mafodotin 1.25 mg/kg during adjuvant therapy with TMZ. Subjects will be randomized to one of 3 prophylactic ophthalmologic treatments (SS, SS/VC, or ES/VC). Depatuxizumab mafodotin will be administered every 2 weeks during standard 6-week RT/TMZ therapy, followed by a 4-week recovery period. During adjuvant therapy, depatuxizumab mafodotin will be administered every 2 weeks for 12 cycles (28 days/cycle).
Date of Protocol Synopsis:	28 May 2019

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Glioblastoma (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 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] Despite this multimodel approach, median survival is 1 – 2 years. There is an urgent need to develop novel therapeutics that can improve outcome in glioblastoma patients.

A substantial proportion of GBM tumors are characterized by Epidermal Growth Factor Receptor (EGFR) overexpression and amplification. When present, EGFR amplification has been shown to be maintained throughout the natural history of the disease. These features make EGFR a target for therapeutic intervention. Depatuxizumab mafodotin (formerly known as ABT-414) is an antibody-drug conjugate (ADC) that incorporates the ABT-806 antibody, which is covalently bound to an auristatin microtubule-disrupting toxin (mono methyl auristatin form [MMAF]) via a non-cleavable maleimido-caproyl (mc) linker. Depatuxizumab mafodotin is currently being investigated in late phase clinical trials of patients with newly diagnosed glioblastoma with amplified EGFR. The dose-limiting toxicities (DLTs) observed after depatuxizumab mafodotin exposure have been limited to ocular side effects (OSEs) with symptoms that manifest as a result of formation of corneal epithelial microcysts, a syndrome referred to as microcystic keratopathy. It is hypothesized that depatuxizumab mafodotin is taken up into rapidly dividing cells of the corneal epithelium, mainly by non-selective, EGFR-unrelated mechanism; toxin is then released inside the cell, causing damage predominantly to the transient amplifying cells located within the basal cell layer, with relative sparing of the more slowly dividing corneal stem cells in the limbus. This damage results in cellular death leading to the formation of epithelial microcysts. The epithelial microcysts then travel towards the central cornea and are sloughed off as part of normal cornea regeneration. Therefore, as the cornea regenerates, the symptoms resolve and the effects of depatuxizumab mafodotin should be transient after treatment discontinuation.

This is the first exploratory study evaluating prophylactic mitigation strategies and treatment options for OSEs associated with depatuxizumab mafodotin.

Ocular side effects are not unique to depatuxizumab mafodotin and have been observed with other ADCs currently in clinical development.[3] For several of these ADCs, prophylactic steroid ophthalmic solution has been found to be effective in reducing the frequency and severity of ADC-induced OSEs. In two Phase 1 dose-escalation studies, SGN-CD19A, which is a conjugate of a humanized anti-CD19 antibody and an auristatin drug (monomethyl auristatin F [MMAF]), was administered to patients with hematologic malignancies and resulted in OSEs that manifested themselves as microcystic keratopathy on corneal examination.[3] In both studies, patients experiencing ocular adverse events (AEs) were prescribed ophthalmic steroids and most experienced resolution or improvement to Grade 1 – 2 by last follow-up. This observation prompted topical steroid prophylaxis in both trials, administered before each ADC dose. At interim analysis, the authors of the latter study reported that this prophylaxis had

reduced the incidence of Grade 3 – 4 events. In one Phase I study with conjugate of a humanized anti-CD70 antibody and MMAF, SGN-75, dose dependent ocular side effects were observed in 57% of patients. Artificial tears and steroid eye drops were prescribed, mitigating the duration and severity of ocular symptoms. Thereafter, steroid eye drops were recommended for all patients with evidence of microcystic corneal epitheliopathy, even if asymptomatic.[3] The steroid eye drops are thought to reduce the cellular turnover in the corneal epithelium and make the cells more resistant to the effects of chemotherapy agents that effect actively replicating cells. Steroid ophthalmic steroids such as prednisolone 1% suspension and dexamethasone 0.1% solution have been required in all depatuxizumab mafodotin clinical trials since dose escalation in the first-in-human (FIH) study.

Supportive-care measures (e.g., lubricating eye drops, therapeutic bandage contact lenses, punctal plugs, etc.) can provide considerable relief for symptoms of depatuxizumab mafodotin-related eye side effects such as blurred vision, photophobia, and eye discomfort. Although supportive care measures have been utilized in depatuxizumab mafodotin clinical trials, the selection and timing of specific interventions to be used were not prescribed by the study protocol, and investigators are allowed to utilize whatever strategies they deem appropriate as per clinical judgment. Feedback from investigators and ophthalmologists experienced with use of depatuxizumab mafodotin has been particularly positive for the use of bandage contact lenses, with subjects reporting improvements in blurred vision and photophobia, as well as ocular discomfort.

An additional prophylactic treatment option proposed for this clinical trial is the use of vasoconstrictors and cold compresses immediately prior, during, and after the infusion. It is hypothesized that vasoconstriction of the conjunctival arterioles by the combination of pharmacologic (topical vasoconstrictors) and physical (cold compresses) methods during and immediately after infusion would significantly decrease exposure of the corneal epithelial cells to depatuxizumab mafodotin, thereby decreasing damage to corneal epithelium. Feedback from ophthalmologists testing this combination vasoconstrictor/cold compress strategy in the depatuxizumab mafodotin development program has been supportive of the potential efficacy of this approach.

Naphazoline HCl is available in 0.012% over the counter eye drop formulations. Naphazoline is an imidazole derivative and acts as an adrenergic receptor agonist that induces vasoconstriction of arterioles of the conjunctiva by stimulation of α-adrenergic receptors of the vascular wall. Short term (approximately 4 hours) tachyphylaxis in response to acute administration of naphazoline is mediated by receptor desensitization; more durable tachyphylaxis occurs after several days use and is mediated by receptor down regulation. Naphazoline HCl 0.012% is approved for administration of 1 – 2 gtt into affected eye every 3 to 4 hours as needed.[4]

The ability to assess the effectiveness of prophylactic and interventional strategies for ocular side effect management has been limited in depatuxizumab mafodotin trials to date. Potential improvements over standard steroid prophylaxis have only recently been identified, and support for them is based on anecdotal reports for a small number of subjects. As important, the standard practice for recording spontaneously reported adverse events in clinical trials (recording the times of onset and complete resolution, and recording changes in severity only if there is an increase) provides limited longitudinal information on symptom severity for assessing effectiveness of supportive care interventions.

This exploratory safety study will systematically assess the effectiveness of different prophylactic strategies, as well as the effectiveness of bandage contact lens intervention for those who demonstrate

inadequate control of ocular side effects by pre-defined criteria. Regular, repeated assessments of symptom severity and eye examinations will provide longitudinal information needed to evaluate the effectiveness of prophylactic regimens and interventions.

Clinical Hypothesis

Improved management of depatuxizumab mafodotin-related OSEs, through prophylactic eye treatment regimens and/or symptom-driven interventions, should minimize depatuxizumab mafodotin dose interruptions and discontinuations and allow subjects with GBM who are treated with depatuxizumab mafodotin to achieve the overall treatment intensity prescribed. The use of novel prophylactic regimens (vasoconstrictor/cold compress [VC] and/or enhanced steroids [ES]) with depatuxizumab mafodotin infusions should decrease the severity of depatuxizumab mafodotin-related OSEs compared to the standard steroid (SS) regimen that was used in previous clinical trials. The VC regimen includes both pharmacologic vasoconstriction with the adrenergic agonist naphazoline 0.012% topical solution and physical vasoconstriction by application of cold compresses to the eyes around the time of infusion. The ES regimen includes a higher frequency of steroid eye drops than the standard steroid (6×/day versus 3×/day), as well as addition of ocular steroid ointment at night. This approach is intended to maximize the effects of steroids on corneal epithelial cell turnover, which is postulated to make them less susceptible to depatuxizumab mafodotin-induced OSEs. In subjects for whom OSEs are not adequately managed with the initial prophylactic eye treatment regimen, intervention with bandage contact lenses should improve tolerability of OSEs.

2.2 Benefits and Risks to Patients

In preclinical studies, depatuxizumab mafodotin has demonstrated efficacy in a range of tumor types, including human GBM cell lines that have a high EGFR expression, and human tumor xenograft models. Depatuxizumab mafodotin also demonstrates a favorable EGFR-binding ratio of tumor to normal tissue.

Depatuxizumab mafodotin has been studied in 6 clinical trials to date. In the randomized Phase 2 Study M14-483 (INTELLANCE-2) in EGFR-amplified, recurrent GBM, the primary comparison of depatuxizumab mafodotin combined with TMZ (n = 88) vs TMZ or lomustine (n = 86) showed a 29% reduction in OS hazard rate (HR = 0.71; 95% CI [0.50, 1.02]) that did not reach statistical significance at the 0.05 two-sided level (p = 0.062). The 1-year OS rate for the depatuxizumab mafodotin combination was 40% [29%, 50%] versus 28% [19%, 38%] for the TMZ/LOM group. No OS difference was observed between depatuxizumab mafodotin monotherapy and TMZ/LOM (HR 1.04; 95%CI [0.73, 1.48]; p = 0.835 two-sided).

Preliminary safety data were available for 809 subjects who received at least 1 dose of depatuxizumab mafodotin at the most recent IB update (version 7.0). A total of 488 subjects have been exposed to depatuxizumab mafodotin in the open-label studies (i.e., Studies M12-356 [N = 202], M13-379 [N = 56], M13-714 [N = 53], and M14-483 [N = 177, adult and pediatric]); in addition, 321 subjects were estimated to have received depatuxizumab mafodotin in the ongoing, blinded Study M13-813. Pharmacokinetic results are available from the following studies of depatuxizumab mafodotin: Studies M13-379 (N = 56), M12-356 (N = 202), M14-483 (N = 177), and M13-714 (N = 53).

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 depatuxizumab mafodotin were fatigue (34.9%), vision blurred (27.3%), headache and keratitis (25.0% for each), dry eye (24.4%) and corneal epithelial microcysts (22.1%). The majority of subjects who received depatuxizumab mafodotin (77.3%) experienced at least 1 treatment-emergent adverse event coded to the System Organ Class of Eye Disorders. In addition to ocular side effects related to corneal epitheliopathy, treatment-emergent adverse events reported by ≥ 10% of subjects in the depatuxizumab 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 depatuxizumab mafodotin/TMZ combination arm, for which the rate was similar to that of subjects receiving TMZ monotherapy.

In the ongoing Study M13-813 (RTOG 3508) blinded study in newly diagnosed GBM, one subject receiving depatuxizumab mafodotin (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 depatuxizumab mafodotin. The sponsor also assessed that there was a reasonable possibility that depatuxizumab mafodotin 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 depatuxizumab mafodotin open-label or blinded studies, in which approximately 809 people have received depatuxizumab mafodotin to date.

Enhanced steroid treatment, proposed in the study, is commonly used for routine postoperative management and treatment of endothelial graft rejection. Potential increase in intraocular pressure and increased risk of fungal infection, associated with intensified topical steroid administration will be mitigated by frequent (bi-weekly) ophthalmologic examinations.

Use of topical vasoconstrictors and cold compresses, both of which are over-the-counter treatments that will be used in accordance to the package insert instructions, present minimal risk to patients. Any potential adverse reactions to these treatments will be addressed during bi-weekly ophthalmologic examinations. Use of bandage contact lens intervention in combination with steroid treatment may potentially increase the risk of fungal and bacterial infection. However, subjects in this study will undergo frequent routine ophthalmologic examinations, and treating ophthalmologists will have an option of using prophylactic topical antibiotics to prevent infections.

Summary of Results from Pre-planned Interim Efficacy Analysis for Study M13-813 (INTELLANCE-1)

Study M13-813/RTOG 3508/INTELLANCE-1 is an ongoing, Phase 3, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of depatuxizumab mafodotin versus placebo, each as concurrent treatment with standard-of-care therapy of radiation therapy/TMZ plus adjuvant TMZ, in subjects with newly diagnosed GBM. This ongoing study is being conducted by AbbVie in collaboration with the Radiation Therapy Oncology Group (RTOG) Foundation. During the 6-week Chemoradiation Phase, subjects receive depatuxizumab mafodotin 2.0 mg/kg or placebo once every 2 weeks concurrently with standard 6-week concomitant radiation therapy/TMZ. The Adjuvant Phase consists of 28-day cycles, with subjects receiving concomitant TMZ (Days 1 to 5 of each cycle) and study drug (depatuxizumab mafodotin 1.25 mg/kg or placebo once every 2 weeks) for the first 6 cycles and study

drug (depatuxizumab mafodotin or placebo) monotherapy for the following 6 cycles, with the option to continue treatment until disease progression.

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 is 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 depatuxizumab mafodotin 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 depatuxizumab mafodotin 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 depatuxizumab mafodotin (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 depatuxizumab mafodotin 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 (depatuxizumab mafodotin or placebo) in the depatuxizumab mafodotin and placebo arms, 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 depatuxizumab mafodotin 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 depatuxizumab mafodotin group was at least 5% and was ≥ 2% greater than in the placebo group included thrombocytopenia, gamma-glutamyltransferase increased, and alanine aminotransferase increased.

The INTELLANCE-1 interim efficacy analysis results overall indicated no survival benefit for adding depatuxizumab mafodotin 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 believed it was appropriate to allow subjects receiving depatuxizumab mafodotin to continue depatuxizumab mafodotin treatment if the investigator and subject believed it is in the subject's best interest.

A total of 40 subjects have been enrolled in Study M16-534 (UNITE). Based on the results from INTELLANCE-1, no new subjects will be enrolled into Study M16-534 (UNITE). Subjects who are currently receiving depatuxizumab mafodotin will be allowed to continue depatuxizumab mafodotin treatment if the investigator and subject believe it is in the subject's best interest. **For those subjects who choose to continue depatuxizumab mafodotin, study procedures have been modified as described in Appendix E.** The appendix provides guidance for study drug administration and collection of only safety data related to AEs and SAEs. No additional efficacy data will be collected.

With all these changes, no statistical testing will be performed for the efficacy endpoints. Given only a small number of patients are enrolled in the study and most of them did not have long-term follow-up, all the efficacy endpoints will only be summarized, and no statistical model will be used to analyze the efficacy data. The statistical section remains unchanged to reflect the original analysis plan.
An abbreviated SAP will be written to document the details about the analysis plan.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

Primary Objective

1. Estimate the percentage of subjects in each prophylactic treatment arm who require a change in OSE management due to inadequate control of OSEs.

Secondary Objective

2. Assess the effects of intervention with bandage contact lenses (BCL) on visual acuity and OSE symptom severity for those subjects who require intervention due to inadequate control of OSEs.

3.2 Primary Endpoint

The primary endpoint is defined as the percentage of subjects with either a ≥ 3-line decline from baseline (≥ +0.3 on LogMAR scale) in visual acuity (with baseline correction) or ≥ Grade 3 OSE severity on the Corneal Epithelial Adverse Event (CEAE) scale, either of which will indicate inadequate control of OSEs requiring a change in OSE management strategy.

Unless otherwise noted, visual acuity will be measured using baseline correction, which will be determined at the screening ophthalmology visit and used to assess visual acuity at all remaining ophthalmology visits, for measuring changes in visual acuity and for determining the visual acuity component of the primary endpoint. Details on determining baseline correction are provided in the operations manual. The primary endpoint will be assessed over 8 weeks after initiation of depatuxizumab mafodotin treatment.

3.3 Secondary Endpoints

Secondary endpoints will be assessed as below over 8 weeks after initiation of depatuxizumab mafodotin treatment, assessed separately for the chemoradiation phase and adjuvant phase, as appropriate, as different doses of depatuxizumab mafodotin are used in each phase. The effectiveness of the initial prophylactic strategy and of the BCL-intervention will be assessed separately, as will be resolution of OSEs after interruption/discontinuation of depatuxizumab mafodotin.

Effectiveness of Prophylactic Regimen	Effectiveness of BCL Intervention
• Maximum change from baseline on LogMAR scale • Time to BCL intervention • Dose interruptions due to OSEs (% subjects) • Dose reductions due to OSEs (% subjects) • Cumulative dose of depatuxizumab mafodotin received (mg/kg) (during chemoradiation and during adjuvant treatment) • CEAE grade, at each visit	• Change in LogMAR (pre- to post-intervention, then followed longitudinally) • Recovery to < 3-line decline from baseline (< +0.3 LogMAR) in visual acuity (% subjects) • Dose interruptions due to OSEs (% subjects) • Dose reductions due to OSEs (% subjects) • Time to restart depatuxizumab mafodotin (if interrupted) • CEAE grade, at each visit, post BCL intervention
Resolution of OSEs	
• Time to OSE symptom resolution after drug discontinuation (reversibility) • Time to re-initiation of depatuxizumab mafodotin after dose interruption	

3.4 Other Safety Endpoints

Non-ocular AEs, laboratory profiles, physical examinations, and vital signs will be assessed throughout the study.

