1.0 Title Page

Statistical Analysis Plan

Study M16-534

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

Date: 01 April 2020

Version 1.0

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3.0 Abbreviation

ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CTC(AE)	Common Terminology Criteria (for Adverse Events)
Depatux-M	Depatuxizumab mafodotin
EGFR	Epidermal Growth Factor Receptor
GGT	Gamma-glutamyl transferase
Gy	Gray
MedDRA	Medical Dictionary for Regulatory Activities
MGMT	O6-methylguaninemethlytransferese
NCI	National Cancer Institute
OSE	Ocular side effect
PT	Preferred Term
RANO	Response Assessment in Neuro Oncology
RT	Radiation Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SGPT	Serum glutamic-pyruvic transaminase
SGOT	Serum glutamic-oxaloacetic transaminase
SOC	Standard of Care
TE(AE)	Treatment Emergent Adverse Event
TMZ	Temozolomide

4.0 Introduction

This abbreviated statistical analysis plan (SAP) will provide detailed statistical methods for the analysis of efficacy and safety data collected in Study M16-534 as outlined in Protocol Amendment 4 (dated 28 May 2019) and will describe analysis conventions to guide the statistical programming work.

The INTELLANCE-1 interim efficacy analysis results (based on data cut of 30 April 2019) overall indicated no survival benefit for adding depatuxizumab mafodotin to standard RT/TMZ therapy in newly diagnosed GBM patients. Based on the results from INTELLANCE-1, it was decided to stop further enrollment into Study M16-534 (UNITE) and collection of efficacy data. At the time of this decision, a total of 40 subjects had been enrolled in Study M16-534 (UNITE). With these changes, no statistical tests are planned to be performed for efficacy endpoints for this study. Given only a small number of patients are enrolled in the study and most of them did not have long-term follow-up, exploratory efficacy endpoints will not be summarized. All summary results will be presented by treatment arm along with the overall results.

All analyses will be performed using SAS Version 9.4 or higher (SAS Institute, Inc., Cary, NC 27513) under the UNIX operating system. The SAP will be signed off before database lock.

5.0 Study Objectives, Design and Procedures

5.1 Objectives

Primary objective

Estimate the percentage of subjects in each prophylactic treatment arm who require a change in ocular side effect (OSE) management due to inadequate control of OSEs.

Secondary objectives

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

5.2 Study Design

5.2.1 Study Design and Design Diagram

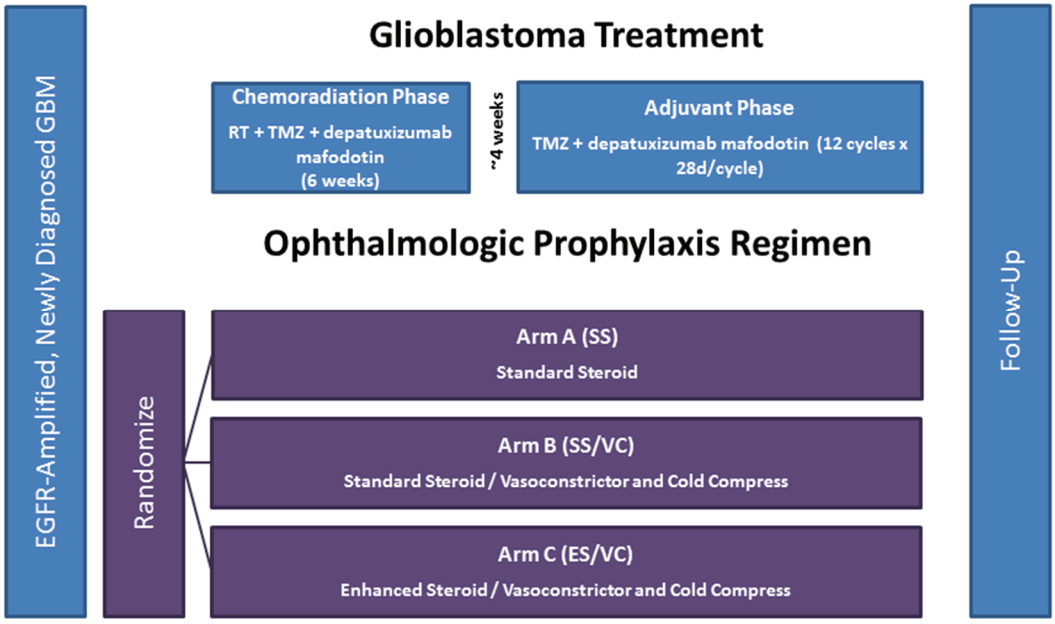
This is a Phase 3b open-label, randomized, exploratory study to evaluate the effect of 3 ophthalmologic prophylactic treatment strategies for the management of OSEs in subjects with newly diagnosed, EGFR-amplified GBM who are being treated with depatuxizumab mafodotin in addition to standard frontline treatment with chemoradiation (RT/TMZ) followed by adjuvant TMZ. Approximately 90 subjects were planned to be randomized to one of the three following prophylactic eye treatment arms in a 1:1:1 fashion:

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

During the Chemoradiation Phase, all subjects should undergo focal RT. TMZ should be administered orally from start of RT to the last day of RT for a maximum of 49 days. All subjects should receive depatuxizumab mafodotin once every 2 weeks during this period. The start of the first cycle during the Adjuvant Phase should be scheduled approximately 28 days after the last day of chemoradiation. During the Adjuvant Phase, all subjects should receive oral TMZ for 6 – 12 cycles (depending on local standard of care) and depatuxizumab mafodotin for 12 cycles. Adjuvant treatment should be discontinued upon determination of tumor progression as defined by Response Assessment in Neuro-Oncology (RANO) Working Group criteria, unacceptable toxicity, or refusal to continue study treatment.

Subjects should receive OSE prophylaxis during both the Chemoradiation and Adjuvant Phases as long as depatuxizumab mafodotin treatment is ongoing. For subjects who demonstrate inadequate control of OSEs with the initial prophylactic strategy, intervention with a BCL should first be employed. Subjects who continue to demonstrate inadequate response to BCL intervention should be eligible for unrestricted OSE management according to investigator discretion. Subjects who discontinue depatuxizumab mafodotin for any reason will receive regular follow-up for assessment of AEs at post-treatment 35 and 49 day follow-up visits and, if necessary, assessments of CEAE and ophthalmologic examinations until resolution of OSEs.

Figure 1. Schema of Study Design



5.3 Endpoints

5.3.1 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) (Bailey IL, Lovie-Kitchin, 2013) in

visual acuity (with baseline correction determined at the screening ophthalmology visit) 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. The primary endpoint is assessed over 8 weeks after initiation of depatuxizumab mafodotin treatment regardless of phases.

5.3.2 Secondary Endpoints

Following secondary endpoints will be assessed:

- Maximum change from baseline on LogMAR scale
- Time to BCL intervention
- Cumulative dose of depatuxizumab mafodotin received (mg/kg) (during chemoradiation and during adjuvant treatment)

5.3.3 Other Safety Endpoints

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

6.0 Analysis Populations

All the analyses will be carried out on the safety population. The **safety population** will comprise all randomized subjects who have received at least 1 dose of Depatux-M. Subjects will be classified according to prophylactic treatment received. The safety population will be the primary analysis population for analysis of all endpoints.

7.0 Analysis Conventions

7.1 Definition of Baseline

Unless otherwise specified, the baseline observation is defined as the last non-missing measurement collected prior to the first dose of any study drug (RT, TMZ and Depatux-M).

7.2 Dealing with Multiple Values on the Same Day

In cases multiple values are collected on the same day at baseline or post-baseline visit the worst value will be used for further analyses.

7.3 Definition of Treatment Emergent Observation

For safety assessments, Treatment Emergent (TE) observations are defined as all newly occurring or worsening safety observation with onset at or following the initiation (date and time) of any study drug and no later than 49 days after the last dose of Depatux-M. If an incomplete onset date is collected for an AE, the AE will be assumed to be treatment-emergent unless there is enough information confirming that is it not (e.g., a month and year is available that precedes the treatment start date).

7.4 Definition of Study Days and Rx Days

Study Day of any observation is defined for post-randomization observations as:

Study Day = Date of observation – Date of randomization + 1,

and for observations predating randomization as:

Study Day = Date of observation – Date of randomization.

Thus, the day of randomization is defined as Study Day 1, while the day prior to the randomization is defined as Study Day –1 (there is no Study Day 0).