3.5 Pharmacokinetic Endpoints

No pharmacokinetic endpoints

3.6 Histopathologic/Biomarker Tissue Evaluation Endpoints

During this study, tumor biomarker samples will be collected. Optional tissue collection may include tumor tissue samples from the subjects' initial surgery, repeated resection(s) and/or post-mortem corneal tissue samples. Tumor samples may be analyzed for genetic factors contributing to the subject's response to depatuxizumab mafodotin, or other study treatment, in terms of tolerability and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, or other genes believed to be related 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 depatuxizumab mafodotin or drugs of this class. The samples may also be used for the development of diagnostic tests related to depatuxizumab mafodotin (or drugs of this class). Corneal tissue will be assessed to further characterize histopathologic features of OSEs. The samples may be retained for no longer than 20 years after study completion or per local requirements.

Exploratory Endpoints of this study are:

Effectiveness of the prophylactic regimen with regard to symptom severity as assessed by:

1. Individual items on the CEAE scale – degree of photophobia at each visit; impact of ocular discomfort on visual Activities of Daily Living (vADLs) at each visit; reading score (impact on blurred vision) at each visit.
2. Visual Quality of Life (vQOL) score changes

Effectiveness of the intervention with regard to symptom severity as assessed by:

1. Individual items on the CEAE scale – degree of photophobia at each visit; impact of ocular discomfort on vADLs at each visit; reading score (impact on blurred vision) at each visit.
2. vQOL score changes
3. % of subjects with improvement on vQOL

Overall survival (OS)

Progression free survival (PFS)

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

A schematic of the study design is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual, Section 3. See Section 5.1 for information regarding eligibility criteria.

This is a Phase 3b open-label, randomized, exploratory study to evaluate the effect of 3 ophthalmologic prophylactic treatment strategies for the management of OSEs in subjects with newly diagnosed, EGFR-amplified GBM who are being treated with depatuxizumab mafodotin in addition to standard frontline treatment with chemoradiation (RT/TMZ) followed by adjuvant TMZ. Approximately 90 subjects will be enrolled at approximately 30 research sites.

During the Chemoradiation Phase, all subjects will undergo focal RT, with one treatment of ~2 Gy given daily 5 days per week over approximately 6 weeks (and no more than 7 weeks), for a total of ~60 Gy. 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. All subjects will receive depatuxizumab mafodotin at 2.0 mg/kg IV infusion once every 2 weeks (on Day 1 of Weeks 1, 3, and 5) during this period.

Treatment in the Chemoradiation Phase 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 last 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 Therapeutic Area Medical Director 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 – 12 cycles, depending on local standard of care. All subjects will receive depatuxizumab mafodotin at 1.25 mg/kg IV infusion once every 2 weeks (on Day 1 and Day 15 of each 28-day cycle) for 12 cycles. Adjuvant treatment will be discontinued upon determination of tumor progression as defined by Response Assessment in Neuro-Oncology Working Group (RANO) criteria (Operations Manual, Appendix I), unacceptable toxicity, or refusal to continue study treatment.

Subjects will be randomized to 1 of 3 prophylactic eye treatment arms (1:1:1), to be administered with each infusion of depatuxizumab mafodotin (during both Chemoradiation Phase and Adjuvant Phase):

- Arm A (SS) – Standard Steroids
- Arm B (SS/VC) – Standard Steroids + Vasoconstrictor + Cold Compress
- Arm C (ES/VC) – Enhanced Steroids + Vasoconstrictor + Cold Compress

Subjects will be monitored at regular intervals for OSEs by AE reports and by ophthalmology examinations (including slit lamp examination and visual acuity testing).

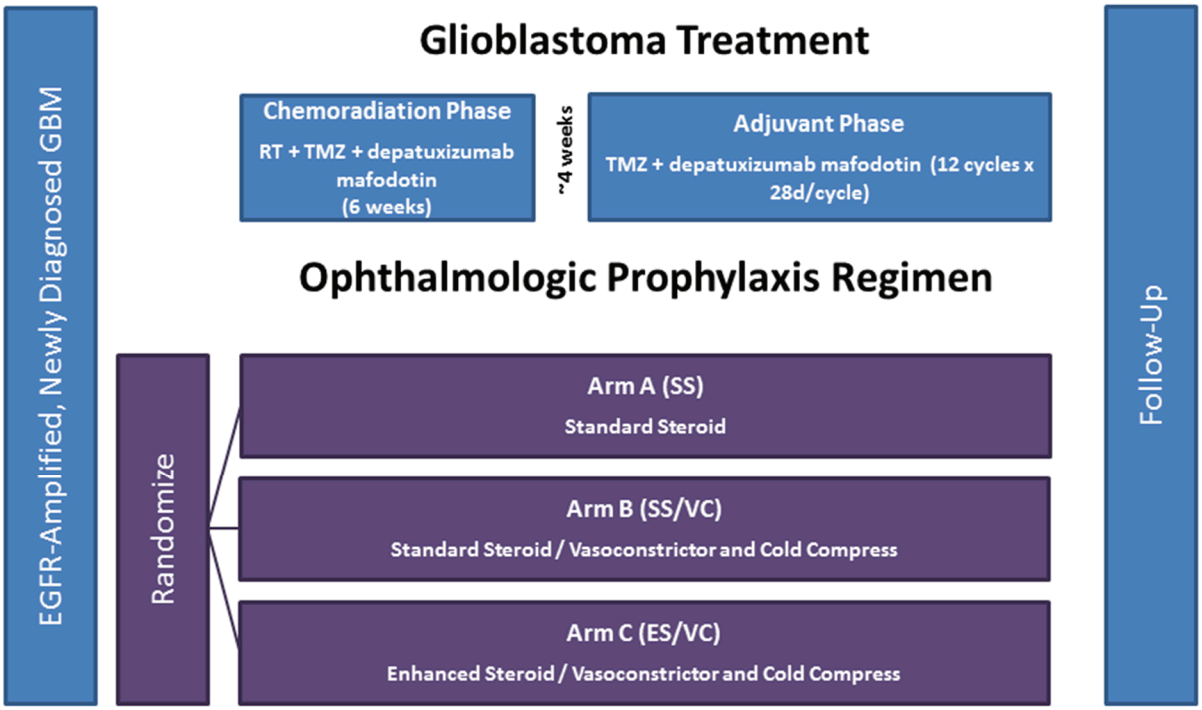
For subjects who demonstrate inadequate control of OSEs with the initial prophylactic strategy, according to predefined criteria for loss of visual acuity and/or OSE symptom severity, intervention with a BCL will first be employed (Figure 2). Subjects who continue to demonstrate inadequate response to BCL intervention (CEAE Grade 3 or higher OSE symptom severity) will be eligible for unrestricted OSE management according to investigator discretion. In this case, depatuxizumab mafodotin dose interruption and/or reduction may be used, and any available prophylactic (including addition of ES and VC regimens if not used initially) or supportive care measures may be employed without restriction, at the discretion of the investigator.

Subjects who complete 8 weeks of adjuvant therapy (8 weeks after the first dose of adjuvant depatuxizumab mafodotin) will be allowed to enter the Investigator Discretion phase regardless of CEAE Grade, visual acuity or BCL intervention.

Visual acuity will be measured using the LogMAR scale for visual acuity, while OSE symptom severity will be measured by the Corneal Epithelial AE grading scale (see Section 6.1 and Operations Manual, Section 4.3), which was developed by the sponsor for assessing and managing corneal epitheliopathy associated with ADCs.

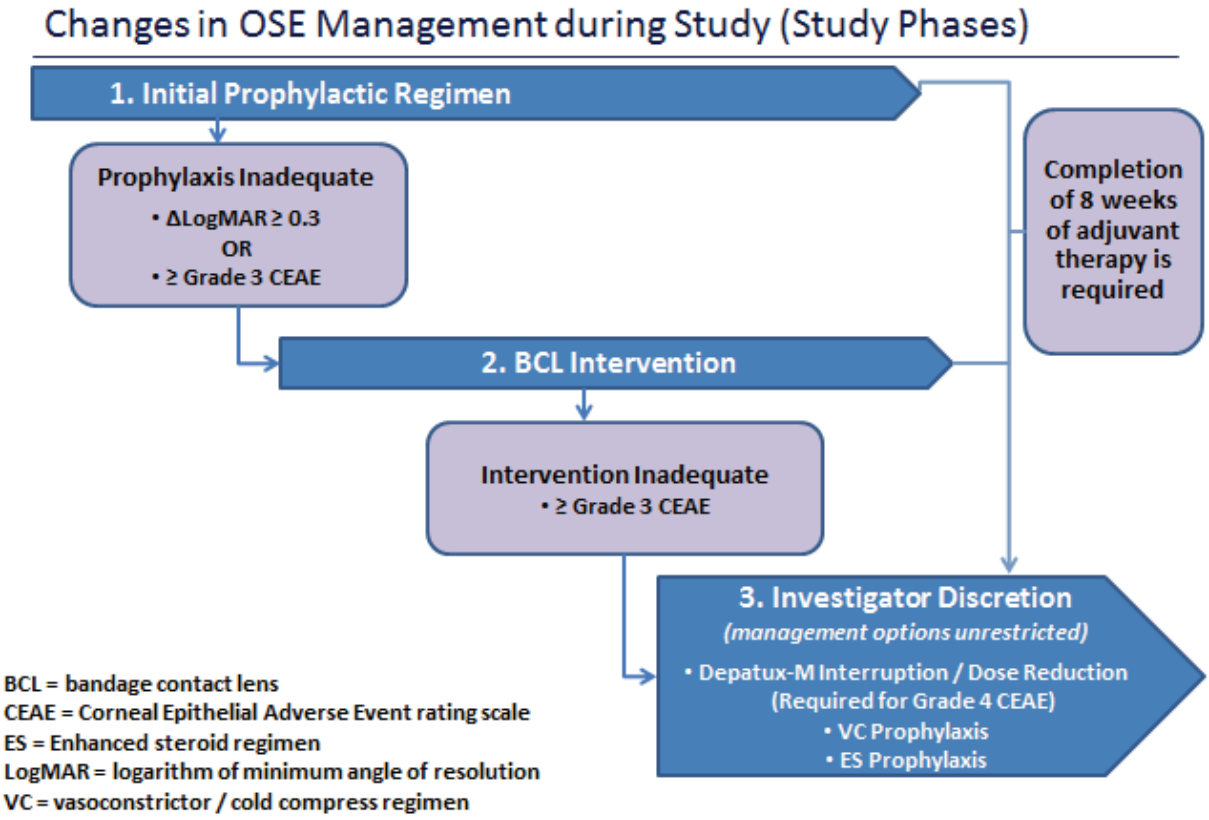
Effectiveness of the prophylactic strategies will be assessed during the first 8 weeks of each phase of treatment (Chemoradiation Phase and Adjuvant Phase). Subjects who discontinue depatuxizumab mafodotin for any reason will receive regular follow-up for assessment of AEs and ophthalmologic examinations until resolution of OSEs to evaluate the reversibility of depatuxizumab mafodotin-related OSEs.

Figure 1. Study Design



Abbreviations: GBM = glioblastoma; RT = radiation therapy; TMZ = temozolomide

Figure 2. Depatuxizumab Mafodotin Intervention Strategy for Inadequate Control of Ocular Side Effects



4.2 Discussion of Study Design

Suitability of Subject Population

The study population of newly diagnosed GBM with amplified EGFR was selected because depatuxizumab mafodotin is currently being investigated in a late phase clinical trial with this subject population. Ocular side effects are noted to occur at a > 80% frequency in GBM patients with doses currently utilized in the ongoing Phase 2b/3 clinical trial.

Choice of Frontline GBM Therapy

Concomitant RT/TMZ therapy followed by adjuvant TMZ therapy is the established standard-of-care treatment for newly diagnosed GBM, and the dose regimens for RT and TMZ for the current study are consistent with standard of care. Addition of depatuxizumab mafodotin to this standard treatment regimen was generally well tolerated in a Phase 1 study, with dose-limiting toxicity restricted to OSEs, and efficacy is being evaluated in a large Phase 2b/3 study in EGFR-amplified, newly diagnosed GBM.

Choice of Prophylactic Regimens and BCL Intervention

Prophylactic steroid eye drops were instituted early on during the first Phase 1 study in solid tumors to support continued dose escalation. In the ongoing Phase 2b/3 clinical trial in newly diagnosed subjects, all subjects receive prophylactic steroid eye drops with each dose of depatuxizumab mafodotin for 7 consecutive days, starting from 2 days prior to infusion and continuing until 4 days after infusion, making it the standard of care in the depatuxizumab mafodotin clinical development program.

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 depatuxizumab mafodotin 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 the drops is around the time of infusion when the levels of MMAF are at their peak.

Enhanced steroid treatment regimen will consist of the same steroid eye drops, as those used in the standard steroid arm, administered with the maximal frequency that can be achieved with reasonable expectation of patient compliance. Steroid ointment will be instilled at night, when the patient cannot be expected to self-administer eye drops. This regimen will maximize the exposure of the corneal epithelium to the steroids, allowing examination of the dose-effect relationship. Safety of enhanced steroid treatment will be insured by frequent (every 2 – 4 weeks) targeted ophthalmologic examinations.

The dose of vasoconstrictor was selected based on the maximum dose and duration of treatment recommended for naphazoline hydrochloride 0.012%solution.[4]

The use of therapeutic BCLs 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 depatuxizumab mafodotin dose interruptions and dose reductions.

Appropriateness of Measurements

The LogMAR scale will be the instrument utilized for measuring visual acuity because it is a well-accepted validated tool used in ophthalmology clinical trials designed to evaluate change in visual acuity.[5]

The CEAE grading scale will be used to measure OSE symptom severity. This measure was developed by AbbVie, based on experience with ADC-related microcystic keratopathy caused by depatuxizumab mafodotin, to address inadequacies of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) system for appropriately capturing symptoms, grading, and making dose modifications for ADC-related corneal toxicity.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects must voluntarily **sign and date an informed consent**, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult **male or female**, at least 18 years old.
- 3. **Laboratory values** meeting the following criteria confirming adequate bone marrow, renal, and hepatic function:
  - Bone marrow
    - Absolute neutrophil count ≥ 1,500 cells/mm^3
    - Platelets ≥ 100,000 cells/mm^3
    - Hemoglobin (Hgb) ≥ 9.0 g/dL (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 × upper limit of normal (ULN). Subjects with Gilbert's syndrome documented in medical history may be enrolled if total bilirubin is < 3 × ULN.
    - AST ≤ 3 × ULN
    - ALT ≤ 3 × ULN
  - Prothrombin time (PT)/international normalized ratio (INR) ≤ 1.5. Subjects on anticoagulant (such as coumadin) will have a target PT and INR as determined by the Investigator.
- 4. Willing or able to comply with procedures required in this protocol.

Disease Activity

- 5. Diagnosis of newly diagnosed GBM, histologically proven, World Health Organization (WHO) Grade IV GBM or WHO Grade IV gliosarcoma
- 6. Tumor must demonstrate EGFR amplification by central laboratory

- 7. Tumor must be supratentorial in location
- 8. Karnofsky performance status of ≥ 70

Subject History

- 9. Electrocardiogram without evidence of acute cardiac ischemia ≤ 21 days prior to randomization.
- 10. Life expectancy of ≥ 3 months.
- 11. No history of hypersensitivity to any component of TMZ or dacarbazine (DTIC).
- 12. No history of prior chemotherapy or radiotherapy for cancer of the head and neck region.
- 13. No history of prior treatment with Gliadel wafers or any other intratumoral or intracavitary treatment.
- 14. No prior anti-cancer therapy (including chemotherapy, immunotherapy, radiotherapy, hormonal therapy, biologic therapy, or any investigational therapy) prior to 5 years of Study Day 1.
- 15. No history of a major immunologic reaction to any Immunoglobulin (IgG) containing agent.
- 16. No clinically significant uncontrolled condition(s) including but not limited to the following:
  - Active uncontrolled infection
  - Symptomatic congestive heart failure
  - Unstable angina pectoris or cardiac arrhythmia
  - Psychiatric illness/social situation that would limit compliance with the study
- 17. No medical condition which in the opinion of the Investigator places the subject at an unacceptably high risk for toxicities.
- 18. No other active malignancy within the past 3 years except for any cancer considered cured or non-melanoma carcinoma of the skin.
- 19. No history of herpetic keratitis.
- 20. No LASIK (laser-assisted in situ keratomileusis) procedure within the last 1 year or cataract surgery within the last 3 months.
- 21. No visual condition that compromises the ability to accurately measure visual acuity or assess visual ADLs (e.g., central tumor affecting visual pathways).
- 22. No infection with hepatitis B virus (i.e., hepatitis B surface antigen) or hepatitis C virus (i.e., positive for hepatitis C antibody). Subjects who have a history of hepatitis C who have documented cures after anti-viral therapy may be enrolled. Subjects with confirmed positive test result for human immunodeficiency virus (HIV), with CD4 count < 200 cells/microliter are excluded.
  - Note that subjects who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ 200 cells/microliter within 30 days prior to registration, as the treatments involved in this protocol may be significantly immunosuppressive.

- Note HIV testing is not required for eligibility for this protocol unless mandated by local regulatory authority or ethics committee/institutional review board.

Contraception

- 23. For all females of childbearing potential, a **negative serum pregnancy test** at the screening visit and a negative urine pregnancy test at baseline prior to the first dose of study drug and monthly throughout the study.
- 24. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control,** as specified in Section 5.2, that is effective from Study Day 1 through at least 6 months after the last dose of depatuxizumab mafodotin. Female subjects of non-childbearing potential do not need to use birth control.
- 25. Female who is not **pregnant, breastfeeding, or considering becoming pregnant** during the study or for at least 6 months after the last dose of depatuxizumab mafodotin.
- 26. **If male**, and subject is **sexually active with female partner(s) of childbearing potential**, he must agree, from Study Day 1 through the entire duration of the study and for at least 6 months after the last dose of depatuxizumab mafodotin, to practice the contraception specified in Section 5.2.
- 27. Male who is not considering **fathering a child or donating sperm** during the study or for at least 6 months after the last dose of depatuxizumab mafodotin.

Concomitant Medications

- 28. Suitable for receiving ocular steroids and has none of the following:
  - Any active viral disease of the cornea or conjunctiva, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, or varicella; mycobacterial infection of the eye; fungal diseases of ocular structures; or any other contraindication for ocular steroid use.
  - A known or suspected hypersensitivity to any ocular steroid.
  - Primary open angle glaucoma or a history of steroid-induced intraocular pressure elevation.
- 29. Subject must not anticipate the use of prohibited medications or foods during study participation (see Section 5.3 for additional prohibited medications or foods).

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

- Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
- Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a Follicle Stimulating Hormone level > 40 IU/L.
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

- Females, of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy throughout the study including at least 6 months after the last dose of depatuxizumab mafodotin.
  - Females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system (IUS).
    - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
    - Practice true abstinence, defined as: 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).

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 30 days prior to Study Day 1.
- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.
- A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).

Contraception Requirements for Males

Male subjects who are sexually active with a female partner of childbearing potential, must agree **to use condoms, even if the male subject has undergone a successful vasectomy**, from Study Day 1 through the entire duration of the study and for at least 6 months after the last dose of depatuxizumab mafodotin:

- His female partner(s) must also use at least 1 of the following methods of birth control:
  - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1
  - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline Day 1
  - bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure)
  - intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy, and is the sole sexual partner of the trial subject)

5.3 Prohibited Medications and Therapy

In addition to the medications and therapy listed in the eligibility criteria (Section 5.1, **Concomitant Medications**), the following medications are **prohibited**:

No other investigational antineoplastic 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. The use of live attenuated vaccines is prohibited during the study and for a period of 49 days after the end of depatuxizumab mafodotin administration. 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 depatuxizumab mafodotin 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.

The uses of concomitant medications that are contraindicated per the national prescribing information are prohibited during the conduct of the study.

Subjects must be able to safely discontinue any prohibited medications 5 half-lives or 4 weeks prior to initial study drug administration. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

5.4 Prior and Concomitant Therapy

Continuous TMZ therapy induces lymphocytopenia and thrombocytopenia. Subjects are at an increased risk for opportunistic infections and bleeding – please consult package insert.[6]

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.

Any medication or vaccine (including over the counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded until completion of study.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie Therapeutic Area Medical Director. Information regarding potential drug interactions with depatuxizumab mafodotin can be located in the depatuxizumab mafodotin Investigator's Brochure.[7]

5.5 Withdrawal of Subjects and Discontinuation of Study

Each subject has the right to withdraw from the study 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.

Each subject must be withdrawn from the study immediately if any of the following occur:

- The subject or subject's legally acceptable representative withdraws consent.
- The subject experiences confirmed disease progression (PD), as determined by 2017 update of the Response Assessment in Neuro-Oncology criteria by Ellingson et al,[8] as described in Appendix I of the Operations Manual.
- Clinically significant abnormal laboratory results or AEs that rule out continuation of the study drug, as determined by the Investigator or the AbbVie Therapeutic Area Medical Director (TA MD).
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug, and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug.

- Subject is significantly non-compliant with study procedures, which would put the subject at risk for continued participation in the trial.
- Subject experiences intercurrent illness that prevents further administration of treatment
- Subject experiences excessive toxicity precluding further therapy with depatuxizumab mafodotin, according to the Investigator.
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the Investigator.

A subject may also be withdrawn if:

- The Investigator believes it is in the best interest of the subject.

Subjects unable to continue TMZ due to excessive toxicity will be allowed to continue therapy with depatuxizumab mafodotin until one of the other criteria above is met.

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.

If subject withdraws consent, the type of withdrawal should be specifically indicated (further treatment with TMZ, depatuxizumab-mafodotin, 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.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. AbbVie may terminate this study prematurely, either in its entirety or at any site. The Investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the Investigator.

5.6 Follow-Up for Subject Withdrawal from Study

After discontinuation of depatuxizumab mafodotin for any reason, subjects must be followed for safety evaluations, including follow-up of OSEs until symptom resolution, unless the subject withdraws consent for safety follow-up.

Unless the subject specifically withdraws consent from follow up of overall survival, subjects will continue to be followed for overall survival, and overall survival will be recorded. Opting out of overall

survival follow-up must be clearly documented. Of note, overall survival may still be obtainable from a query of publicly available information unless prohibited by local regulations.

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 study, their study samples will continue to be stored and analyzed until consent is withdrawn as well.

5.7 Study Drug and Radiation Therapy

Information about Depatuxizumab Mafodotin (ABT-414) formulations to be used in this study is presented in Table 1.

Table 1. Identification of Investigational Product(s)

Study Drug	Mode of Administration	Dosage Form	Strength (mg)	Manufacturer
Depatuxizumab Mafodotin (ABT-414)	Intravenous (IV) infusion	Sterile lyophilisate in a vial	20 mg 30 mg	AbbVie

Administration and doses of depatuxizumab mafodotin during Chemoradiation Phase and Adjuvant Phase are described below.

AbbVie will not supply drug other than depatuxizumab mafodotin. Prophylactic therapies will be obtained commercially, except if otherwise required by local regulation.

Depatuxizumab mafodotin vials will be packaged in cartons with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. All blank spaces on the label will be completed by the site staff prior to dispensing to subjects. Study drug will only be used for the conduct of this study.

Instructions for drug preparation will be provided by AbbVie.

TMZ will not be provided by AbbVie. Study sites must refer to the TMZ package insert for detailed pharmacologic and safety information.

Chemoradiation Phase

Treatment in the Chemoradiation Phase must begin ≤ 7 weeks after most recent surgery/biopsy unless prior approval is obtained from the TA MD. During the Chemoradiation Phase, all subjects will undergo fractionated focal RT, with 1 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) according to local standard-of-care practice. TMZ will be administered continuously from Day 1 of radiotherapy to the last

day of radiation (including weekends and holidays) at a daily oral or intravenous dose of 75 mg/m^2 for a maximum of 49 days. Subjects will receive depatuxizumab mafodotin at 2.0 mg/kg IV infusion over 30 to 40 minutes once every 2 weeks (Day 1 of Weeks 1, 3, and 5 of the 6-week regimen).

Adjuvant Phase

The start of the first cycle during the Adjuvant Phase will be scheduled approximately 28 days after the last day of chemoradiation; the AbbVie TA MD should be notified if Adjuvant Phase treatment is to be started more than 42 days after the last day of chemoradiation. All subjects will receive oral TMZ 150 – 200 mg/m^2 once daily on Days 1 – 5 of each 28-day cycle for 6 – 12 cycles (6 – 12 months) as per local standard prescribing practice. Subjects receive depatuxizumab mafodotin as a 30- to 40-minute infusion at 1.25 mg/kg on Day 1 and Day 15 of each 28-day cycle for a total of 12 cycles (12 months).

OSE Prophylaxis

Subjects will receive OSE prophylaxis during both the Chemoradiation and Adjuvant Phases as long as depatuxizumab mafodotin treatment is ongoing.

Subjects will be randomized to one of the following prophylactic eye treatment arms. Equivalent steroid or vasoconstrictor medications may only be used with pre-approval by the AbbVie Therapeutic Area Medical Director.

Arm A (Standard Steroid)

- Steroid Eye Drops (for example, Prednisolone acetate 1% suspension), 1 drop in each eye 3 times per day starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days.
- Use of Prednisolone acetate is strongly recommended as the initial steroid eye drop due to the greater potency. Alternative steroids eye drops (for example, 0.1% dexamethasone phosphate solution, or equivalent) may be used if prednisolone acetate is not tolerated.

Arm B (Standard Steroid/Vasoconstrictor and Cold Compress)

- Steroid Eye Drop (for example, Prednisolone acetate 1% suspension), 1 drop in each eye 3 times per day starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days.
- Use of Prednisolone acetate is strongly recommended as the initial steroid eye drop due to the greater potency. Alternative steroids eye drops (for example, 0.1% dexamethasone phosphate solution, or equivalent) may be used if prednisolone acetate is not tolerated.
- Vasoconstrictor Eye Drop (for example, Naphazoline HCl 0.012% solution or equivalent), 1 drop in each eye 4 - 6 times on day of infusion in total (5 – 10 minutes before infusion; at end of infusion; and 2 - 4 times during the remainder of the infusion day). Continuing 4 - 6 times/day on Day 1 and Day 2 after infusion. In cases when an alternative to Naphazoline HCl 0.012% vasoconstrictor eye drop is used, please refer to prescribing information for maximal frequency of administration. However, duration of administration should remain constant (3 days total) in all cases.

    - Steroid and Vasoconstrictor eye drops to be given at least 5 minutes apart.
- Cold compress: Starting 5 minutes prior to start of infusion and continuing for 30 minutes past end of infusion; then at least 2 hours total/day during remainder of infusion day and for 2 days after infusion. The cold compress should be applied in increments no longer than 30 min (could be shorter if the patient is uncomfortable).

Arm C (Enhanced Steroid/Vasoconstrictor and Cold Compress)

- Steroid Eye Drop (for example, Prednisolone acetate 1% suspension), 1 drop in each eye 6 times per day starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days.
- Use of Prednisolone acetate is strongly recommended as the initial steroid eye drop due to the greater potency. Alternative steroids eye drops (for example, 0.1% dexamethasone phosphate solution, or equivalent) may be used if prednisolone acetate is not tolerated.
- Ophthalmic Steroid Ointment (for example, fluorometholone ophthalmic 0.1%, betamethasone eye ointment 0.1%, or equivalent) in each eye once daily before sleep starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days.
- Vasoconstrictor Eye Drop (for example, Naphazoline HCl 0.012% solution or equivalent), 1 drop in each eye 4 – 6 times on day of infusion in total (5 to 10 minutes before infusion; at end of infusion; and 2 - 4 times during the remainder of the infusion day). Continuing 4 - 6 times/day on Day 1 and Day 2 after infusion.
    - Steroid and Vasoconstrictor eye drops to be given at least 5 minutes apart.
- Cold compress: Starting 5 minutes prior to start of infusion and continuing for 30 minutes past end of infusion; then at least 2 hours total/day during remainder of infusion day and for 2 days after infusion. The cold compress should be applied in increments no longer than 30 min (could be shorter if the patient is uncomfortable).

With the exception of care measures described below as allowed at any time, other prophylactic or supportive measures are not allowed during the initial prophylaxis phase, unless prior approval is obtained from the AbbVie Medical Monitor.

Bandage Contact Lens (BCL) Intervention

If any subject in Arm A, Arm B, or Arm C has a ≥ 3-line loss in visual acuity (≥ +0.3 change from baseline by LogMAR) OR a CEAE ≥ Grade 3 ocular side effect, the subject will then receive BCL intervention in addition to the assigned initial prophylactic regimen.

With the exception of care measures described below as allowed at any time, additional measures besides BCL and the original prophylactic regimen are prohibited during the BCL intervention phase, unless prior approval is obtained from the AbbVie Medical Monitor.

Investigator Discretion

Subjects who have a ≥ Grade 3 CEAE event despite/after addition of BCL intervention to the initial prophylactic regimen will enter the Investigator Discretion phase, at which point there will be no restrictions on prophylactic or supportive measures used for OSE management.

Subjects who complete 8 weeks of adjuvant therapy (8 weeks after the first adjuvant dose of depatuxizumab mafodotin) will be allowed to enter in the Investigator Discretion phase regardless of CEAE Grade, visual acuity or BCL intervention.

Supportive Care Measures Allowed at Any Time

The following supportive care measures are allowed at any time, regardless of the current phase of OSE management:

- Lubricant Eye Drops
- Artificial Tears
- Antibiotics
- Sunglasses

Information on other allowable medications (prior to eligibility for the Investigator Discretion phase) may be described in the Operations Manual.

Please reference Section 5 "Study Drug" of the Operations Manual for more information on treatments administered in this study.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the Interactive Response Technology (IRT) at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie.

Subjects will be randomized in a 1:1:1 ratio to 1 of 3 prophylactic eye treatment regimens (Arm A, Arm B, or Arm C), as described in Section 4.1.

5.9 Protocol Deviations

The Investigator is responsible for complying with all protocol requirements, written instructions and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified), the Investigator is responsible for notifying Independent Ethics Committee (IEC)/Institutional Review Board (IRB), regulatory authorities (as applicable) and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

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/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE 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 AE 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.

The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event within 24 hours of the site 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.
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.

All adverse events reported will be collected from the time of study drug administration until 49 days after last depatuxizumab mafodotin administration, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and *protocol-related* (considered by the investigator to be causally related to protocol-required study procedures) nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

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

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects

Corneal Epithelial Adverse Events and Other Adverse Events of Special Interest

Because longitudinal assessment of corneal epithelial findings is central to the goals of this study, corneal epithelial adverse events will be assessed regularly, and severity will be re-graded at every assessment. Adverse events related to corneal epithelial abnormalities will be reported using the term "corneal epitheliopathy," and associated signs and symptoms will be recorded and graded using the Corneal Epithelial Adverse Event eCRF. Grading of corneal epithelial events is based on effects on visual ADLs, as shown in Table 2. Corneal epithelial AEs will be followed until symptom resolution or return to baseline.

Table 2. Corneal Epithelial Adverse Event (CEAE) Grading Scale

Grading of Corneal Epithelial Adverse Events
0 – Asymptomatic
1 – Symptomatic, but no effect on visual ADLs
2 – Instrumental ADLs* affected, but can perform instrumental ADLs independently
3 – Instrumental ADLs* require assistance
4 – Self-care ADLs** require assistance
5 – Corneal perforation or corneal ulceration with impending perforation

Abbreviation: ADL = activities of daily living

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

For eye disorders that are unrelated to corneal epithelial abnormalities (related to lens, retina, etc.), adverse events will be reported per usual practice and graded according to CTCAE criteria as described below.

Additional AEs of special interest that will be monitored during the study:

- Allergic reactions (see Section 6.3)
- Dermatologic toxicities (see Section 6.3)

Adverse Event Severity and Relationship to Study Drug

With the exception of corneal epithelial adverse events (described previously) the table of clinical toxicity grades modified from the NCI CTCAE Version 4.0 (available on the Cancer Therapy Evaluation Program [CTEP] home page http://ctep.cancer.gov) will be used in the grading of AEs and laboratory abnormalities that are reported as AEs, each of which will be followed to satisfactory clinical resolution.

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

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.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. The administration of depatuxizumab mafodotin must be

discontinued immediately in the event that a positive result is obtained on a pregnancy test for a subject, or a subject reports becoming pregnant during the study. If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected. In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. A separate consent will be provided by AbbVie for this purpose. Pregnancies in study subject's partners will be collected from the date of the first dose through at least 6 months following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.2 SUSAR Reporting

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

6.3 Toxicity Management

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

For the purpose of medical management, all AEs 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 5.0 (available on the CTEP home page http://ctep.cancer.gov) is to be used in the grading of all non-corneal adverse events and laboratory abnormalities that are reported as adverse events (corneal epithelial adverse events are to be assessed as detailed in Section 4.3 of the Operations Manual), 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.

Depatuxizumab Mafodotin Toxicity Management

Subjects will be closely monitored for treatment-related adverse events, especially allergic reactions, during all infusions. For the initial depatuxizumab mafodotin 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 depatuxizumab mafodotin 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 depatuxizumab mafodotin, experience with EGFR inhibitors or antibodies, and/or experience with MMAF ADCs, potential toxicities may include corneal epitheliopathy, fatigue, liver transaminase elevations, thrombocytopenia, allergic reactions, and rash.

Corneal Epithelial Adverse Events

For more information related to corneal epithelial adverse events, refer to the Operations Manual, Section 3.15, Section 4.3, and Appendix H.

All supportive care measures should be recorded in appropriate eCRFs.

The following supportive care measures may be used at any time without restriction, regardless of CEAE grade, current prophylactic arm, or use of BCL intervention:

- Non-steroid lubricant eye drops
- Sunglasses (for photophobia)
- Antibiotic eye drops

BCL Intervention After Inadequate Prophylaxis

The schematic in Figure 2 outlines the criteria and sequence of OSE management changes for subjects who have inadequate control of OSE with the assigned prophylactic regimen (CEAE Grade 3 or 4 or ≥ +0.3 LogMAR change in visual acuity). Topical antibiotics may be added to reduce the risk of infection associated with combined BCL and steroid.