Study Treatment (Rx) Day of any post-baseline observation is defined as the number of days from the day of the first dose of any study drug (RT, TMZ, and Depatux-M) to the date of observation. It is calculated for each post-treatment observation as follows:

Study Rx Day = Date of observation – Date of first dose of any study drug + 1

7.5 Definition of Visit Windows

Visit windows for all the assessments are displayed in Table 1.

Table 1. Visit Window

Scheduled Visit	Nominal study Rx Day	Time Window (Study Rx Day Range)
Baseline	≤ –1	–21 to –1 days
Week 1 Day 1	1	1 to 8 days
Week 3 Day 1	15	9 to 22 days
Week 5 Day 1	29	23 to 36 days
…	…	…
Week (2*X - 1) Day 1	14*X - 13	14*X – 19 to 14*X – 6 days

8.0 Demographics, Baseline Characteristics, Medical History and Previous/Concomitant Medications

Demographic and baseline characteristics, medical history, and prior/concomitant medications will be summarized by treatment groups using the safety population by treatment groups and in overall study population.

8.1 Demographic and Baseline Characteristics

The following demographic, current disease history and baseline disease characteristics will be summarized descriptively.

<table>
<tr><th>Demographic Variable</th><th>Baseline Disease Characteristics</th></tr>
<tr><td rowspan="3">Age
Weight
BMI
Sex
Race (White, Black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or Pacific Islander)
Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
History of tobacco product use and alcohol use (current, former, never, unknown)</td><td>Histology (Glioblastoma, Gliosarcoma, Other)
Level of neurological function (worse than minor neurofunction impairment, no worse)
MGMT methylation status (methylated, unmethylated, indeterminate)
EGFRvIII status (mutated or other).
Karnofsky performance status (KPS)</td></tr>
<tr><td>Baseline Disease Status</td></tr>
<tr><td>Time since diagnostic GBM surgery to start of study treatment
Type of surgery (Gross total resection, partial resection, biopsy)</td></tr>
</table>

8.2 Medical and Surgical History

Medical and surgical history data will be summarized and presented using body systems and conditions/diagnoses (e.g., fatigue, gait disturbance) as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects will be summarized for each condition/diagnosis per arm. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

8.3 Prior/Concomitant Medications (Excluding Protocol-Required Prophylactic Eye Drops)

Prior medications are any medications excluding the protocol-required prophylactic eye treatment taken after screening visit and prior to the first dose of study drug. Concomitant medications are any medications excluding eye drops, other than study drug, taken after the first dose of study drug and within 49 days of the last dose of study drug, regardless of the start and stop date. Medications taken on the day of the first dose of study drug are counted as concomitant medications.

Prior and concomitant medications will be summarized separately by the generic name coded by the World Health Organization (WHO) dictionary. Subjects reporting the same medication generic name two or more times will be counted only once for that generic name. Subjects reporting more than one medication will be counted only once in the total number of subjects taking a concomitant medication.

8.4 Prior/Concomitant Medications (Protocol-Required Prophylactic Eye Drops)

Concomitant use of eye drops from screening will be summarized by generic name for ophthalmic steroids and Vasoconstrictor eye drops and Cold compress, separately. Listing of eye-drops used will be provided along with dosing information, start date, end date and investigator assessed compliance.

9.0 Subject Disposition and Study Drug Exposure

9.1 Subject Disposition

Subject disposition summary will be presented for all screened subjects by investigator site and overall. The following information will be presented: subjects screened, subjects randomized, subjects who received at least 1 dose of study drug, subjects who received prophylactic treatment, subjects who entered adjuvant phase, and subjects discontinued from the study. In addition, a subject disposition summary will be presented by prophylactic treatment group and overall, including the following information.

- Subjects randomized
    i. Subjects did not receive any prophylactic treatment
    ii. Subjects received randomized prophylactic treatment
    iii. Subjects received treatment different from randomized prophylactic treatment
- Subjects entered in adjuvant phase
- Subjects entered in survival follow-up phase
- Reason for discontinuation from study

In addition, reason for study drug discontinuations will be summarized by treatment arms.

9.2 Study Drug Exposure

Treatment duration for Depatux-M and TMZ are defined as below:

Treatment duration for Depatux-M (in days) = last Depatux-M dose date – first Depatux-M dose date + 15.

Treatment duration for TMZ (in days) = last TMZ dose date – first TMZ dose date + 1.