Investigator Discretion after Inadequate Response to BCL Intervention

- Subjects who continue to experience CEAE Grade 3 or 4 OSEs for at least 2 weeks after addition of BCL intervention to the initial prophylactic regimen will be considered to have an inadequate response to BCL intervention and thus will be eligible for unrestricted OSE management according to investigator discretion. In this case, any available prophylactic (including addition of ES and VC regimens if not used initially) or supportive care measures may be used without restriction, as well as depatuxizumab mafodotin dose interruption and/or reduction, at the discretion of the investigator. Initiation of BCL intervention prior to meeting the above criterion requires approval of by the AbbVie Therapeutic Area Medical Director. Subjects who complete 8 weeks of adjuvant therapy (8 weeks after the first dose of depatuxizumab mafodotin in the adjuvant phase) will be allowed to enter in the Investigator Discretion phase regardless of CEAE Grade, visual acuity or BCL intervention. Depatuxizumab mafodotin dose modifications for OSEs – suggested increments for dose reduction are described in Table 5; larger decreases may be made at the discretion of the investigator.
    - CEAE Grade 3 – Dose interruptions/dose reduction optional

- CEAE Grade 4 – Dose interruption required. Resumption at a reduced dose allowed upon OSE resolution to CEAE Grade 2 or lower
- If the depatuxizumab mafodotin dose is decreased during the chemoradiation phase, it is not required to start the adjuvant phase at a reduced dose (i.e., starting adjuvant phase at the target 1.25 mg/kg is allowed)

- Once inadequate response to BCL intervention has been determined, additional supportive care measures may be used without restriction at the discretion of the investigator in consultation with the ophthalmologist. These may include exploratory measures suggested by the ophthalmologist that are not described in the study protocol.
- Treatment Options during Investigator Discretion Phase:

  Enhanced Steroids (if not already part of initial regimen)

  Vasoconstrictor Eye Drops and Cold Compress (if not already part of initial regimen)

  Autologous Serum Eye Drops

  Dilute with artificial tears

  Scleral Contact Lens

  Punctal Plugs

  Other interventions per Investigator Discretion

If a subject experiences CEAE corneal ulceration with impending perforation (CU) or corneal perforation (CP) at any time, depatuxizumab mafodotin will be permanently discontinued, and the event will be reported as a serious adverse event, as described in the Operations Manual, Section 4.5.

If, after a dose reduction for CEAEs, changes in the prophylactic and/or supportive care regimens lead to significant improvement CEAEs for subsequent study drug doses, the depatuxizumab mafodotin dose may be re-escalated at the investigator's request if approved by the AbbVie Therapeutic Area Medical Director.

Allergic reactions require the following dose modifications:

- Severe allergic reactions (CTCAE Grade 3 or Grade 4): Immediate discontinuation of depatuxizumab mafodotin 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.
- Moderate allergic reactions (CTCAE Grade 1 or Grade 2): Immediate interruption of depatuxizumab mafodotin 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.

Dermatologic toxicities dose modifications:

- Monitor for the development of inflammatory or infectious sequelae, and initiate appropriate treatment of these symptoms. 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, depatuxizumab mafodotin treatment adjustments should be made based on a discussion between the Investigator and AbbVie Therapeutic Area Medical Director. Subjects who experience a grade 3 or higher dermatological toxicity will be treated as following:
    - The subject will require a dose interruption and depatuxizumab mafodotin may be reintroduced at a reduced dose (per the guidance previously stated above) if the toxicity returns to ≤ grade 1 within 4 weeks.

Hepatic Laboratory Abnormalities (Depatuxizumab Mafodotin)

Guidelines for depatuxizumab mafodotin dose modifications related to hepatic laboratory abnormalities are presented in Table 3.

Table 3. Depatuxizumab Mafodotin Dose Modification Guidelines for Hepatic Laboratory Abnormalities

Hepatic Laboratory Abnormality	Depatuxizumab Mafodotin
ALT or AST > 5 × ULN* but ≤ 20 × ULN (and TBL ≤ 2 × ULN)	• **Hold drug regardless of assessed relationship to drug.** See Section 4.6 of the Operations Manual 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 5)** 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 4.6 of the Operations Manual 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 5x the baseline value or 8x ULN, whichever is lower.

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

Other Depatuxizumab Mafodotin toxicities (excluding corneal epithelial, allergic, and dermatologic toxicities and hepatic laboratory abnormalities)

General guidelines for other toxicities (excluding corneal epithelial, allergic, and dermatologic toxicities) are shown in Table 4, with suggested dose level reductions shown in Table 5. 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 corneal epithelial adverse events and hepatic laboratory abnormalities as previously described, all dose reductions are permanent unless a toxicity initially attributed as potentially related to depatuxizumab mafodotin is later re-attributed as not potentially related and discussed with the AbbVie Therapeutic Area Medical Director or their designee.

Table 4. General Guidelines for Depatuxizumab Mafodotin Dose Interruptions and Re-Initiation (Except Corneal Epithelial, Allergic, and Dermatologic Toxicities and Hepatic Laboratory Abnormalities)

CTCAE Grade	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
CU/CP	Permanently discontinue drug	N/A

CP = corneal perforation; CU = corneal ulceration with impending perforation; N/A = not applicable

Table 5. Depatuxizumab Mafodotin Dose Modification Table during Chemoradiation and Adjuvant Phase

Dose Level	Chemoradiation Phase	Adjuvant Phase
Starting Dose	2.0 mg/kg	1.25 mg/kg[a]
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

a. If dose was reduced to 1.0 mg/kg during the chemoradiation phase, 1.0 mg/kg is the recommended starting dose for the Adjuvant Phase.

Temozolomide Toxicity Management

Safety monitoring for temozolomide-related toxicities, including clinical laboratory testing for temozolomide-related hematological toxicity, temozolomide dose modifications, and management of

toxicities attributable to temozolomide should be managed according to the guidelines in the local prescribing information or local institutional guidelines. See Section 4.6 of the Operations Manual for guidelines on repeat testing and evaluation of hepatic laboratory abnormalities regardless of the assessed relationship to study treatments.

Temozolomide can continue if depatuxizumab mafodotin is interrupted. Depatuxizumab mafodotin may continue if TMZ toxicity is observed.

Radiation Toxicity Management

Toxicities attributable to radiation should be managed according to institutional guidelines or at the discretion of the Investigator.

Management of Toxicities Related to Ophthalmologic Prophylactic Regimens

Monitoring for intraocular pressure (IOP), cataracts, other steroid-related AEs in ophthalmology exams

Toxicities attributable to prophylactic regimens should be managed according to or at the discretion of the Investigator.

Steroid Eye Drops

Monitor IOP during each ophthalmologic examination. Qualified medical personnel will perform the ophthalmologic examination as outlined in Section 2.1 and Section 2.2 of the Operations Manual. If increase in IOP occurs it should be controlled with IOP-lowering medication according to the investigator discretion.

Bacterial keratitis has been reported in patients who have received ophthalmic preparations that were dispensed in multi-dose containers. This reaction most likely is due to contamination of the solution, so patients should be instructed not to allow the tip of the applicator to touch the eye or any other surfaces. Fungal cultures should be taken when appropriate. Prophylaxis and treatment of fungal infections should be implemented according to or at the discretion of the Investigator and consistent with the institutional standard of care.

Vasoconstrictor Eye Drops

IOP will be monitored during each ophthalmologic examination, as outlined in Section 2.1 and Section 2.2 of the Operations Manual. Other side effects should be managed according to or at the discretion of the Investigator and consistent with the institutional standard of care.

Study Drug Administration in Cases of Surgery

If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. Elective surgery should be scheduled at least 2 weeks after the most recent depatuxizumab mafodotin dose. After surgery, allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

6.4 Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

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 (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 1 business day of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

For the primary endpoint, the focus will be the point estimate, and determination of sample size is based on practical consideration rather than power calculation. It is planned to randomize a total of 90 subjects, 30 subjects per arm.

For the point estimate, with 30 subjects per arm, the precision of the estimates of the primary endpoint is provided by the following 95% confidence intervals (Table 6):

Table 6. Primary Endpoint Precision of Estimates

Sample Size	Number of Subjects Meeting the Primary Endpoint	Point Estimate (%)	95% Confidence Interval
30	8	26.7	(10.8, 42.5)
30	10	33.3	(16.5, 50.2)
30	12	40	(22.5, 57.5)
30	14	46.7	(28.8, 64.5)

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the interim database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The intent-to-treat (ITT) population will comprise all randomized subjects regardless of whether they receive study treatment (depatuxizumab mafodotin) or steroid-related OSE treatment. Since the

primary endpoint is a safety endpoint, the ITT will be used only for summary of enrollment and randomization.

The safety population will comprise all randomized subjects who have received at least 1 dose of depatuxizumab mafodotin. Subjects will be classified according to steroid-related treatment received. The safety population will be the primary analysis population for analysis of all endpoints including efficacy and safety endpoints.

7.3 Statistical Analyses for Efficacy

The efficacy endpoints for the study are OS and progression-free survival (PFS) and they are exploratory endpoints for the study. The OS is 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. The PFS is defined as time from randomization to progression of disease (per RANO criteria, as determined by the investigator) or death, whichever occurs first.

The survival distribution of OS and PFS will be estimated by the Kaplan-Meier method. The comparisons between the 3 groups will be made by log-rank test.

7.4 Statistical Analyses for Safety

For the primary endpoint of the study, the percentage of subjects with either a ≥ 3-line decline from baseline (≥ + 0.3 on LogMAR scale) in visual acuity (with baseline correction) or ≥ Grade 3 OSE severity on the Corneal Epithelial Adverse Event [CEAE] scale will be calculated for each arm and associated 95% confidence intervals will be provided. Comparisons between arms will be made using Chi-square test.

For secondary safety endpoints, continuous variables will be summarized with N, mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be computed for the category variables. For time to event variables, Kaplan-Meier survival curves with median time and associated 95% confidence interval will be provided.

Detailed statistical analysis methods for primary and secondary safety endpoints will be provided in the statistical analysis plan (SAP).

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

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

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

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

12 REFERENCES

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADC	Antibody-Drug Conjugate
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BCL	Bandage Contact Lens
CEAE	Corneal Epithelial Adverse Event
CP	Corneal Perforation
CU	Corneal Ulceration with impending perforation
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
EGFR	Epidermal Growth Factor Receptor
ES	Enhanced Steroids
GBM	Glioblastoma
GCP	Good Clinical Practice
Gy	Gray
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IgG	Immunoglobulin
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LASIK	Laser-Assisted in Situ Keratomileusis
MMAF	Mono Methyl Auristatin F
MRI	Magnetic Resonance Imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	Overall Survival
OSE	Ocular Side Effect

PD	Progressive Disease
PFS	Progression Free Survival
PT	Prothrombin time
RANO	Response Assessment in Neuro-Oncology Working Group
RT	Radiation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SS	Standard Steroid
TA MD	Therapeutic Area Medical Director
TMZ	Temozolomide
ULN	Upper Limit of Normal
vADL	Visual Activities of Daily Living
VC	Vasoconstrictor/cold compress
vQOL	Visual Quality of Life
WHO	World Health Organization

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-534: Phase 3b Study for Management of Ocular Side Effects in Subjects with EGFR-amplified Glioblastoma Receiving Depatuxizumab Mafodotin (ABT-414)

Protocol Date: 28 May 2019

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
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., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
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 protocol and all of its 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. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date
Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]		Clinical Program Development Medical Writing Global Medical Affairs Oncology Clinical Development Data and Statistical Sciences

APPENDIX D. ACTIVITY SCHEDULE

The individual activities are described in detail in the Operations Manual.

Study Activities Table

	Screening	Chemoradiation Phase					Adjuvant Phase						Follow-Up		
		Randomization	Week 1 Day 1	Week 3 Day 1 and Week 5 Day 1	Week 7 Day 1	Week 9 Day 1	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15	Day 1 and Day 15 of Cycle 3 to Cycle 12	Final Study Drug Visit	Post-Treatment 35 Day and 49 Day Follow Up Visit	Long-Term Follow-Up Until Symptom Resolution	Survival Follow-Up
INTERVIEWS & QUESTIONNAIRES															
Subject Information and Informed Consent	✓														
Eligibility criteria	✓		✓												
Medical history	✓		✓												
Corneal Epithelial Adverse Event Assessment (CEAE)			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Every 4 weeks	
Adverse event assessment			✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		
Prior/concomitant therapy			✓	✓			✓	✓	✓	✓	✓	✓	✓		
Visual Quality of Life Questionnaire (vQoL) and PRO-CTCAE™ Visual Symptoms Questionnaire			✓	✓	✓		✓				Day 1 of every other cycle	✓	✓	Every 4 weeks	
Perception of Treatment Value question												✓		✓ Every 4 weeks	
Karnofsky Performance Status	✓											✓	✓		

	Screening	Chemoradiation Phase					Adjuvant Phase						Follow-Up		
		Randomization	Week 1 Day 1	Week 3 Day 1 and Week 5 Day 1	Week 7 Day 1	Week 9 Day 1	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15	Day 1 and Day 15 of Cycle 3 to Cycle 12	Final Study Drug Visit	Post-Treatment 35 Day and 49 Day Follow Up Visit	Long-Term Follow-Up Until Symptom Resolution	Survival Follow-Up
LABS & EXAMS															
Central Laboratory Tests	✓		✓	✓	✓		✓		✓		Every Day 1	✓	✓ 35 Day visit only		
Height	✓														
Weight	✓		✓	✓			✓	✓	✓	✓	✓	✓	✓		
Vital signs	✓		✓	✓			✓	✓	✓	✓	✓	✓	✓		
Physical exam (repeated at any visit if clinically indicated)	✓														
ECG	✓														
Pregnancy test	✓ (Serum)		✓ (Urine)								✓ Monthly (Urine)		✓ (Urine)		
Tissue sample for EGFR amplification testing (required)	✓														
Archival Tumor Sample (optional)	✓												✓		
Ophthalmology Exams	✓		Repeat Ophthalmology exam on Week 1 Day 1 if > 2 weeks from screening	✓	✓		✓	✓	✓	✓	Every 4 weeks	✓	✓	Every 8 weeks	
Survival Assessment															✓

	Screening	Chemoradiation Phase					Adjuvant Phase						Follow-Up		
		Randomization	Week 1 Day 1	Week 3 Day 1 and Week 5 Day 1	Week 7 Day 1	Week 9 Day 1	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15	Day 1 and Day 15 of Cycle 3 to Cycle 12	Final Study Drug Visit	Post-Treatment 35 Day and 49 Day Follow Up Visit	Long-Term Follow-Up Until Symptom Resolution	Survival Follow-Up
℞ TREATMENT															
Radiation			✓	✓											
Temozolomide			✓	✓			✓		✓		Day 1 of Cycles 6 – 12				
Prophylactic Treatments for OSE		✓	✓				✓	✓	✓	✓	✓				
Depatuxizumab mafodotin			✓	✓			✓	✓	✓	✓	✓				

APPENDIX E. SUBJECTS CONTINUING PARTICIPATION

This appendix outlines the modifications to the study procedures and depatuxizumab mafodotin dosing in subjects who are currently receiving depatuxizumab mafodotin and who choose to continue depatuxizumab mafodotin treatment after the results from the pre-planned interim efficacy analysis for Study M13-813 (INTELLANCE-1).

As a result of the interim efficacy analysis for INTELLANCE-1 study, AbbVie determined it was appropriate to allow subjects who are receiving depatuxizumab mafodotin to continue doing so based on investigator and subject decision.

Subjects who decide to continue treatment with depatuxizumab mafodotin 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 the table below.

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 1 of Cycle 2	Day 15 of Every Cycle[b]	Day 22 of Every Cycle[c]			
Symptom-directed Physical Exam	X[f]			X[f]				
Ophthalmology Exams		X[g]					X[g]	X[g]
Chemistry	X					X	X	
Hematology	X				X	X	X	
Adverse Event Assessment and Concomitant Medications	X			X		X	X	X[k]
Temozolomide Administration	X[h]							
Depatuxizumab Mafodotin Administration	X[i]			X[i]				
Treatments for OSE	X[j]			X[j]				

F/U = Follow-up; OSE = ocular side effect

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 depatuxizumab mafodotin 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 depatuxizumab mafodotin 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 depatuxizumab mafodotin.

e. To be performed 35 days (± 3 days) after the last dose of depatuxizumab mafodotin. 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 AE/SAE reporting.

g. Ophthalmology exams will be performed only as needed for safety management and AE/SAE reporting. The last ophthalmology exam following discontinuation of depatuxizumab mafodotin 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. Depatuxizumab mafodotin infusion will be administered on Day 1 and Day 15 of each 28-day cycle for 12 cycles.

j. Patient will receive management of ocular side effects as per investigator discretion. In this case, depatuxizumab mafodotin 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. Refer to Section 5.7 of the protocol.

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.

Depatuxizumab Mafodotin Administration and Individual Subject Discontinuation

Depatuxizumab mafodotin will be administered as described in the protocol.

Subjects may continue receiving depatuxizumab mafodotin while drug supply is available, as long as disease progression has not been determined.

Depatuxizumab Mafodotin Toxicity Management and Individual Subject Dose Modifications

Section 6.3 of the protocol provides guidance for toxicity management and dose modifications.

Adverse Events and Concomitant Medications

Adverse event and concomitant medications data will be collected to support regulatory safety reporting requirements.

APPENDIX F. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	18 December 2017
Version 2.0	02 July 2018
Version 2.1 (Country Specific – Germany)	07 November 2018
Version 3.0	14 December 2018

Rationale for protocol amendment: For another depatuxizumab mafodotin study in newly diagnosed GBM patients, (Study M13-813 [INTELLANCE-1]), an independent review committee recently performed a review of early data. This committee recommended that the Study M13-813 study be stopped because the results indicated no survival benefit was observed for depatuxizumab mafodotin compared with placebo when added to the standard first-line regimen of temozolomide and radiation. However, given that no new clinically significant safety risks were identified, AbbVie believes it is appropriate to allow subjects who are currently receiving depatuxizumab mafodotin to continue depatuxizumab mafodotin treatment if the investigator and subject believe it is in the subject's best interest.

The purpose of this amendment (version 4.0) is to:

- Add brief summary of results for the protocol-specified interim efficacy analysis for INTELLANCE-1 in the Introduction
- Provide modified study procedures and instructions for depatuxizumab mafodotin dosing in Appendix E for those subjects who are currently receiving depatuxizumab mafodotin and who choose to continue depatuxizumab mafodotin. 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.

APPENDIX G. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M16-534

Glioblastoma: Management of Depatuxizumab Mafodotin (ABT-414) Ocular Side Effects

SPONSOR:	AbbVie Inc.	ABBVIE INVESTIGATIONAL PRODUCT:	Depatuxizumab Mafodotin (ABT-414)

FULL TITLE: Phase 3b Study for Management of Ocular Side Effects in Subjects with EGFR-Amplified Glioblastoma Receiving Depatuxizumab Mafodotin (ABT-414)

1 CONTACTS

Sponsor/ Emergency Contact	[redacted] 1 North Waukegan Road North Chicago, IL 60064 Email: [redacted] **EMERGENCY 24 hour Number:** [redacted]	Office: Mobile: [redacted] If not available: Phone: [redacted]
Safety Concerns	Oncology Safety Team [redacted] 1 North Waukegan Road North Chicago, IL 60064	Phone: [redacted] Email: [redacted]
SAE Reporting outside of RAVE	Email: [redacted]	Fax: [redacted]
Protocol Deviations	[redacted] 1 North Waukegan Road North Chicago, IL 60064 OR	Phone: Email: [redacted] OR
	[redacted] 1 Waukegan Road North Chicago, IL 60061 OR	Phone: Email: [redacted]
	[redacted] 1 Waukegan Road North Chicago, IL 60061	Phone: Email: [redacted]
Certified Clinical Lab	Covance Central Laboratory Services Indianapolis (North America/Latin America): 8211 SciCor Drive Indianapolis, IN 46214-2985 USA	Phone: +1 (317) 271 1200 (local calls) Fax: +1 (317) 273 4030
	Covance Central Laboratory Services Geneva (EMEA) Rue Moïse-Marcinhes 7 CH - 1217 Meyrin/Genève Switzerland	Phone: +41 58 822 7901 Fax: +41 58 822 7521

Covance Central Laboratory Services
Singapore (APAC)
1, International Business Park
#04-14 The Synergy
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2 INVESTIGATION PLAN

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Patient Reported Outcome [PRO], Exam, etc.). Further information about each activity is provided in Section 3. Information on adverse events (AEs) is presented in Section 4 and treatments in Section 5.

Screening:

INTERVIEW	• Informed consent • Medical and oncology history	• Karnofsky Performance Status • Eligibility criteria
EXAM	• Ophthalmology Exam • Complete physical examination including height and weight	• Vital signs • ECG
CENTRAL LAB	• Serum pregnancy test • Urinalysis • Coagulation • HIV, HBV and HCV tests	• Chemistry • Hematology • Tumor sample for EGFR amplification testing (required) • Archival Tumor Samples (optional)

Abbreviations: ECG = electrocardiogram; EGFR = epidermal growth factor receptor; HIV = human immunodeficiency virus; HBV = hepatitis B virus; HCV = hepatitis C virus

Randomization:

TREATMENT	• Prophylactic regimen* (Arm A = SS treatment, Arm B = SS/VC, or Arm C = ES/VC)

Abbreviations: ES = enhanced steroids; SS = standard steroids; VC = vasoconstrictors and cold compress

* Prophylactic regimen details are outlined in Section 5.1.

Note: Randomization Visit for Prophylactic Treatment performed in the Interactive Response Technology (IRT) System

Chemoradiation Phase: Week 1 Day 1:

INTERVIEW	• Medical history • Prior/concomitant therapy • Adverse event assessment	• Corneal Epithelial Adverse Event Assessment • Eligibility criteria
PRO	• Visual Quality of Life (vQOL) • Visual Symptoms Questionnaire	
EXAM	• Weight • Ophthalmology exam (if greater than two weeks from screening exam)	• Vital signs • Physical exam if clinically indicated • Urine pregnancy test (if Week 1 Day 1 is greater than 7 days from screening)
CENTRAL LAB	• Chemistry • Urinalysis	• Hematology
TREATMENT	• Radiation and TMZ • Depatuxizumab mafodotin	• Prophylactic regimen* (Arm A = SS treatment, Arm B = SS/VC, or Arm C = ES/VC)

Abbreviations: ES = enhanced steroids; SS = standard steroids; TMZ = temozolomide; VC = vasoconstrictors and cold compress

* Prophylactic regimen details are outlined in Section 5.1.

Chemoradiation Phase: Week 3 Day 1 and Week 5 Day 1

INTERVIEW	• Adverse event assessment • Prior/concomitant therapy	• Corneal Epithelial Adverse Event assessment
PRO	• Visual Quality of Life (vQOL) • Visual Symptoms Questionnaire	
EXAM	• Ophthalmology exam • Weight	• Vital signs • Physical exam if clinically indicated
CENTRAL LAB	• Chemistry	• Hematology
TREATMENT	• Prophylactic regimen* (Arm A = SS treatment, Arm B = SS/VC, or Arm C = ES/VC)	• Radiation and TMZ • Depatuxizumab mafodotin

Abbreviations: ES = enhanced steroids; SS = standard steroids; TMZ = temozolomide; VC = vasoconstrictors and cold compress

* Prophylactic treatment details are outlined in Section 5.1.

Chemoradiation Phase: Week 7 Day 1

INTERVIEW	• Adverse event assessment	• Corneal Epithelial Adverse Event assessment
PRO	• Visual Quality of Life (vQOL) • Visual Symptoms Questionnaire	
EXAM	• Ophthalmology exam	
CENTRAL LAB	• Chemistry	• Hematology

Chemoradiation Phase: Week 9 Day 1

INTERVIEW	• Corneal Epithelial adverse event assessment (by phone)

Adjuvant Phase: Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1 and Cycle 2 Day 15:

INTERVIEW	• Adverse event assessment	• Prior/concomitant therapy • Corneal Epithelial Adverse Event assessment
PRO	• Visual Quality of Life (vQOL) (Cycle 1 Day 1 only)	• Visual Symptoms Questionnaire (Cycle 1 Day 1 only)
EXAM	• Ophthalmology exam • Weight • Vital signs	• Physical exam if clinically indicated • Urine pregnancy test (monthly or per local requirements/guidelines)
CENTRAL LAB	• Chemistry (only Day 1)	• Hematology (only Day 1)
TREATMENT	• Prophylactic treatments* (Arm A = SS treatment, Arm B = SS/VC, or Arm C = ES/VC)	• Depatuxizumab mafodotin • TMZ (Only administered on Days 1 - 5 of every 28 day cycle)

Abbreviations: ES = enhanced steroids; SS = standard steroids; TMZ = temozolomide; VC = vasoconstrictors and cold compress

* Prophylactic treatment details are outlined in Section 5.1.

Adjuvant Phase: Day 1 and Day 15 of Cycle 3 to Cycle 12:

INTERVIEW	• Adverse event assessment	• Prior/concomitant therapy • Corneal Epithelial Adverse Event assessment
PRO	• Visual Quality of Life (vQOL) (Day 1 every other visit, beginning Cycle 3)	• Visual Symptoms Questionnaire (Day 1 every other visit, beginning Cycle 3)
EXAM	• Ophthalmology exam (every 4 weeks from Cycle 3 Day 1) • Weight • Vital signs	• Physical exam if clinically indicated • Urine pregnancy test (monthly or per local requirements/guidelines)
CENTRAL LAB	• Chemistry (only Day 1)	• Hematology (only Day 1)

In the case where a local laboratory value is used to make a treatment decision, this result will also be collected and used as part of data analysis.

TREATMENT	• Prophylactic treatments* (Arm A = SS treatment, Arm B = SS/VC, or Arm C = ES/VC)	• Depatuxizumab mafodotin • TMZ (6 – 12 cycles total, depending on local standard of care)

Abbreviations: ES = enhanced steroids; SS = standard steroids; TMZ = temozolomide; VC = vasoconstrictors and cold compress

* Prophylactic treatment details are outlined in Section 5.1.

FINAL STUDY DRUG VISIT:

INTERVIEW	• Adverse event assessment • Prior/concomitant therapy	• Corneal Epithelial Adverse Event assessment • Karnofsky Performance Status
PRO	• Visual Quality of Life (vQOL) • Perception of Treatment Value question	• Visual Symptoms Questionnaire
EXAM	• Ophthalmology exam • Weight	• Vital signs • Physical exam if clinically indicated
CENTRAL LAB	• Chemistry	• Hematology

2.2 Individual Post-Treatment Period Visit Activites

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Post-Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is presented in Section 3.

POST-TREATMENT 35 DAY FOLLOW UP:

INTERVIEW	• Adverse event assessment • Prior/concomitant therapy	• Corneal Epithelial Adverse Event assessment • Karnofsky Performance Status
PRO	• Visual Quality of Life (vQOL)	• Visual Symptoms Questionnaire
EXAM	• Ophthalmology exam • Weight	• Vital signs • Physical exam if clinically indicated • Urine pregnancy test
CENTRAL LAB	• Chemistry	• Hematology • Archival tumor samples (optional)

POST-TREATMENT 49 DAY FOLLOW UP:

INTERVIEW	• Adverse event assessment • Prior/concomitant therapy	• Corneal Epithelial Adverse Event assessment • Karnofsky Performance Status
PRO	• Visual Quality of Life (vQOL)	• Visual Symptoms Questionnaire
EXAM	• Ophthalmology exam • Weight	• Vital signs • Physical exam if clinically indicated • Urine pregnancy test
CENTRAL LAB	• Archival Tumor Samples (optional)	

NOTES: Forty-nine (49)-day safety follow-up procedures will be performed on subjects who discontinue from the study unless the Final Visit is more than 49 days after the last dose of depatuxizumab mafodotin.

LONG TERM FOLLOW UP (UNTIL SYMPTOM RESOLUTION)	
INTERVIEW	• Corneal Epithelial Adverse Event Assessment (every 4 weeks until resolution of corneal epithelial adverse events)
PRO	• Visual Quality of Life (vQOL) and Visual Symptoms Questionnaire (every 4 weeks until resolution of corneal epithelial adverse events) • Perception of Treatment Value question (every 4 weeks until resolution of corneal epithelial adverse events)
EXAM	• Ophthalmology exam (every 8 weeks until resolution of corneal epithelial adverse events)

SURVIVAL FOLLOW UP:	
INTERVIEW	• Survival assessment (progression-free survival, overall survival)

NOTES: Survival information will be collected for all subjects in the study.
In case of death, optional post-mortem tumor tissue samples and corneal biopsy samples should be collected.

3 STUDY PROCEDURES

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 do not receive at least one depatuxizumab mafodotin infusion will not be included in the safety analyses.

3.1 Subject Information and Informed 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. 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.

With the exception of mandatory tumor samples that will be collected at screening for EGFR amplification testing, pre/post-treatment tissue collection and analysis will only be performed if the subject has voluntarily signed and dated a separate pre/post-treatment tissue informed consent (or indicated consent within the main study informed consent form), approved by an Institutional Review Board (IRB)/Independent ethics committee (IEC), after the nature of the testing has been explained and

the subject has had an opportunity to ask questions. The pre/post-treatment tissue informed consent must be signed before the tissue collection and analysis is performed. If a subject does not consent to the pre/post-treatment tissue collection and analysis, it will not impact the subject's participation in the study.

Additionally, this study has optional post mortem tissue submission consent for subject's cornea after death. This post mortem tissue collection and analysis will only be performed if the subject has voluntarily signed and dated a separate post-mortem tissue informed consent, approved by an Institutional Review Board (IRB)/Independent ethics committee (IEC), after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The post-mortem tissue informed consent must be signed before the tissue collection and analysis is performed. If a subject does not consent to the post-mortem tissue collection and analysis, 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.

3.2 Medical/Oncology 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 electronic case report form (eCRF).

3.3 Karnofsky Performance Status

Karnofsky Performance Status will be assessed at Screening, Final Visit, and Post-Treatment 35 Day and 49 Day Follow-Up Visit (Appendix B).

3.4 Eligibility Criteria

Eligibility Criteria will be assessed at Screening, see Protocol Section 5.1.

3.5 Ophthalmology Exam

Qualified medical personnel will perform the ophthalmologic examination as outlined in Section 2.1, Section 2.2, and Appendix C. Additional exams may be performed as clinically indicated. Ophthalmology exams are to be performed 7 to 14 days after the 2nd and 3rd infusions of Depatux-M and must be completed prior to the next infusion of Depatux-M. Exams will at a minimum include assessment of visual acuity (as described below, using LogMAR scale and Appendix D), intraocular pressure, and slit lamp examination, as well as assessment for symptoms of eye pain and photophobia, and results will be recorded in the corresponding CRF (Appendix C).

Visual Acuity (VA) and Best corrected visual acuity (BCVA)

Instructions for obtaining visual acuity assessments at each ophthalmology visit (including the visual correction to be used for VA assessments, when BCL should be in place during VA assessment, and when manifest refraction is to be performed to assess BCVA) are described below. Visual acuity will be measured using the LogMAR scale in all cases. Visual acuity will be captured with baseline glasses (VAcc) or without glasses (VAsc) if the subject does not require correction at baseline during all ophthalmology visits. Best Corrected Visual Acuity (BCVA) will be assessed with manifest refraction during specified visits outlined in the protocol.

Baseline Ophthalmic Examination

- VA with baseline correction (cc or sc) *without BCL* – OD, OS, OU
  - Record glasses prescription if applicable
  - Record without glasses if subject does not require correction at baseline
  - *The same prescription will be used to measure VA (cc or sc) for all post-baseline visits*
- BCVA (with manifest refraction) – OD, OS, OU will be recorded

Post-baseline visits (prior to BCL intervention)

- VA with baseline correction (cc or sc) *without BCL* – OD, OS, OU
- *If VA OU (cc or sc) has declined ≥ 0.3 LogMAR from baseline OR if CEAE Grade≥ 3, place BCL and obtain the following:*
  - VA with baseline correction (cc or sc) *with BCL* – OD, OS, OU
  - BCVA (manifest refraction) with *BCL* – OD, OS, OU

Post-baseline visits (if BCLs are being used)

- VA with baseline correction (cc or sc) *without BCL* – OD, OS, OU – omit if BCL is not changed at the visit
- VA with baseline correction (cc or sc) *with BCL* – OD, OS, OU
- *If VA OU (cc or sc) with BCL decline ≥ 0.3 LogMAR from baseline remains, obtain the following:*
  - BCVA (manifest refraction) *over BCL* – OD, OS, OU – repeat every ~8 weeks

Post-baseline visits (if BCL intervention not tolerated)

- VA with baseline correction (cc or sc) *without BCL* – OD, OS, OU
- *If VA OU (cc or sc) without BCL decline ≥ 0.3 LogMAR from baseline remains, obtain the following:*
  - BCVA (manifest refraction) without BCL – OD, OS, OU – repeat every ~8 weeks

Ophthalmoscopic examination and dilation of the pupil are not required. Results will be entered into electronic data capture (EDC) for data collection. All adverse events involving ocular side effects (OSEs) must be followed until symptom resolution.

All ophthalmology exam reports will be reviewed by the Investigator (or medically qualified delegate) to assess for potential adverse events not identified by subject interview.

Advanced imaging techniques, where available, such as confocal microscopy, ocular coherence tomography (OCT), and Heidelberg Retina Tomographer (HRT3), are optional and may be performed on an exploratory basis to assess whether such techniques may aid in evaluation or management of OSEs.

3.6 Physical Examination

Physical examination will be performed at the designated study visits as specified in Section 2.1 and Section 2.2. A complete physical examination (PE) will be performed at Screening. A symptom directed physical examination will be performed at all other designated visits as clinically indicated.

All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page. Clinically significant changes from baseline will be documented in the source documentation and electronic case report forms (eCRFs) as adverse events.

3.7 Height & Weight

Height will be measured at screening only. Body weight will be measured at scheduled visits as specified in Section 2.1 and Section 2.2. The subject will wear lightweight clothing and no shoes during weighing.

3.8 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, and body temperature will be obtained at visits as specified in Section 2.1 and Section 2.2. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes.

3.9 12-Lead Electrocardiogram

A 12-lead ECG will be performed at Screening as specified in Section 2.1. The ECG should be performed prior to blood collection.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source folder. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

3.10 Clinical Laboratory Tests

All subjects will have the laboratory analyses performed as outlined in the Clinical Laboratory Tests Manual. 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 in Section 2.

Screening laboratory tests will be performed within 21 days 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.