Exposure to Depatux-M and TMZ will be summarized for chemoradiation phase, adjuvant phase and overall study. Following information will be summarized:

- Overall treatment duration for Depatux-M and TMZ, separately
- Percentage of patients received cumulative dose of RT < 57 Gy, 57 - 63 Gy, > 63 Gy
- Cumulative doses (mg/kg) of Depatux-M and total dose (mg) of TMZ in chemoradiation phase, separately
- Cumulative doses (mg/kg) of Depatux-M and total dose (mg) of TMZ in adjuvant phase, separately
- Cumulative doses (mg/kg) of Depatux-M and total dose (mg) of TMZ in overall study (i.e., combining the chemoradiation and adjuvant phase), separately
- Number of cycles of Depatux-M and TMZ in adjuvant phase, separately

10.0 Efficacy Analysis

No efficacy endpoints will be analyzed in the study.

11.0 Safety Analysis

11.1 General Considerations

Safety analyses will be carried out on Safety population. Categorical safety endpoints (e.g., incidence of AEs, incidence of potentially clinically significant laboratory values) will be summarized using frequencies and percentages.

11.2 Analysis of Primary Endpoint

The proportion of patients who met the primary endpoint defined as (a) either ≥ +0.3 change on LogMAR scale in baseline adjusted visual acuity or (b) incidence of ≥ Grade 3 Corneal Epithelial Adverse Event (CEAE, CMQ: 80000184), anytime over 8 weeks after initiation of Depatux-M and prior to BCL intervention will be summarized by treatment arms and in overall population. This analysis will also be repeated for the Post-BCL intervention period. For the Post-BCL intervention period, analysis will be

limited to the patients who received BCL intervention and baseline will be re-set to the last assessment prior to start of BCL intervention.

Time to the first occurrence (onset) of any CEAE will be assessed using Kaplan Meier methodology and median time to first onset of any corneal AE (along with 95% CI). This analysis will be repeated for Grade 3 or higher corneal AEs.

Time to onset will be measured in days relative to the date of first dose date to the start date of the first occurrence of CEAE. If a subject has not experienced an CEAE, the subject will be censored on the subject's last assessment date (i.e., the day of the subject's last known laboratory assessment, last known vital sign assessment, last known physical exam, last known ocular exam, last known tumor assessment, or last known follow-up visit, whichever is the latest) or 49 days from the subject's last treatment (Depatux–M), whichever is earliest. If the subject has no post-baseline assessment, the data will be censored on the day of first dosing date.

11.3 Analysis of Secondary Endpoints

The maximum change from baseline in visual acuity on baseline corrected LogMAR scale prior to BCL intervention will be summarized by treatment arms and in overall population.

Kaplan-Meier plot for Time to BCL intervention will be produced. Time to BCL is defined as time from the randomization to the start date of BCL (as recorded in "Study Drug Administration - Bandage contact lens" CRF page). For subjects did not use BCL will be right-censored on the last assessment date.

In addition, Time to either ≥ +0.3 change on LogMAR scale in baseline adjusted visual acuity or grade 3 or higher CEAE prior to BCL intervention will also be analyzed. For this analysis, +0.3 change on LogMAR scale in baseline adjusted visual acuity before the start date of BCL or grade 3 or higher CEAE prior to the start date of BCL intervention will be considered as events. If a patient receives BCL intervention without experiencing any one of these two events will also be considered as event on the start date of BCL

intervention. If a patient neither receives BCL intervention nor experiences any one of these two events, his/her time will be right-censored on the last assessment date.

11.4 Analysis of Adverse Events

Treatment Emergent Adverse events (TEAEs) are defined as any AE with onset or increased severity after the first dose of study drug (RT/TMZ/Depatux–M) and no more than 49 days after the last dose of Depatux-M. All AE will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or higher.

Adverse Event Overview: The summary of subjects experiencing TEAEs by treatment arms will be summarized for the following adverse event categories.