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study.

- For laboratory results that are required per protocol to make study treatment decisions (e.g., to determine eligibility to continue TMZ or depatuxizumab mafodotin), results from a certified local lab may be used if central results may not be available prior to dosing.

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- 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 (depatuxizumab mafodotin, TMZ or radiation [RT]) or from the study, or requires a subject to receive treatment (medical intervention) will be recorded as an adverse event.

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Clinical Chemistry</th><th>Urinalysis</th></tr>
<tr><td>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)</td><td rowspan="3">Blood urea nitrogen (BUN)
Creatinine
Total bilirubin
Direct bilirubin
Albumin
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Alkaline phosphatase (ALP)
Gamma-glutamyl transferase (GGT)
Sodium
Potassium
Calcium
Inorganic phosphorus
Lactate dehydrogenase (LDH)
Magnesium
Chloride
Bicarbonate</td><td rowspan="3">Specific gravity
Ketones
pH
Protein
Blood
Glucose
Microscopic examination if dipstick results are positive</td></tr>
<tr><td>Coagulation</td></tr>
<tr><td>Prothrombin time (PT)
Activated Partial Thromboplastin Time (aPTT)
International normalized ratio (INR)</td></tr>
</table>

Serum Pregnancy Test

For female subjects of childbearing potential, a serum pregnancy test will be completed at Screening (≤ 21 days before Day 1 of chemoradiation). If Week 1 Day 1 is greater than 7 days from the screening visit, the procedure will be repeated.

The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated to determine eligibility.

A lactating or pregnant female will not be eligible for participation in this study.

Pregnancy testing is not required for females of nonchildbearing potential. Determination of postmenopausal status will be made during the screening period based on the subject's history.

Local Clinical Laboratory Testing

Laboratory tests used to make dosing decisions for standard temozolomide therapy will be performed as usual per local standard of care by a certified local laboratory. A certified local laboratory may perform laboratory testing as needed for immediate subject management.

Local laboratory results that are considered clinically significant by the Investigator will be followed as appropriate and reported as adverse events if they meet the criteria as specified in Section 4.2.

Local laboratory results will be entered into the EDC system only if the local result leads to a different eligibility, treatment, or safety-reporting decision than would have been supported based on central laboratory results.

Hepatitis Screen

HBV and HCV tests will be performed at screening. The hepatitis test panel will be performed by a certified laboratory.

HIV Screen

Subjects will have blood tested by a certified laboratory for the presence of HIV at screening. The results of the HIV testing will be retained by the study site under confidential restriction.

3.11 Tumor Samples

Tumor samples will be tested during the screening for EGFR amplification at a centralized testing laboratory. The study specific laboratory manual will provide instructions regarding the collection, processing, and shipping of samples. The tumor sample must test positive for EGFR amplification in order for the subject to be eligible for enrollment.

If available, optional tumor tissue samples from the subjects' initial surgery and at recurrence will be collected when available. Additional, optional post-mortem tissue samples from the cornea will be collected. Participation in post-mortem corneal tissue collection is not mandatory. If collected, post-mortem corneal tissue samples should be sent to:

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

3.12 Prior/Concomitant Therapy

Prior/concomitant therapy will be assessed at visits as specified in Section 2.1 and Section 2.2.

3.13 Patient-Reported Outcomes

Subjects will complete the self-administered patient-reported outcome (PRO) instrument Visual Quality of Life Questionnaire (vQOL; when allowed per local regulatory guidelines; Appendix E) and the PRO-CTCAE™ Visual Symptoms Questionnaire (when allowed per local regulatory guidelines; Appendix F). Subjects will also complete the Perception of Treatment Value question (see Appendix G) at the final study visit and every 4 weeks during the follow-up phase until resolution of corneal epithelial adverse events. Subjects should be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaire to them. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items.

The subject should complete the questionnaire before site personnel perform any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the subject's response.

The assessments will be translated into the local languages.

3.14 Dispense Study Drug

Study drug will be dispensed to subjects beginning at Week 1 Day 1 and as specified in Section 2.1. The first dose of study drug will be administered after all other Week 1 Day 1 procedures are completed.

3.15 Corneal Epithelial Adverse Event Assessment

Corneal epithelial adverse events (CEAEs) will be monitored on a regular basis from initiation of study treatment until symptom resolution after depatuxizumab mafodotin discontinuation, as specified in Section 2.1 and Section 2.2, using the CEAE rating scale and recorded using the CEAE electronic case report form (eCRF; Appendix H). The CEAE rating scale is designed to describe the overall severity symptoms associated with ADC-related corneal epitheliopathy under a single CEAE grade, while capturing additional information about specific domains (ocular discomfort, photophobia, and blurred vision/visual acuity) that are commonly affected.

It is designed for routine use by the treating physician based on subject reporting without a requirement for formal eye examination, with the exception that a finding of corneal ulceration with impending perforation (CU) or corneal perforation (CP) would be diagnosed on examination by an eye care specialist. To maximize collection of CEAE assessments according to the study schedule, particularly to assess reversibility of OSEs after drug discontinuation, the CEAE assessment may be conducted by telephone and may incorporate information from caregivers.

For the current study symptoms related to the corneal epithelium will be recorded in this eCRF and should NOT be recorded as adverse events in the standard adverse event log.

CEAE Grade (Overall Severity of symptoms/findings related to corneal epithelial abnormalities):

- Only the impact of corneal epithelial abnormalities should be considered in evaluating the CEAE grade.
    - These symptoms generally include blurred vision (decreased visual acuity), photophobia, and ocular discomfort (various terms may be used to describe ocular discomfort).
- If visual ADL impairment is caused primarily by a condition unrelated to the corneal epithelium (e.g., central nervous system [CNS] lesion, retina, lens, optic nerve, etc.), this field should be recorded as "Not evaluable."
- Examples of Instrumental ADLs include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Examples of self-care ADLs include bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Ocular Discomfort

- Symptoms: Specific symptoms contributing to ocular discomfort will be recorded. Check all symptoms that apply; additional symptoms not included on this list should be entered as free text.
- Impact of ocular discomfort on visual ADLs: Only the impact of ocular discomfort on visual ADLs should be considered for this assessment (i.e., degree of ADL impairment in the absence of blurred vision or phobia should be estimated).

Photophobia

- Severity of photophobia will be rated by the intensity of light that produces photophobia.

Reading (due to blurred vision)

- The impact of blurred vision on the subject's ability to read is rated on the degree of adaptation needed for the subject to read.
- If the subject's reading is impaired by factors unrelated to blurred vision, or if the subject does not attempt to read for reasons unrelated to blurred vision, this field should be recorded as "Not applicable (N/A)."

Please refer to Section 4.3 for additional details.

3.16 Other Adverse Event Assessment

Please refer to Section 4.2.

3.17 Disease Progression and Survival Assessments

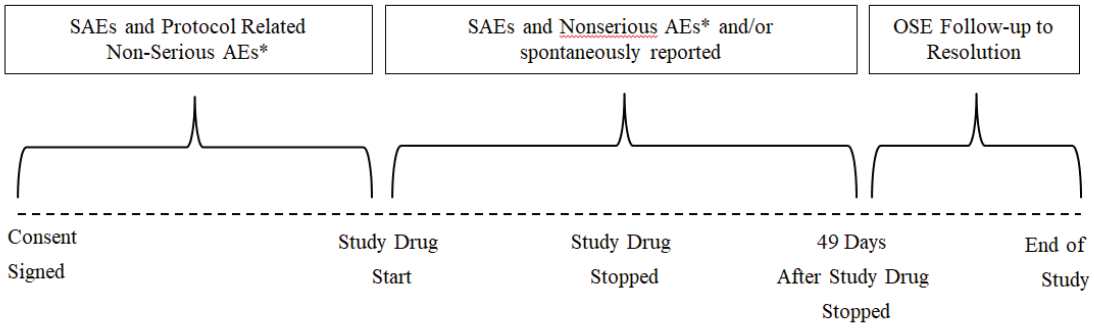
Subjects enrolled in the study will have survival assessments, including date and cause of death collected monthly or as requested by AbbVie to support data analysis for a period of 2 years after the subject's last study visit or until the subject becomes lost to follow-up or until study termination by AbbVie.

Clinical and neuroimaging assessments for GBM disease progression will be performed per local standard of care, and the date of disease progression will be determined according to the 2017 update of Response Assessment in Neuro-Oncology (RANO) criteria (Appendix I).

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All adverse events reported will be collected from the time of study drug administration until 49 days after last depatuxizumab mafodotin administration, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related (considered by the investigator to be causally related to protocol-required study procedures) nonserious adverse events will be collected from the time the subject signs the study-specific informed consent. After 49 days following completion of study treatment and throughout the Post-Treatment Period, only OSEs will be collected until symptom resolution or return to baseline; (SAEs and non-serious AEs will not be collected).



Abbreviations: AE = adverse event; OSE = ocular side effect; SAE = serious adverse event
* Only if considered by the Investigator to be causally related to study required procedures.

4.2 Definition of Adverse Event

An AE 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 AE. Worsening in severity of an AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation

from the study, necessitate therapeutic medical intervention, meet protocol specified criteria (see Section 6.3 in the Protocol regarding toxicity management), and/or if the investigator considers them to be AEs.

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

All AEs will be followed to a satisfactory conclusion.

Disease progression and signs, symptoms or test abnormalities that, in the opinion of the investigator, are unequivocally due to disease progression should not be reported as AEs, even if serious or fatal (see also Section 4.3).

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure was preplanned before 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 AE. Hospitalization of a subject who is in Post Treatment Follow-Up or Survival, following discontinuation of study drug, for subsequent line of therapy will not be captured as an SAE. A treatment-emergent AE is defined as any AE reported by a subject with onset or worsening from the time that the first dose of study drug is administered until 90 days have elapsed following discontinuation of study drug administration.

4.3 Expected Adverse Events

Corneal Epithelial Adverse Events

For adverse events related to corneal epithelial abnormalities, associated signs and symptoms will be recorded and graded by the study investigator using the Corneal Epithelial Adverse Event eCRF, which was created by AbbVie, based on experience with ADC-related corneal epitheliopathy caused by depatuxizumab mafodotin, to address inadequacies of the CTCAE system for appropriately capturing symptoms, grading, and making dose modifications for ADC-related corneal epitheliopathy. Grading of corneal epithelial events is based on effects on visual ADL, as shown in Table 2 of the study protocol, and the eCRF is detailed in Appendix H.

Events recorded in the Corneal Epithelial Adverse Event eCRF events will **not** be recorded in standard adverse event eCRFs, with the exception of a CEAE finding of CU/CP. A CEAE CU/CP would be considered a serious adverse event and would be reported as such as described below.

For eye disorders that are unrelated to corneal epithelial abnormalities (related to lens, retina, etc.), events will be reported as adverse event per usual practice using standard eCRFs and graded according to CTCAE criteria.

Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of GBM should be recorded only on the study completion eCRF with disease progression as the reason for discontinuation and not on the AE eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the AE eCRF and immediately reported to the sponsor.

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 AE eCRF. Generally, only 1 such event should be reported. The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death because of presumed cardiac causes in a subject with or without pre-existing heart disease within 1 hour after 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 AE eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. During survival follow-up, deaths attributed to progression of GBM should be recorded only on the survival eCRF.

Lack of Efficacy or Worsening of Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease, including transformation to a more aggressive histology, are also considered an expected outcome for this study and will NOT be recorded as AEs. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, the event should be reported as an AE.

4.4 Recording Data and Analyses of Safety Findings

The Investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. Corneal epithelial adverse events will be assessed and recorded as described in Section 4.3. Otherwise, the Investigator will assess and record any AE 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 SAEs considered as having "no reasonable possibility" of being associated with study drug, the Investigator will provide another cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. AEs, 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 resolution, or to improvement to Grade 1 unless the subject has died before this could be determined.

With the exception of the corneal epithelial adverse events as described in Section 4.3, the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4 will be used for AE reporting/grading of event severity.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins

or worsens in severity after initiation of study drug through 49 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term. The tabulation of the number of subjects with treatment-emergent adverse events by severity grade and relationship to study drug also will be provided. Subjects reporting more than 1 adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe grade according to the severity grade table and the most related according to the relationship to study drug tables. Subjects reporting more than 1 type of event within an SOC will be counted only once for that SOC.

The number and percentage of subjects with adverse events in the MedDRA Eye Disorders SOC (e.g., infection, increased intraocular pressure, cataract, etc.) will be compared between prophylactic arms across PT and SOC using Fisher's exact test.

4.5 Reporting Adverse Events

In the event of an SAE, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: [redacted]
FAX to: [redacted]

For safety concerns, contact the Oncology Safety Team at:

Oncology Safety Team [redacted]
1 North Waukegan Road North Chicago, Illinois 60064
Email: [redacted]

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

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted]
AbbVie Inc.
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Office: [redacted]
Mobile:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director 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 AbbVie Therapeutic Area Medical Director:

HOTLINE: [redacted]

The sponsor 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 countries will be the most current version of the Investigator's Brochure.

4.6 Evaluation of Subjects with 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 in the Protocol.

5 STUDY DRUG

5.1 Treatments Administered

Depatuxizumab mafodotin must not be dispensed without contacting the Interactive Response Technology (IRT) system and may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the Premature D/C visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit. Destruction of the study drug may be performed at the site if allowable per institutional guidelines.

Radiation Therapy

RT treatment planning and administration will be done as per local institutional guidelines. Minor changes to the RT dose schedule described above due to logistical or safety reasons that are considered in the best interest of the subject are allowed and will not be considered protocol deviations.

TMZ Treatment

TMZ will be administered according to local standard of care. Duration of TMZ treatment will be 6 – 12 cycles in the adjuvant phase and is at the discretion of the investigator as supported by local standard of care. TMZ will not be provided by the sponsor.

IV administration of TMZ is allowed for subjects who are unable to take oral TMZ for any reason.

Depatuxizumab Mafodotin Treatment

Depatuxizumab mafodotin will be given by IV infusion over 30 to 40 minutes, at the time points outlined in Section 2.1 beginning at baseline (Day 1). The mg/kg dose of depatuxizumab mafodotin will be determined from the weight on Day 1 of the Chemoradiation Phase and need not change unless there is a weight change of more than 10% from the weight being used for the calculation. 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.

Depatuxizumab Mafodotin Administration during Chemoradiation

During the Chemoradiation Phase, subjects will receive depatuxizumab mafodotin 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). The interval between depatuxizumab mafodotin doses may be adjusted as needed for safety or logistical reasons under the following limitations:

- No more than 3 doses of depatuxizumab mafodotin are given during the Chemoradiation Phase.
- Successive doses of depatuxizumab mafodotin must be at least 12 days apart.
- All depatuxizumab mafodotin doses must be administered no later than the last day of radiation treatment.

Depatuxizumab Mafodotin Administration during Adjuvant Treatment

During the Adjuvant Therapy Phase, subjects in all arms will receive depatuxizumab mafodotin 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 for 12 cycles.

If TMZ treatment is discontinued due to intolerance during either the Chemoradiation Phase or Adjuvant Phase, subjects will continue receiving depatuxizumab mafodotin infusions according to the same study schedule.

Steroid Eye Drops

Administration of steroid eye drops and any other eye drops should be separated by at least 5 minutes to ensure that there is no washout of the prior drug. Formulations combining eye drops with another drug (e.g., antibiotic) is allowed. Prophylactic use of antibiotic eye drops may be used in all treatment arms; however, it is especially important to use antibiotic eye drops with enhanced steroid regimens and bandage contact lenses in order to prevent infection.

Standard Regimen:

1 drop each eye, 3 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days.

Enhanced Regimen:

1 drop each eye, 6 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days.

Ophthalmic Steroid Ointment

Ointment in each eye once daily before sleep, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days.

Vasoconstrictor Eye Drops

One drop each eye 4 – 6 times on day of infusion in total (5 – 10 minutes before infusion; at end of infusion; and 2 – 4 times during the remainder of the infusion day). Continuing 4 – 6 times/day on Day 1 and Day 2 after each depatuxizumab mafodotin infusion.

Cold Compress

Starting 5 minutes prior to start of infusion and continuing for 30 minutes past end of infusion, and then use at least 2 hours total/day on Days 1 – 3 with each depatuxizumab mafodotin infusion. The cold compress should be applied in increments no longer than 30 min (could be shorter if the patient is uncomfortable).

Bandage Contact Lens

For subjects who demonstrate inadequate control of OSEs with the initial prophylactic strategy, according to predefined criteria for loss of visual acuity and/or OSE symptom severity, intervention with a BCL will first be employed.

5.2 Packaging and Labeling

Vials containing depatuxizumab mafodotin lyophilized powder will be packaged in cartons. Each vial and carton will be labeled per country requirements. Refer to the Medication Preparation Guidelines provided for reconstitution and dilution of the lyophilized powder.

Depatuxizumab mafodotin will be provided by AbbVie as 20 mg and 30 mg vials. The total volume administered will be dependent upon the assigned dose for that dosing period and/or the tolerability of depatuxizumab mafodotin.

The labels must remain affixed to the vial and carton. All blank spaces should be completed by site staff prior to dispensing to subject.

Cold compresses will be supplied to the site by AbbVie.