- Any TEAE
- Any TEAE possibly related to Depatux‑M
- Any TEAE with CTCAE grade 3 or higher
- Any Grade 3 or higher TEAE possibly related to Depatux‑M
- Any TE serious AE (SAE)
- Any TEAE leading to discontinuation of Depatux‑M
- Any treatment emergent CEAE
- Any treatment emergent CEAE with CTCAE grade 3 or higher
- Any treatment emergent CEAE leading to discontinuation of Depatux‑M
- Deaths (within 49 days from last dose and after 49 days from last dose)

Summary of Adverse Event: Following summary of AE would be produced:

	Regardless of Any Relationship	Relationship to Depatux-M
Any AE (by PT in the descending order)	X	
Any Grade 3 or higher AE (by PT in the descending order of difference in incidence)	X	
Any AE (by SOC and PT)	X	
Any AE (by SOC, PT and Grade)	X	
Grade 3 or higher (by SOC and PT)	X	
SAE (by SOC and PT)	X	X
Leading to ABT-414 discontinuation (by SOC and PT)	X	X
Summary of CEAE (by SOC and PT)	X	
CEAE by highest grade for subjects (by SOC and PT)	X	
Leading to ABT-414 discontinuation (by SOC and PT)	X	

Listings of Adverse Event: The following listings of adverse events will be prepared.

- Listing of treatment-emergent serious adverse events.
- Listing of treatment-emergent AE that led to discontinuation of study drug.
- Listing of treatment-emergent fatal adverse events.
- Listing of Grade 3 or higher adverse events

11.5 Analysis of Laboratory and Vital Signs Data

NCI CTCAE grading criteria for laboratory abnormalities are shown in Table 2 and Table 3. Pre-defined criteria for potentially clinically significant vital signs values are given in Table 4.

Subjects with maximum treatment-emergent laboratory values meeting the potentially clinically significant criteria will be summarized. Similarly, subjects with treatment emergent post baseline values meeting criteria for potentially clinically significant Vital Signs values will be provided.

Table 2. Criteria for NCI CTCAE Grades for Laboratory Values - Hematology

	Units	NCI CTCAE Grade ≥ 3		NCI CTCAE Grade ≥ 4	
		Low	High	Low	High
Hematology Variables					
Hemoglobin	g/L	< 80			
White blood cell count	10^9/L	< 2		< 1	
Neutrophil count	10^9/L	< 1		< 0.5	
Lymphocyte count	10^9/L	< 0.5		< 0.2	
Absolute Platelet count	10^9/L	< 50		< 25	
Coagulation Variables					
INR increased	ratio		> 2.5 × ULN		

Table 3. Criteria for NCI CTCAE Grades for Laboratory Values - Chemistry

Chemistry Variables	Units	NCI CTCAE Grade ≥ 3		NCI CTCAE Grade ≥ 4	
		Low	High	Low	High
Creatinine	mcmol/L		> 3 × ULN		> 6 × ULN
Total bilirubin	mcmol/L		> 3 × ULN		> 10 × ULN
ALT	U/L		> 5 × ULN		> 20 × ULN
AST	U/L		> 5 × ULN		> 20 × ULN
ALP	U/L		> 5 × ULN		> 20 × ULN
GGT			> 5 × ULN		> 20 × ULN
Sodium	mmol/L	< 130	> 155	< 120	> 160
Potassium	mmol/L	< 3	> 6	< 2.5	> 7
Calcium	mmol/L	< 1.75	> 3.1	< 1.5	> 3.4
Magnesium	mmol/L	< 0.4	> 1.23	< 0.3	> 3.3

Table 4. Criteria for Potentially Clinically Significant Vital Signs Values

Vital Signs Variables	Criterion	Definition of Potentially Clinically Significant Values
Systolic blood pressure	High	Value ≥ 160 mmHg
Diastolic blood pressure	High	Value ≥ 100 mmHg
Heart rate	Low	Value ≤ 50 bpm
	High	Value ≥ 120 bpm
Temperature	Low	Value ≤ 32°C
	High	Value > 40°C

12.0 References

1. Bailey IL, Lovie-Kitchin JE. Visual acuity testing. From the laboratory to the clinic. Vision Res. 2013;90:2-9.

13.0 Appendix: Activity Schedule

	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	

	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
Karnofsky Performance Status	✓											✓	✓		
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)	✓														

	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
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															✓
℞ TREATMENT															
Radiation			✓	✓											
Temozolomide			✓	✓			✓		✓		Day 1 of Cycles 6 – 12				
Prophylactic Treatments for OSE		✓	✓				✓	✓	✓	✓	✓				
Depatuxizumab mafodotin			✓	✓			✓	✓	✓	✓	✓				