Prophylactic therapies will be obtained commercially, except if otherwise required by local regulation.

Storage and Disposition of Study Drug

The depatuxizumab mafodotin 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 depatuxizumab mafodotin 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. Evaluation of a prolonged infusion time may necessitate the need for depatuxizumab mafodotin to be reconstituted into two IV bags so that adequate stability measures may be maintained. Reconstitution should be completed per the depatuxizumab mafodotin Extemporaneous Dose Preparation Guidelines.

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.

5.3 Method of Assigning Subjects to Prophylactic Groups

This is an open-label, randomized, 3-arm study. All eligible subjects will receive the same dosage of depatuxizumab mafodotin (2.0 mg/kg depatuxizumab mafodotin during chemoradiation and 1.25 mg/kg depatuxizumab mafodotin during adjuvant therapy) for 1 year. Subjects will be randomized in a 1:1:1 ratio to 1 of 3 prophylactic eye treatment regimens (Arm A, Arm B, or Arm C), as described in Section 4.1 of the protocol.

At the screening visit, all subjects will be assigned a unique subject number through the use of the 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. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

5.4 Selection and Timing of Dose for Each Subject

The same dose (2.0 mg/kg depatuxizumab mafodotin during chemoradiation and 1.25 mg/kg depatuxizumab mafodotin during adjuvant therapy) will be administered by intravenous (IV) infusion over 30 – 40 minutes every 2 weeks to all subjects. Subjects will receive prophylactic eye treatment according to their prophylactic treatment regimen assignment as described in Section 5.7 of the protocol.

6 REFERENCES

1. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol. 1984;2(3):187-93.
2. Ellingson BM, Wen PY, Cloughesy TF. Modified Criteria for Radiographic Response Assessment in Glioblastoma Clinical Trials. Neurotherapeutics. 2017;14(2):307-20.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
BCVA	Best Corrected Visual Acuity
BUN	Blood urea nitrogen
CEAE	Corneal Epithelial Adverse Event
CNS	Central Nervous System
CP	Corneal Perforation
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CU	Corneal Ulceration with impending perforation
D/C	Discontinuation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ES	Enhanced Steroids
GGT	Gamma-Glutamyl Transferase
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRT3	Heidelberg Retina Tomographer
IEC	Independent ethics committee
IMP	Investigational Medical Product
INR	International normalized ratio
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	Lactate Dehydrogenase

MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI(1)	post RT MRI (baseline)
MRI(N)	scans that start after the first cycle of adjuvant therapy, but prior to suspected progression
MRI(N + 1)	first scan after progression is suspected
MRI(M)	additional follow-up MRI scans, if based on MRI (N + 1) suspected progression was deemed to be pseudoprogression
N/A	Not Applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OSE	Ocular Side Effect
PE	Physical Examination
PRO	Patient Reported Outcome
PT	Prothrombin Time
RANO	Response Assessment in Neuro-Oncology
RBC	Red blood cells
RT	Radiation
SAE	Serious adverse event
SD	Stable Disease
SOC	System Organ Class/Standard of Care
SS	Standard Steroids
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total bilirubin
TMZ	Temozolomide
VA	Visual Acuity
VA OU	VA OU Visual Acuity both eyes oculus uterque
VAcc	Visual Acuity with Correction
VAsc	Visual Acuity without Correction
VA OD	Visual Acuity Right Eye
VA OS	Visual Acuity Left Eye
VC	Vasoconstrictors and Cold Compress
vQOL	Visual Quality of Life
WBC	White Blood Cell

APPENDIX B. KARNOFSKY PERFORMANCE STATUS

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

Cross reference: Schag 1984[1]

APPENDIX C. OPHTHALMOLOGY EXAM

Date of exam:	**M16-534 Site Number:**
M16-534 Subject number:	**Name of Ophthalmologist performing exam:**

Eye Pain and Photophobia	
OD (Right eye)	**OS (Left eye)**
Eye pain? *(circle one)* No Yes	**Eye pain (OS)?** *(circle one)* No Yes
Photophobia? *(circle one)* **None** **Mild** (Bright Light) **Moderate** (Ambient light) **Severe** (Constant)	**Photophobia?** *(circle one)* **None** **Mild** (Bright Light) **Moderate** (Ambient light) **Severe** (Constant)

Eyeglasses Prescription at Baseline(entered during baseline exam only)

☐ Check box if no glasses at baseline

		Sphere	Cylinder	Axis	Prism	Base
Distance	OD					
	OS					
Add	OD					
	OS					

Visual Acuity with Baseline Correction (VAcc or VAsc) without BCL □ Check box if not completed		
OD (Right eye)	**OS (Left eye)**	**Both Eyes**
LogMAR: ____	LogMAR: ____	LogMAR: ____
Visual Acuity with Baseline Correction (VAcc or VAsc) with BCL □ Check box if no BCL(s) used □ Check box if BCL(s) was indicated but not tolerated		
OD (Right eye) □ Check box if no BCL OD	**OS (Left eye)** □ Check box if no BCL OS	**Both Eyes**
LogMAR: ____	LogMAR: ____	LogMAR: ____
Best Corrected Visual Acuity (with Manifest Refraction) □ Check box if not completed Was BCL(s) in place for Manifest Refraction? □ Yes □ No		
OD (Right eye)	**OS (Left eye)**	**Both Eyes**
LogMAR: ____	LogMAR: ____	LogMAR: ____

INTRAOCULAR PRESSURE	
OD (Right eye)	**OS (Left eye)**
_____ mm Hg	_____ mm Hg
Time of measurement: _____:_____ AM PM *(circle one)*	
Instrument Used: __Goldmann (Slit Lamp tonometer) __Tonopen (tonometer) __Icare (tonometer) __Other, specify:_____	

abbvie

CORNEA – *Grades must be recorded for Microcysts/Edema and Superficial Punctate Keratopathy (even if normal)*									
OD (Right eye)					**OS (Left eye)**				
Microcysts/Edema – ******Grades for <u>both</u> eyes must be recorded (even if normal)******									
0 (None) Normal	+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	0 (None) Normal	+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 – ******Grades for <u>both</u> eyes must be recorded (even if normal)******									
0 (None) Normal	+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)	0 (None) Normal	+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)
Other corneal pathology (specify):									

LENS ☐ Check box if no abnormal findings							
OD (Right eye)				**OS (Left eye)**			
Cataract present? ☐ Check box <u>if YES</u>, and specify location:				**Cataract present?** ☐ Check box <u>if YES</u>, and specify location:			
Nuclear	Posterior subcapsular	Cortical	Anterior cortical	Nuclear	Posterior subcapsular	Cortical	Anterior cortical
Other lens pathology (specify):							

OTHER FINDINGS
Other pathology (specify, including severity if applicable)

APPENDIX D. VISUAL ACUITY EVALUATIONS FOR OPHTHALMOLOGY VISITS

Baseline
○ VA with baseline correction (cc or sc) *without BCL* – OD, OS, OU ▪ Record glasses prescription if applicable ▪ Record without glasses if subject does not require correction at baseline ▪ The same prescription will be used to measure VA (cc or sc) for all post-baseline visits ○ BCVA (with manifest refraction) OD, OS, and OU will be recorded
Post-baseline visits (prior to BCL intervention)
• VA with baseline correction (cc or sc) *without BCL* – OD, OS, OU • ***If*** *VA OU (cc or sc) declined ≥ 0.3 LogMAR from baseline* ***OR*** *if CEAE Grade ≥ 3*, place BCL and obtain the following: ○ VA with baseline correction (cc or sc) *with BCL* – OD, OS, OU ○ BCVA (manifest refraction) *with BCL* – OD, OS, OU
Post-baseline visits (if BCLs are being used)
• VA with baseline correction (cc or sc) *without BCL* – OD, OS, OU – omit if BCL is not changed at the visit • VA with baseline correction (cc or sc) *with BCL* – OD, OS, OU • ***If*** *VA OU (cc or sc) with BCL decline ≥ 0.3 LogMAR from baseline remains,* obtain the following: ○ BCVA (manifest refraction) *over BCL* – OD, OS, OU – repeat every ~8 weeks
Post-baseline visits (if BCL intervention not tolerated)
• VA with baseline correction (cc or sc) *without BCL* – OD, OS, OU • ***If*** *VA OU (cc or sc) without BCL decline ≥ 0.3 LogMAR from baseline remains*, obtain the following: ○ BCVA (manifest refraction) *without BCL* – OD, OS, OU – repeat every ~8 weeks

APPENDIX E. VISUAL QUALITY OF LIFE QUESTIONNAIRE

Please rate the intensity of the following ocular symptoms by circling the appropriate number for each of the questions below:

1) **Blurred vision:** On a scale of 0 to 10, how blurred is your vision:

0-------1----------2----------3----------4----------5----------6----------7----------8----------9----------10
Not blurred at all Extremely blurred

2) **Sensitivity to light:** On a scale of 0 to 10, how sensitive are your eyes to light:

0-------1---------2---------3---------4---------5---------6---------7---------8---------9---------10
Not sensitive at all Extremely sensitive

3) **Dryness in the eyes:** On a scale of 0 to 10, how dry are your eyes:

0-------1----------2----------3----------4----------5----------6----------7----------8----------9----------10
Not dry at all Extremely dry

4) **Painful or sore eyes:** On a scale of 0 to 10, how severe is the pain in your eyes:

0-------1----------2----------3----------4----------5----------6----------7----------8----------9----------10
Not painful at all Extremely painful

5) **Watery eyes:** On a scale of 0 to 10, how watery/teary are your eyes:

0-------1----------2----------3----------4----------5----------6----------7----------8----------9----------10
Not watery at all Extremely watery

6) **Irritation in the eyes:** On a scale of 0 to 10, how irritated are your eyes:

0-------1----------2----------3----------4----------5----------6----------7----------8----------9----------10
Not irritated Extremely irritated

Impact of ocular symptoms on your functioning:

Please ✓the appropriate category for each question below (check NA for not applicable if the activity does not apply):

1) Over the last week, have problems with your eyes limited you in performing any of the following? Reading

All the time	Most of the time	Half of the time	Some of the time	None of the time	NA

2) Driving

All the time	Most of the time	Half of the time	Some of the time	None of the time	NA

3) Working with a computer

All the time	Most of the time	Half of the time	Some of the time	None of the time	NA

4) Watching TV

All the time	Most of the time	Half of the time	Some of the time	None of the time	NA

5) Seeing in bright light

All the time	Most of the time	Half of the time	Some of the time	None of the time	NA

6) Performing normal chores around the house

All the time	Most of the time	Half of the time	Some of the time	None of the time	NA

7) Judging distances, and depth (of steps, such as curbs or doorstep)

All the time	Most of the time	Half of the time	Some of the time	None of the time	NA

8) Recognizing faces/people

All the time	Most of the time	Half of the time	Some of the time	None of the time	NA

APPENDIX F. PRO-CTCAE™ VISUAL SYMPTOMS QUESTIONNAIRE

Please rate the severity of the following ocular symptoms by circling the appropriate response for each of the questions below.

41. **PRO-CTCAE™ Symptom Term:** Blurred vision				
In the last 7 days, what was the SEVERITY of your BLURRY VISION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
In the last 7 days, how much did BLURRY VISION INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

44. **PRO-CTCAE™ Symptom Term:** Watery eyes				
In the last 7 days, what was the SEVERITY of your WATERY EYES (TEARING) at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
In the last 7 days, how much did WATERY EYES (TEARING) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

Abbreviations: PRO-CTCAE™ = Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events

Source: https://healthcaredelivery.cancer.gov/pro-ctcae/measurement.html

APPENDIX G. PERCEPTION OF TREATMENT VALUE QUESTION

Perception of treatment value:

On a scale of 0 to 10, where 0 is least likely and 10 is most likely, how likely are you to recommend this medication to friends and family if they were diagnosed with GBM?

0	1	2	3	4	5	6	7	8	9	10

1. **Note:** Adapted from Net Promoter Score (Customer loyalty measure adapted to assessing patient loyalty and perception of treatment value)

APPENDIX H. CORNEAL EPITHELIAL ADVERSE EVENT ECRF

CEAE Grade (Overall Severity of Symptoms/Findings Related to Corneal Epithelial Abnormalities):

NE – Not evaluable (Severity of Visual ADL impairment is determined primarily by visual problems unrelated to cornea [lens, retina, optic nerve, CNS lesion, etc.])

0 – Asymptomatic

1 – Symptomatic, but no effect on visual ADLs

2 – Instrumental ADLs* affected, but can perform instrumental ADLs independently

3 – Instrumental ADLs require assistance

4 – Self-care ADLs** require assistance

5 – Corneal perforation or corneal ulceration with impending perforation

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Ocular Discomfort (Including Eye Pain, Dry Eye, Foreign Body Sensation, etc.)

Symptoms: *Record all symptoms contributing to ocular discomfort (check those that apply):*

___ dry eye

___ eye pain

___ foreign body sensation

___ itching

___ other (specify) _____

___ other (specify) _____

___ other (specify) _____

Impact of ocular discomfort on visual ADLs:

0 – Asymptomatic

1 – Symptomatic, but no effect on visual ADLs

2 – Instrumental ADLs affected, but can perform instrumental ADLs independently

3 – Instrumental ADLs require assistance

4 – Self-care ADLs require assistance

Reading (Due to Blurred Vision)

N/A – Not Applicable (subject does not read for reasons unrelated to blurred vision)

1 – No difficulties reading

2 – Reading requires large fonts or magnification

3 – Unable to read due to blurred vision

Photophobia

0 – None

1 – Mild (bright light)

2 – Moderate (ambient light)

3 – Severe (constant)

APPENDIX I. RANO CRITERIA FOR TUMOR ASSESSMENTS IN NEWLY DIAGNOSED GBM

For the current study, Response Assessment in Neuro-Oncology (RANO) criteria will be used to determine the time of disease progression (PD) for the purpose of determining progression-free survival (PFS) only; determination of complete response (CR) or partial response (PR) is not required and will not be recorded.

Criteria for RANO assessment of newly diagnosed GBM subjects are described below as per the 2017 RANO update by Ellingson et al.[2] as follows.

Post-Radiation MRI Examination as the Reference for Evaluating Radiographic Response in Newly Diagnosed GBM

For GBM patients, reliability of tumor assessment on the post-surgical MR scans can be problematic primarily because of the highly unpredictable, transient radiographic changes that often accompany the initial chemoradiation phase (i.e., external beam radiation therapy plus concurrent temozolomide) with or without experimental therapeutics. Within 1 month after completion of standard chemoradiation therapy, approximately 50% of patients will experience radiographic changes suggestive of early tumor progression in reference to the post-surgical MRI exam, of which 50% are likely to have pseudoprogression (i.e., 25% of all patients at 1 month post-chemoradiation are estimated to have pseudoprogression). This proportion of patients with both early progression and pseudoprogression decreases steadily during the subsequent standard adjuvant chemotherapy phase.

Additionally, post-operative MR scans are often contaminated with post-surgical changes and the timing may not be standardized across patients further confounding accurate tumor assessments.

Hence post-radiation examination (i.e., the first scan following completion of concurrent radiation therapy and chemotherapies such as temozolomide and/or experimental therapeutics) will be used as the baseline for response assessment.

Bidimensional and/or Volumetric Measurements

Either bidimensional or volumetric assessments of tumor size may be used, as long as they are consistently used within each subject. Two-dimensional, perpendicular measurements of contrast enhancing tumor size, excluding the resection cavity along with any cysts or areas of central macroscopic necrosis, should be used for response assessment if volumetric tools are not available. Table 1 outlines suggested volumetric conversions from two- to three-dimensional measurements for consistency in response definitions.

Table 1. Bidimensional to Volumetric Definitions of Radiographic Response and Progression

State of Disease	Change in bidimensional product	Estimated volumetric change
Complete response (CR)	100% Decrease	100% Decrease
Partial response (PR)	≥ 50% Decrease	≥ 65% Decrease
Progressive disease (PD)	≥ 25% Increase	≥ 40% Increase
Stable disease (SD)	< 50% Decrease to < 25% Increase	< 65% Decrease to < 40% Increase

Definition of Measurable Disease, Non-Measurable Disease, and Target Lesions

Measurable disease should be defined as contrast enhancing lesions with a minimum size of both perpendicular measurements greater than or equal to 10 mm. For example, if the largest diameter is 15 mm but the perpendicular diameter is 8 mm, this would constitute non-measurable disease.

Additionally, if the slice thickness plus interslice gap is greater than 5mm, then the minimum size for both perpendicular measurements should be twice the sum of the slice thickness and interslice gap (e.g., if the slice thickness is 5 mm with 1.5 mm interslice gap, the minimum tumor size on both perpendicular dimensions should be 13 mm). Up to a total of five target measurable lesions should be defined and ranked from largest to smallest.

Non-measurable disease should be defined as lesions that are too small to be measured (less than 1 cm in both perpendicular dimensions), lesions that lack contrast enhancement (non-enhancing disease), or lesions that contain a poorly defined margin that cannot be measured or segmented with confidence.

Detailed Definitions Used for Radiographic Response Assessment Criteria

Radiographic response should be determined in comparison to the tumor measurements obtained at baseline (post-radiation scan will be baseline for newly diagnosed GBM, and pretreatment scans will be the baseline for recurrent GBM) for determination of response, and the smallest tumor measurement at either pre-treatment baseline or following initiation of therapy for determining progression.

Because novel treatments are likely to result in a higher than normal incidence of treatment-related increase in contrast enhancement ("pseudoprogression," PsP) or decrease in contrast enhancement ("pseudoresponse," PsR), patients should continue therapy with close observation (e.g., 4 – 8 week intervals) if there is a suspicion of PsP or PsR. If subsequent imaging studies and/or clinical observations demonstrate that progression in fact has occurred, the date of confirmed progression should be noted as the scan at which the potential progression was first identified. Definitions for complete response, partial response, progressive disease, and stable disease should be defined as follows for all target lesions.

Complete Response (CR): Requires all of the following:

1. Disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks. The first scan exhibiting disappearance of all enhancing measurable and non-measurable disease is considered "preliminary CR." If the second scan exhibits measurable

enhancing disease with respect to the "preliminary CR" scan, then the response is not sustained, noted as pseudoresponse, PsR, and is now considered "preliminary PD" (note confirmed PD requires at least two sequential increases in tumor volume). If the second scan continues to exhibit disappearance of enhancing disease or emergence of non-measurable disease (less than 10 mm bidimensional product), it is considered a durable CR and the patient should continue on therapy until confirmed PD is observed.

2. Patients must be off corticosteroids (or on physiologic replacement doses only).
3. Stable or improved clinical assessments (i.e., neurological examinations).

   Note: Patients with non-measurable disease only at baseline cannot have CR; the best response possible is stable disease (SD). (For the current study subjects without measureable disease at baseline are ineligible for study entry.)

Partial Response (PR): Requires all of the following:

1. ≥ 50% decrease in sum of products of perpendicular diameters or ≥ 65% decrease in total volume of all measurable enhancing lesions compared with baseline, sustained for at least 4 weeks. The first scan exhibiting ≥ 50% decrease in sum of products of perpendicular diameters or ≥ 65% decrease in total volume of all measurable enhancing lesions compared with baseline is considered "preliminary PR." If the second scan exhibits PD with respect to the "preliminary PR" scan, then the response is not sustained, noted as pseudoresponse, PsR, and is now considered "preliminary PD" (note confirmed PD requires at least two sequential increases in tumor volume). If the second scan exhibits SD, PR, or CR, it is considered a durable PR and the patient should continue on therapy until confirmed PD is observed.
2. Steroid dose should be the same or lower compared with baseline scan.
3. Stable or improved clinical assessments.

   Note: Patients with non-measurable disease only at baseline cannot have PR; the best response possible is stable disease (SD). (For the current study subjects without measureable disease at baseline are ineligible for study entry.)

Progressive Disease (PD): Defined by any of the following:

1. At least two sequential scans separated by at ≥ 4 weeks both exhibiting ≥ 25% increase in sum of products of perpendicular diameters or ≥ 40% increase in total volume of enhancing lesions. The first scan exhibiting ≥ 25% increase in sum of products of perpendicular diameters or ≥ 40% increase in total volume of enhancing lesions should be compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response (on stable or increasing steroid dose) and is noted as "preliminary PD." If the second scan at least 4 weeks later exhibits a subsequent ≥ 25% increase in sum of products of perpendicular diameters or ≥ 40% increase in total volume of enhancing lesions relative to the "preliminary PD" scan, it is considered "confirmed PD" and the patient should discontinue therapy. If the second scan at least 4 weeks later exhibits SD or PR/CR, this scan showing "preliminary PD" is noted as "pseudoprogression," PsP, and the patient should continue on therapy until a second increase in tumor size relative to the PsP scan is observed. Note that any new measurable (> 10 mm ×

10 mm) enhancing lesions should not be immediately considered PD, but instead should be added to the sum of bidimensional products or total volume representing the entire enhancing tumor burden.

2. In the case where the baseline or best response demonstrates no measurable enhancing disease (visible or not visible), then any new measurable (> 10 mm × 10 mm) enhancing lesions are considered PD after confirmed by a subsequent scan ≥ 4 weeks exhibiting ≥ 25% increase in sum of products of perpendicular diameters or ≥ 40% increase in total volume of enhancing lesions relative to the scan first illustrating new measurable disease. The first scan exhibiting new measurable disease is noted as "preliminary PD." If the second scan at least 4 weeks later exhibits a subsequent ≥ 25% increase in sum of products of perpendicular diameters or ≥ 40% increase in total volume of enhancing lesions relative to the "preliminary PD" scan it is considered "confirmed PD" and the patient should discontinue therapy. If the second scan at least 4 weeks later exhibits SD, CR, PR, or becomes non-measurable, this scan showing "preliminary PD" is noted as "pseudoprogression," PsP, and the patient should continue on therapy until a second increase in tumor size relative to the "preliminary PD," or PsP, scan is observed. Note that any new measurable (> 10 mm × 10 mm) enhancing lesions on the subsequent scan following the preliminary PD scan should not be immediately considered confirmed PD, but instead should be added to the sum of bidimensional products or total volume representing the entire enhancing tumor burden.
3. Clear clinical deterioration not attributable to other causes apart from tumor (e.g., seizures, medication adverse effects, therapy complications, stroke, infection) or attributable to changes in steroid dose.
4. Failure to return for evaluation as a result of death or deteriorating condition.

Stable Disease (SD): Requires all of the following:

1. Does not qualify for CR, PR, or PD as defined above. Note this also applies to patients that demonstrate PsR when the confirmation scan does not show PD or PsP when the confirmation scan does not show PR/CR.
2. In the event that corticosteroid dose was increased (for new symptoms/signs) without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that the steroid increase was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Symptomatic Deterioration & Reporting Clinical Status

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. Neurological exam data should be provided to the independent radiologic facility as "stable, better, worse" in case report forms or from study sponsor. Clinical status should be recorded as "worse" if the neurological exam is worse; otherwise the clinical status should be set to "not

worse." In the event that necessary clinical data is not available, clinical status should be recorded as "not available" and that particular time point can only be reviewed for PD (otherwise "non-evaluable"). Neurological data must be within ± 7 days of the time-point response date, otherwise the data is considered "not available."

Steroid Use and Dose

Steroid use should be derived from the concomitant medications on the case report forms and recorded as "Yes," "No," or "not available." A value of "No" should be assigned if, at the timepoint, the subject is not on steroids or on physiologic replacement doses only (< 1.5 mg dexamethasone or equivalent per day).

Systemic steroid dose should be derived from the concomitant medications on the case report forms. Average steroid dose no greater than 2 mg change from baseline should be abstracted to "stable." If outside this range the steroid dose should be abstracted to "increased" or "decreased" accordingly. Steroid data should be within ± 5 days of the time-point response date; otherwise the data is considered "not available."

Overall Objective Status

The overall objective status for an evaluation should be determined by combining the patient's radiographic response on target lesions, new disease, neurological status, and steroid dose/usage as defined in Table 2 for patients with measurable (> 10 mm × 10 mm) disease. Note that patients with possible PsP or pseudoresponse should be given the Objective Status of "Preliminary Progression" or "Preliminary Response," respectively. Once PsP, pseudoresponse, or true progression/response are confirmed, the Objective Status can be changed accordingly.

Detailed Modified Radiographic Response Assessment Rubric

In order to provide both clinical guidelines for continuing therapy beyond suspected radiographic progression if the treating physician believes there may be a therapeutic benefit and to provide criteria for defining progression and early drug failure while also allowing for the possibility of PsP and PsR, modified response rubrics should be employed, depending on whether the patient is newly diagnosed or enrolled in a trial for recurrent disease. The response rubric for *newly* diagnosed GBM is shown in Figure 1 below.

It is important to note that the primary differences between conventional RANO and the proposed modified criteria are: (1) use of the post-radiation time point as the baseline for response evaluation in newly diagnosed GBM, (2) considering only objectively defined, measurable enhancing disease in the definition of response and progression (i.e., exclusion of qualitatively assessed T2/FLAIR changes), and (3) repeating radiographic assessments to confirm disease progression if initial radiographic evidence of PD is identified in the absence of clinical/neurologic decline.

Table 2. Guidelines for Determining Comprehensive Objective Status

Target Lesions (Current Scan)	Target lesions (previous scan)	New Sites of Measureable Disease[a]	Neurological Status	Steroid Usage	Steroid dose	Overall Objective Status
CR	Not evaluated	No	Stable/Better	No	N/A	Preliminary CR
PR	Not evaluated	No	Stable/Better	Any	Stable/Decreasing	Preliminary PR
PD	Not evaluated	Yes or No	Stable/Better	Any	Stable/Increasing	Preliminary PD
PD	Preliminary or Confirmed PR/CR	No	Stable/Better	Any	Stable/Increasing	Preliminary PD
SD	Preliminary or Confirmed PR/CR or SD/NE	No	Stable/Better	Any	N/A	SD
PR	Preliminary PR	Yes or No	Stable/Better	Any	Stable/Decreasing	Confirmed PR
SD	Preliminary PR	Yes or No	Stable/Better	Any	Stable/Decreasing	SD (preliminary PR → confirmed PR)
SD	Preliminary CR	Yes or No	Stable/Better	Any	Stable/Decreasing	SD (preliminary CR → confirmed CR)
CR	Preliminary CR	No	Stable/Better	No	N/A	Confirmed CR
SD	Preliminary PD	No	Stable/Better	Any	Stable/Decreasing	SD (Confirmed PsP)
CR/PR/SD /PD/NE	CR/PR/SD/PD /NE	Yes or No	Worse	Any	Stable/Increasing	Confirmed PD
PD	Preliminary PD	Yes or No	Any	Yes	Stable/Increasing	Confirmed PD

a. Note that new sites of measurable disease are added to the sum of bidimensional products or total lesion volume, or constitutes preliminary PD in the case of no measurable disease at baseline or best response.

Baseline Assessments for Newly Diagnosed GBM

Newly diagnosed GBM patients will usually undergo an MRI scan for initial diagnosis prior to entry in the study and prior to therapy. The post-operative scan is desired in order to assess residual enhancing disease volume for use as a covariate in survival analyses, as described previously. Patients will then start on standard or experimental therapy with concurrent radiation therapy (RT).

The Post-RT scan should be used as the baseline scan for which response and disease progression will be determined. Following the first cycles of adjuvant therapy, patients will receive additional required MRI scans.

Details Common to Both Newly Diagnosed and Recurrent GBM

Preliminary Radiographic Progression. If the lesion size has increased ≥ 25% sum of bidirectional product or ≥ 40% in volume between MRI Scan 1 and N, these patients should be categorized as "preliminary radiographic progression." If the investigator believes the patient can safely continue on therapy, then they should continue to treat and acquire a follow-up confirmatory scan [MRI(N + 1)] at the next scan interval (8 weeks ± 4 weeks from MRI Scan (N) or no less than 4 weeks minimum duration between preliminary PD and confirmed PD scans) to verify tumor growth and progression. For patients with gross-total resection (GTR) and no measurable enhancing disease, preliminary radiographic progression is defined as a transition from no measurable disease to nonmeasurable (but present) disease (< 10 mm × 10 mm) or measurable disease (> 10 mm × 10 mm). If the investigator feels it is safe to keep the patient on, a confirmatory scan at MRI(N + 1) should be obtained to verify tumor progression.

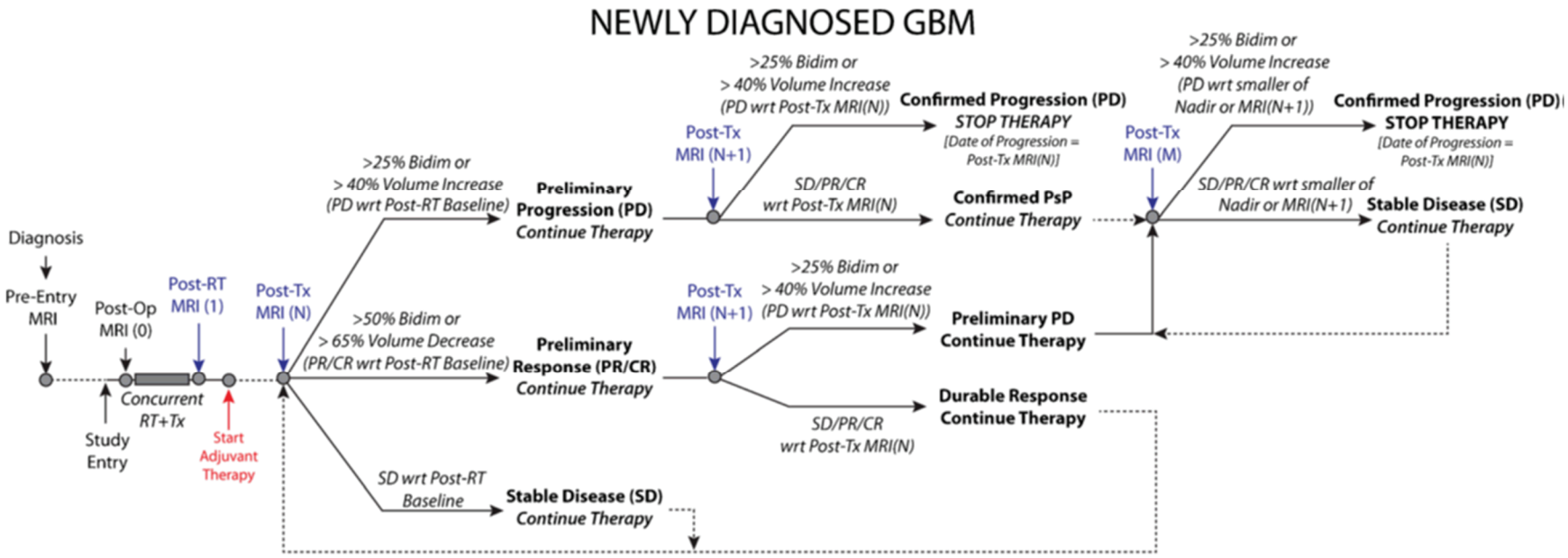
Confirmed Progression. If the patient has an increase ≥ 25% sum of bidirectional product or ≥ 40% in volume between MRI Scan N and N + 1, this is "Confirmed Progression," the patient should stop therapy and the date of radiographic progression is the date of suspected progression, MRI(N). If the patient has SD/PR/CR on MRI(N + 1) with respect to MRI(N), PsP is confirmed and the patient should continue on therapy. Patients will then continue on therapy and receive additional follow-up MRI scans [MRI(M)]. If the lesion size has increased ≥ 25% sum of bidirectional product or ≥ 40% in volume on MRI(M) relative to the smaller of Nadir or MRI(N + 1), then the patient has "Confirmed Progression," the patient should stop therapy (unless otherwise allowed per protocol) and the date of radiographic progression is the new date, MRI(M). For patients with no measurable disease at the Post-RT baseline, "Confirmed Progression" will be defined as a transition from non-measurable (but present) disease (< 10 mm × 10 mm) on MRI(N) to measurable disease (> 10 mm × 10 mm) on MRI(N + 1). For patients with confirmed PsP and no measurable disease at Nadir, "Confirmed Progression" should be defined as a transition from no measurable disease to measurable disease (> 10 mm × 10 mm). In all cases, patients with confirmed progression should stop therapy.

Preliminary & Confirmed Radiographic Response. If a measurable lesion has decreased ≥ 50% sum of bidirectional product or ≥ 65% in volume between MRI(1) and MRI(N), these patients should be categorized as "preliminary radiographic responders" and will be monitored for an additional time point and/or treatment cycle. After an additional cycle of therapy (8 weeks ± 4 weeks from MRI(N)), patients will receive a confirmatory MRI(N + 1). If the lesion(s) have increased ≥ 25% sum of bidirectional product or ≥ 40% in volume from MRI(N) (indicating radiographic progression from MRI(N)), this is considered an "unsustained radiographic response" or "pseudoresponse." The date of radiographic progression for these patients will be MRI(N + 1) and the patient should stop therapy. Alternatively, if the lesion has not increased from MRI(N), this is considered a "durable radiographic response," the patient will continue on therapy, and the date of preliminary radiographic progression is the time point of an increase ≥ 25% sum of bidirectional product or ≥ 40% in volume (from Nadir) during the remainder of the study. The investigator can then decide whether to continue safely on therapy until progression has been confirmed and at the subsequent time point stop therapy if they feel the patient cannot safely continue therapy.

Stable Disease. If the lesion size has not increased or decreased beyond the set thresholds between Scan 1 and N, the patient is considered "stable." Such patients will continue on therapy, and the date of preliminary progression is the time point of an increase ≥ 25% sum of bidirectional product or ≥ 40% in

volume (from Nadir) during the remainder of the study. Upon preliminary progression the investigator can choose to either continue therapy and confirm progression or discontinue therapy. For cases with significant neurologic decline at the time of imaging progression as determined from MRI(N), a confirmatory scan at time point MRI(N + 1) may not be possible or necessary. For these cases, it is appropriate to define MRI(N) as the progression time point.

Figure 1. Radiographic Response Assessment Rubric for Newly Diagnosed Glioblastoma



GBM = glioblastoma; MRI = magnetic resonance imaging; PD = progressive disease; PR = partial response; PsP = pseudoprogression; RT = radiation; SD = stable disease; Tx = treatment; wrt = with regard to